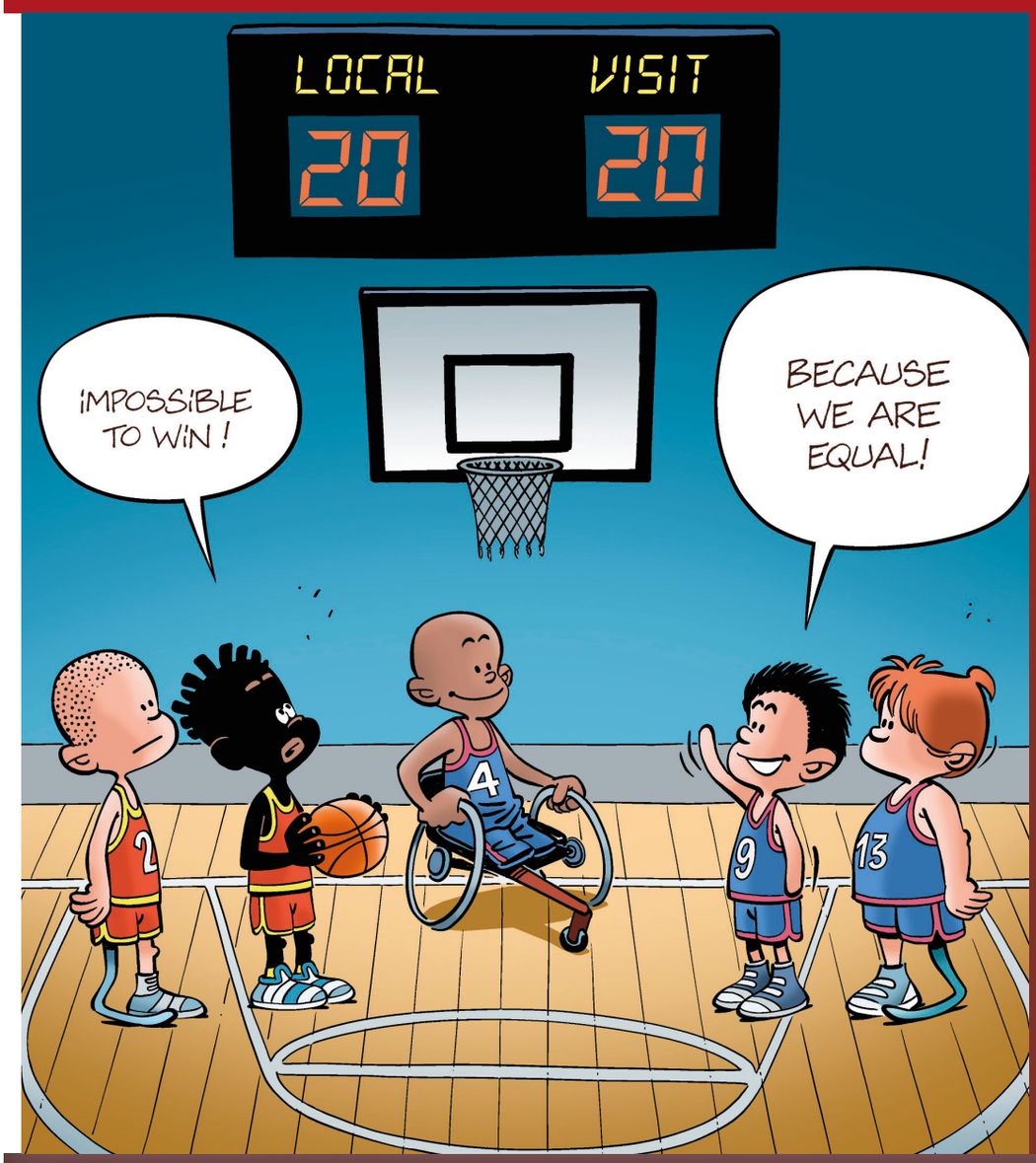
# BJP Belgian Journal of Paediatrics

Publication of the Belgian Society of Paediatrics

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

2024 - Volume 26 - number 3 - Septembre





Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

**QUARTERLY**
ISSN 2466-8907 (printed version)
ISSN 2566-1558 (digital version)

V.U./E.R. C. Chantrain (CHC-Liège), M. Raes (KUL)
UZ Leuven, Herestraat 49, 3000 Leuven
E-mail: BJ-Ped@hotmail.com


**BEXSERO is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B.[1]**

**VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN:** Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL:** Bexsero suspensie voor injectie in voorgevulde spuit. Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd), EU/1/12/812/001-EU/1/12/812/002-EU/1/12/812/003-EU/1/12/812/004. Farmacotherapeutische categorie: meningokokkenvaccins, ATCcode: J07AH09. **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING: Een dosis (0,5 ml) bevat:** Recombinant Neisseria meningitidis groep B NHBAfusieeiwit[1,2,3]: 50 microgram • Recombinant Neisseria meningitidis groep B NadAeiwit[1,2,3]: 50 microgram • Recombinant Neisseria meningitidis groep B fHbpfusieeiwit[1,2,3]: 50 microgram • Buitenmembraanvesikels (BMV) van Neisseria meningitidis groep Bstam. NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat[2]: 25 microgram • [1] Geproduceerd in E. colicellen door recombinantDNAtechnologie - [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg $Al^{3+}$) - [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit). Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de volledige SPK. **FARMACEUTISCHE VORM:** Suspensie voor injectie. Melkwitte vloeibare suspensie. **KLINISCHE GEGEVENS: Therapeutische indicaties:** Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door Neisseria meningitidis groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **Dosering en wijze van toediening:** Dosering: **Tabel 1. Samenvatting van de dosering: Leeftijd bij eerste dosis: Zuigelingen van 2 tot en met 5 maanden[a]: Primaire immunisatie:** Drie doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b,c]. - **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b,c]. • **Leeftijd bij eerste dosis: Zuigelingen van 6 tot en met 11 maanden: Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis[c]. • **Leeftijd bij eerste dosis: Kinderen van 12 tot en met 23 maanden: Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis[c]. • **Leeftijd bij eerste dosis: Kinderen van 2 tot en met 10 jaar: Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • **Leeftijd bij eerste dosis: Adolescenten (11 jaar of ouder) en volwassenen*: Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • [a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. - [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. - [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld. - [d] Zie rubriek 5.1 van de volledige SPK. - * Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening: Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **Contraindicaties:** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **Bijwerkingen:** Overzicht van het veiligheidsprofiel: De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38°C) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen: Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥ 1/10) - Vaak: (≥ 1/100, < 1/10) - Soms: (≥ 1/1.000, < 1/100) - Zelden: (≥ 1/10.000, < 1/1.000) - Zeer zelden: (< 1/10.000) - Niet bekend: (kan met de beschikbare gegevens niet worden bepaald). De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar):** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Voedings en stofwisselingsstoornissen: Zeer vaak: eetstoornissen. Zenuwstelselaandoeningen: Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn. - Soms: insulten (inclusief febriele insulten). - Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen: Soms: bleekheid (zelden na booster). - Zelden: ziekte van Kawasaki. Maagdarmstelselaandoeningen: Zeer vaak: diarree, braken (soms na booster). Huid en onderhuidaandoeningen: Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster). - Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar). - Soms: eczeem. - Zelden: urticaria. - Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: koorts (≥ 38 °C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid. Soms: koorts (≥ 40 °C). - Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). **Adolescenten (van 11 jaar en ouder) en volwassenen:** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Zenuwstelselaandoeningen: Zeer vaak: hoofdpijn. - Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Maagdarmstelselaandoeningen: Zeer vaak: misselijkheid. Huid en onderhuidaandoeningen: Niet bekend: huiduitslag. Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: myalgie, artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise. - Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België:** Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Afdeling Vigilantie - Postbus 97 - 1000 Brussel - Madou - Website: www.eenbijwerkingmelden.be - e-mail: adr@fagg.be. **Luxemburg:** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN:** GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië. **DATUM VAN DE GOEDKEURING VAN DE TEKST:** 26/04/2023 (v15). **AFLEVERINGSWIJZE:** Op medisch voorschrift.

**References: 1.** SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

PM-BE-BEX-ADVR-230001 - Augustus 2023 | VU: GlaxoSmithKline Pharmaceuticals s.a./n.v. Site Apollo Avenue Pascal, 2-4-6 1300 Waver Belgium

## Editorial Board

**Founding editors**
L. Corbeel, W. Proesmans

**Chief Editors**
C. Chantrain, M. Raes

**Associate Editors**
C. Barrea, O. Danhaive, I. Decuyper, E. Duval, V. Guy-Viterbo, L. Hoste, L. Panneel, I. Roggen, K. Van De Maele, Y. Vandenplas, K. van Hoeve, A. Vuckovic, M. Wojciechowski

**Secretariat**
N. Meignen

**Universities**
G. Buyse (UZ Leuven), MF Dresse (ULG), P. Smeesters (ULB), S. Van Daele (UZ Gent) I. Gies (VUB), S. Moniotte (UCL), S. Verhulst (UZA)

**BVK-SBP Executive Committee**
M. Raes, President
S. Moniotte, Vice-president
G. Buyse, Secretary
P. Smeesters, Secretary
A. Raes, Treasurer
A. Malfroot, Past-president
D. Van Gysel, International societies
K Van De Maele , Social Media

**Associations**
A. Bael (VVK)
P. Philippet (GBPF)

**Belgian Academy of Paediatrics**
A. De Guchtenaere, President
S. Moniotte, vice-president
T. Jonckheer, Secretary
P. Philippet, treasurer


# Contents

# RECHAUFFEMENT GLOBAL : UNE BONNE HYDRATATION EST CRUCIALE POUR PROTEGER LES REINS DES NOUVEAU-NES !

Divers facteurs influencent la santé rénale des nouveau-nés. Parmi ceux-ci, les conséquences du changement climatique, et en particulier les vagues de chaleur, peuvent impacter le développement des reins pendant la grossesse et, plus tard dans la vie, la fonction rénale.[1]

## UNE BONNE HYDRATATION, IMPÉRATIVE DÈS LA GROSSESSE

Les femmes enceintes sont particulièrement vulnérables aux effets du changement climatique, car elles ont plus de problèmes de thermorégulation, sont davantage sensibles aux effets de la déshydratation et sont plus susceptibles de contracter des infections. L'exposition à la chaleur et à ses conséquences climatiques (p.ex. feux de forêts, pics de pollution de l'air…) sont associées à un faible poids à la naissance, à un risque accru de naissance prématurée et de prééclampsie. Ces facteurs sont eux-mêmes associés à une réduction du nombre de néphrons, à des dysfonctionnements rénaux et à une pression artérielle plus élevée chez les enfants plus tard dans la vie.[1]

## UNE BONNE HYDRATATION, IMPÉRATIVE DÈS LA GROSSESSE

Un faible poids à la naissance (<2,5 kg), un faible poids pour l'âge gestationnel (SGA, <10$^{e}$ percentile de poids), une naissance prématurée (PTB, <37 semaines) et/ou un évènement de prééclampsie pendant la grossesse sont ultérieurement associés à une pression artérielle plus élevée, à un risque de protéinurie et à des dysfonctionnements rénaux.[1]

Des études ont mis en lumière la sensibilité de la néphrogénèse liée aux expositions durant la grossesse : si le nombre de néphrons augmente avec le poids à la naissance et l'âge gestationnel, ce nombre n'augmente toutefois plus après la naissance. Les expositions durant la grossesse ont donc un impact sur le réservoir de néphrons d'un individu à vie.[1,2]

De multiples médiateurs moléculaires sont également impliqués dans le développement des reins, notamment des altérations de l'expression génique, une modulation de l'apoptose, une sénescence accélérée et les effets du sexe, qui peuvent tous être sensibles aux expositions de chaleur durant la grossesse. D'autres facteurs comme la prééclampsie peuvent également contribuer à la variabilité individuelle du risque à long terme de développement d'une maladie rénale chronique tout au long de la vie.[1]

## DE NOMBREUX BÉBÉS À RISQUE DE TROUBLES RÉNAUX

En 2020, près de 20 millions de bébés sont nés dans le monde avec une insuffisance pondérale. On estime que 10% des naissances sont prématurées, et un bébé sur 5 est petit par rapport à l'âge gestationnel. Ainsi, les risques liés à des facteurs environnementaux tels que le climat méritent une attention particulière à l'échelle de la population. Malgré cela, tous les bébés nés trop petits ou trop tôt ne développent pas pour autant une maladie rénale, et il est fort probable que d'autres facteurs interviennent après la naissance.[1]

## IMPORTANCE D'UNE EAU FAIBLEMENT MINÉRALISÉE, AU BON MOMENT

L'allaitement maternel est recommandé dans la mesure du possible chez tous les nourrissons, même par temps chaud. Dans ce cas de figure, il n'est pas nécessaire de leur proposer de l'eau avant l'introduction d'aliments solides, vers l'âge de 6 mois. Toutefois, s'il fait exceptionnellement chaud ou si le bébé montre des signes de déshydratation, on peut lui proposer une toute petite quantité d'eau.

Pour les nourrissons nourris au lait maternisé, l'eau peut être introduite avant 6 mois. L'introduction de l'eau doit se faire progressivement et en petites quantités. Par temps très chaud, il peut être nécessaire d'adapter les quantités d'eau données.[3]

La fonction rénale des nouveau-nés n'ayant pas encore atteint une maturité suffisante, il est important d'opter pour une eau pure, faiblement minéralisée et de préférence en bouteille.[4,5]

Les changements climatiques peuvent avoir un double effet, en impactant à la fois le développement des reins du fœtus et en contribuant à l'accumulation de lésions rénales postnatales. Face aux vagues de chaleur, il est donc essentiel d'assurer une bonne hydratation des futures mères, ainsi que celle des nourrissons.[1]


SPA
NATURAL SINCE 1583

Spa soutient la
SOCIÉTÉ BELGE DE PÉDIATRIE

Références: 1. Alvarez-Elias A.C., Brenner B.M., Luyckx V.A., Climate change and its influence in nephron mass. Curr Opin Nephrol Hypertens. 2024 Jan 1;33(1):102-109. doi: 10.1097/MNH.0000000000000932. Epub 2023 Oct 6. PMID: 37800660; PMCID: PMC10715706. 2. Puelles, Victor, et al., Glomerular number and size variability and risk for kidney disease. Current Opinion in Nephrology and Hypertension 20(1):p 7-15, January 2011. | DOI: 10.1097/MNH.0b013e3283410a7d. 3. What are the recommendations for giving water during infancy? NHS, 2022. 4. Conseil Supérieur de la Santé. Qualité microbiologique de l'eau destinée à la préparation des biberons CHS 8123 2005. 5. Azoulay A. et al., Comparison of the mineral content of tap water and bottled waters. J. Gen. Intern. Med 2001.16 : 168-175.ed 2001.16 :168-175.

**Mieux boire. Mieux vivre.**

# Editorial

## Difference and diversity…

As autumn approaches, we hope that for each of you the summer and holidays have been synonymous with rejuvenation, joy and shared happiness.

September draw to a close with the Paralympic Games, which took place after the “Paris 2024” Olympic Games. First of all, we would like to congratulate all the athletes of the Belgian teams on their journey to Paris and, of course, on the many medals they brought home: 10 and 14 medals respectively at the Olympic and Paralympic Games. We also want to dedicate this editorial and the cover of this issue to such international events.

The Paralympic Games were originally founded by a medical doctor, the German-born and British neurologist Ludwig Guttman. In 1948, he had the idea of organising competitions on the grounds of Stoke Mandeville Hospital, near London, for amputees and paraplegics who had been victims of the Second World War. He explained that these sports competitions would encourage the patients in their rehabilitation and that together they could more easily regain confidence in their abilities. Later, these events officially became the Paralympic Summer Games, the first of which was held in Rome in 1960 under the impetus of Dr Guttman and his Italian colleague Dr Antonio Maglio. In a March 2021 issue of our Belgian Journal of Paediatrics devoted to rehabilitation in children, several colleagues described the importance of sporting activities in the long-term management of various medical and surgical pathologies.

These Paralympic Games are, of course, a tribute to the courage, determination of the athletes. They are also an ode to difference and diversity. A very important message at a time and in a world where difference is too often associated with tension, violence and exclusion. At the beginning of this year, the French biologist Olivier Hamant, in a new essay entitled "*De l'incohérence, philosophie politique de la robustesse*", cited numerous examples observed in nature to describe how diversity and the development of relationships between living beings enable to overcome limits and resolve extreme situations. He explains that trees, although competing with each other in the valleys, are able to cooperate in order to grow and develop in the unfavourable conditions of mountains. This inclusion of diversity and cooperation sometimes takes a little more time and may seem a little less effective, but it allows the creation of robust ecosystems that are better able to adapt and respond. As we -including our children or our patients- head back to school, we thought it was important to be aware and to keep in mind the benefits of diversity. For our patients and their families, we wish their differences, their uniqueness, their talents and sometimes their weaknesses or vulnerabilities will be welcomed with respect and even valued. And of course, This state of mind can also be positive in our work, in our teams and even in our personal lives.

In this autumn issue we are delighted to present the results of two surveys: one about the knowledge on clinical signs of child maltreatment among childcare workers by Jacobs *et al.* and the other concerning the recognition of abusive head trauma by emergency physicians and paediatricians by Marcelis *et al.* France *et al.* describe the results of a qualitative study of the knowledge of primary schoolchildren about illness symptoms in Flanders. Nikitas and colleagues report on regional inequity in 4CMenB vaccination in Belgium. We also publish a literature review leading to a new treatment protocol on antibiotherapy post-appendectomy by Goovaerts *et al.* The consensus recommendation for paediatric intravenous maintenance fluid is explained by the Be-PIV group. The Made in Belgium section presents the Ph D thesis of Sam Geuens from KULeuven. Dr Geuens has explored the impact of corticosteroid treatment and genotype on brain morphology and their correlations with neurobehavioral outcomes in patients with Duchenne muscular dystrophy. In addition to these studies, several informative clinical observations are reported by our young colleagues in training.

On behalf of the editorial team, we wish you a pleasant and informative read.

**Christophe Chantrain and Marc Raes**

**Uw vragen of commentaar**
**Vos questions ou commentaires**

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

**Comité de rédaction - Redactieraad**
**M. Raes - C. Chantrain**

Gasthuisberg - Kindergeneeskunde

Herestraat 49 - 3000 Leuven
E-mail BJ-Ped@hotmail.com


**Verzacht doeltreffend de huid met neiging tot atopie**
geeft rust aan de ouders.

**Herlipiderende crème anti-jeuk**


99% ingrediënten van natuurlijke oorsprong

COSMETIQUE BIO CHARTE COSMEBIO

Zonder parfum

Verzacht onmiddellijk

Anti-recidief

ECOCERT COSMOS ORGANIC

# Knowledge on Clinical Signs of Child Maltreatment among Childcare Workers: A Survey

Noor Jacobs [a], David De Coninck [b,c], Jaan Toelen [c,d,e]

[a] Faculty of Medicine, KU Leuven, Belgium
[b] Centre for Sociological Research, KU Leuven, Belgium
[c] KU Leuven Child and Youth Institute, KU Leuven, Belgium
[d] Department of Pediatrics, University Hospital Leuven, Belgium
[e] Department of Development and Regeneration, KU Leuven, Belgium

jaan.toelen@uzleuven.be

## Keywords

Child abuse and neglect; childcare workers; clinical symptoms and signs.

## Abstract

***Objective***

Child maltreatment is a global health concern often underreported, making early detection crucial. Recognizing signs of abuse, especially in childcare settings where attendance rates are high, is pivotal.

***Methods***

This prospective study using an online survey included 16 hypothetical cases accompanied by a clinical image. Qualtrics was used to distribute the survey. Participation was completely voluntary and anonymous. Childcare workers were asked to give a risk-assessment about the case using a Likert scale.

***Results***

93 respondents fully completed the questionnaire. The overall mean score on the survey was 67.8% (Std. Deviation 12.0%). In general, the percentage of correct answers on the cases suggestive for child maltreatment (67.8%) and the one not suggestive for child maltreatment (67.9%) were the same. No significant correlation was obtained between the variables 'gender', 'age', 'number of children', 'number of years of work experience' and the outcome 'overall score'. However, there was a positive correlation between previous contact with suspected child maltreatment and an adequate assessment of the situation (p-value 0.005).

***Conclusions***

The knowledge about physical signs of child maltreatment does not depend on the age or work experience of the childcare worker. However, knowledge could be positively influenced by previous experiences with suspected child maltreatment and additional training on this topic.

## Introduction

Child abuse and neglect are global health problems occurring across all communities regardless of social, racial, and economic backgrounds (1-3). These include various types of abuse - physical (22.6%), sexual (12.7%), and emotional (36.3%) - linked to significantly higher levels of psychopathology in affected children. Child maltreatment is widely under-reported, potentially prolonging or exacerbating cases of abuse (5). Children under the age of three, particularly infants under six months, account for 25% of victims, vulnerable due to their inability to defend themselves or articulate the abuse (6, 7).

In the context of physical abuse, skin lesions such as hematomas and ecchymoses are common manifestations, serving as logical sentinels for early detection to prevent future harm (8). Sentinel injuries, visible minor injuries in infants that are poorly explained, are suspicious of physical maltreatment (9). Caregivers should be familiar with injury patterns and distributions in order to appropriately identify child physical abuse (3). Although external signs may be subtle, identifying the pattern and location of any skin finding can help differentiate accidental from abusive injury, facilitating timely referral to clinical experts (10). Any missed diagnosis carries the risk of recurrence and further child maltreatment (12).

With half of European Union children under three attending daycare, Belgium, particularly Flanders, reflects this trend, with 94,681 licensed daycare places in 2021 and 53.4% attendance among infants and toddlers (13, 14). Daycare staff, deeply involved in children's lives, have unique insights into their well-being, potentially surpassing physicians' assessments.

Belgium's 'Confidential Centers for Child Abuse' and helpline '1712' provide avenues for anonymous reporting, receiving 7,535 reports in 2021, 14% concerning children under three years of age (15). However, childcare education in Flanders, while emphasizing reporting guidelines, lacks focus on recognizing physical signs of maltreatment, hindering professionals' ability to accurately identify abuse (16, 17).

Few publications address recognizing abuse in this professional population. A comparative study among preschool teachers revealed inconsistent reporting despite high prevalence, attributed to a lack of knowledge and insufficient evidence of abuse. Developing standardized training programs and guidelines to support teachers is crucial (7). Research indicates that teachers' awareness of child neglect and abuse increases after training, with reporting rates significantly improving (18). Another study found that daycare workers have limited knowledge about reporting procedures and their legal protections (19).

This study aimed to assess childcare workers' familiarity with physical signs of child neglect and abuse in Flanders.

**Table 1** : Case scenario description of the survey

| | Vignette | Image description |
|---|---|---|
| **Case 1** | Matteo, a 3-month-old boy, has started nursery today for the first time. During the welcome interview, the parents didn't mention anything unusual about the child. They seemed enthusiastic and friendly. Matteo has cried frequently today, which is expected on his first day in a new environment. While changing his diaper, you notice a blue tint on his bottom. He doesn't react when you apply pressure to the spot. When Matteo's mom comes to pick him up, she explains that Matteo has had this since birth. | The clinical image shows the lower back of a newborn infant with several confluent blueish to blue-grey nummular spots, typical of dermal melanosis. |
| **Case 2** | Amélie is a cheerful girl who has been attending daycare for 1.5 years. You're familiar with her mother, who picks her up daily, but you've never met her father. Today, Amélie is unusually quiet and uses her left arm sparingly. In the evening, you inquire about her arm, and her mother explains, "She went to the woods with her dad yesterday. They were walking hand in hand, and while trying to jump in puddles, Amélie slipped, but her dad managed to pull her up by the arm." Her mom also noticed yesterday that Amélie's arm was bothering her but decided to wait and see. Now, she is decided they will visit the doctor tonight for sure. | The clinical image shows a child on a hospital stretcher with her left arm stretched out parallel to her side, the right arm is in use. |
| **Case 3** | Louis, a 1.5-year-old boy, comes from a family of 6, none of whom have attended this nursery before. Today marks the last day before summer vacation, and Louis' family is leaving for Spain tonight for a 2-week trip. His dad drops him off in the morning in a rush. Later in the day, you notice that Louis' ear appears blue, and he cries when you touch it. When you ask his dad in the evening what happened, he explains, "The older siblings were playing with a plastic jump rope yesterday, and Louis accidentally got hit on the ear with it." Louis' dad works as a nurse in an assisted living facility, and his mom is currently unemployed and dealing with depression. His dad dismisses the blue ear, saying, "Kids grow up with bumps and bruises, especially with boys and brothers." | The clinical image shows the left ear of a child. There is a clear ecchymosis on the antihelical crura and scapha. The rest of the earlobe is normal. |
| **Case 4** | The nursery has been closed for collective leave for 2 weeks and reopened today. In the morning, the mother of Fien, a 4-month-old girl, did not mention anything in particular when she dropped her daughter. While changing Fien's diaper later that day, you notice the following image on her bottom. Fien comes from a family of 5. Her parents are very kind, and you are familiar with them because her older sister also attended the nursery. Unfortunately, Fien's family isn't very well-off, and you often notice that Fien wears the same dirty clothes. In the evening, you ask her mom if and when she noticed this redness on Fien's bottom. She replies that she first noticed it yesterday morning before giving Fien a bath. | The clinical image shows the anogenital region of a female infant with a severe erythematous rash with papulovesicular lesions, fissures, and erosions. It is more severe than the 'common' phenotype of a diaper dermatitis. |
| **Case 5** | As a new employee in this nursery, you have only known the children for 2 weeks. Today, you notice a bruise on the back of Lola, a 13-month-old girl. When you touch it, she does not react, but it does feel swollen. In the evening, Lola's mom explains that she has had this bruise since she was little. She appreciates your concern for the health of the children in the nursery. | The clinical image shows a circular elevation in the interscapular region of an infant. The skin at the site of the nummular elevation has a pale bluish colour and in the middle there are some small regions of purple colour. It has the aspects of a deep haemangioma. |
| **Case 6** | Yentel is a 14-month-old boy who's quite energetic who attends your nursery. Different people, including the parents, grandparents, or an aunt, drop him off and pick him up every day. In the evening, Yentel's mom sends a WhatsApp message stating another child must have bitten Yentel on his arm and sends a picture as evidence. You inquire with your colleagues if they noticed anything, but they didn't observe any incidents. Yentel wore a sweatshirt all day, so you had not noticed these injuries either. You recall that Yentel had a burn on his knee a month ago. There have been some challenges in communicating with the parents, and Yentel has been absent from the nursery more frequently lately when he was expected to attend. | The image shows 2 red circular skin lesions on the left arm consistent with superficial bite injuries. |
| **Case 7** | The nursery has been closed for collective leave for 2 weeks and reopened today. In the morning, Ella's father, a, informed you that his daughter - a 3-month-old infant -has had a rash in the diaper region for several days. They took her to the paediatrician, who prescribed a cream. Otherwise, Ella has been declared healthy. The father requests that you apply the cream once during the day as well. | The clinical image shows a bright erythematous rash in the anogenital region of a female infant. The skin folds are involved, and satellite lesions are visible at the edges of the rash, suggestive for a Candida infection. |
| **Case 8** | Vic is a 16-month-old boy. He is usually quiet and makes little eye contact when spoken to. When his grandmother drops him off, she mentions that he bumped into the corner of a table yesterday and now has a 'black eye'. You have not seen his parents in a while. Vic's mother has been in the hospital due to alcohol-related issues. You have heard from the father that the couple is going through a divorce. | The clinical image shows a toddler with an orbital ecchymosis of the right eye. The discoloration is most pronounced above the medial commissure. The eyebrow is intact and there is no swelling around the eye. |
| **Case 9** | Lars (1.5 years old) was adopted at 3 weeks old. His adoptive parents shared with you during the first meeting that they've faced numerous challenges since then. Lars has been prone to crying for extended periods, and he has also experienced allergies and feeding difficulties. You have had several conversations with his concerned father, who often feels insecure about parenting and sometimes feels overwhelmed with the responsibilities. However, things have been improving lately. Lars is usually very quiet around his parents, but he becomes one of the loudest kids once he's in the nursery. Suddenly, you notice an injury under his ear and ask Lars himself what happened. Lars responds, "daddy." In the evening, his father mentions he had not noticed it yet, and they assume Lars might have "bumped himself" during the day. | The clinical image shows a rectilinear superficial excoriation with a length of 4 cm and a width of 0.3cm behind the lower part of the ear. |
| **Case 10** | On Monday morning, Félicia is brought to the nursery by a friend of her mother. Félicia is a 10-month-old girl who cannot yet walk but enjoys crawling. She is a sociable child who actively seeks out interaction with other children. When you tried to pick her up on the playmat, she pulled her leg away and started crying. Nothing out of the ordinary had happened in the nursery that day until then. While changing her diaper, you notice bruises on her legs. When you ask her dad about the bruises, he says he does not know how or when they originated. Félicia was with her mom last week due to co-parenting. | The clinical image shows the lower legs of an infant with several ecchymoses on the anterior side below the knee, two on the left leg and seven on the right leg. The largest has a diameter of 2cm, the smallest 0.5 cm. |
| **Case 11** | The parents of Noah, who is 3 months old, express concern about feeding problems. Noah has been experiencing frequent regurgitation of milk, and according to the parents, he appears to have some cramps and often cries in the evening. Today, Noah vomits milk, prompting you to change his clothes. While changing him, you notice red streaks on his right leg. When you inquire about the cause of the rash, the parents explain that they found him this morning with his leg wedged between the bed's pillars. | The clinical image shows both lower legs of an infant with linear reddish lesions in the conformation of a negative imprint of adult digits on the right lower leg. |

| | Vignette | Image description |
|---|---|---|
| **Case 12** | When Matthies' mother drops him off at the daycare centre in the morning, she informs you that yesterday he had a serious fight with his sister, who bit him. Matthies (23m old) never likes to say goodbye to his mother and always cries when she leaves. However, after a few minutes, he calms down and becomes a happy boy again. When asked who bit him, Matthies says, "sister." | The clinical image shows a toddler with a small and superficial bite wound on the left cheek. |
| **Case 13** | When you receive Jesse (1.5 years old) in the nursery in the morning, you are startled by the bump on his forehead. His dad responds with a laugh, explaining that Jesse was too wild while playing yesterday and fell on his head while running with his toys in his hands. They visited the doctor on call, who reassured them that it was just an insignificant bump. Jesse is indeed one of the more energetic kids in the group and always makes a lot of noise while playing. | The clinical image shows a toddler with a small hematoma on the left frontal part of the skull. There are no additional lesions. |
| **Case 14** | Simon (16 months) is brought to the nursery by his mom this morning. She is in tears as she explains that Simon returned from his father's house yesterday with a "blue cheek". The parents are currently going through a difficult divorce, and the father is seeking full custody of Simon. Simon always gets excited when he sees someone entering the nursery, but when his parents show up, he often hides away. | The clinical image shows a toddler with a 'slap mark'. One can notice the imprint of a hand (imprint of digits) on the right cheek of the child. |
| **Case 15** | Emma's father reports today that Emma burned herself this morning with a hot cup of tea that fell over during breakfast. He immediately held her arm under running cold water and then had it checked by the neighbour, who is a nurse. She has already applied an anti-burn product (Flamigel°) to it. Emma's parents are both very ambitious and work hard, so she spends a lot of time in the nursery. | The clinical image shows an oval-shaped second degree burn on the forearm of a child. The skin is red and there are central regions with desquamation present. |
| **Case 16** | Sofie's mother reports today that Sofie has been reluctant to put weight on her right leg since this morning. Yesterday, there did not seem to be any problems, and she was playing normally. However, this morning, she cried when her mom tried to help her walk after changing her clothes. Sofie is 13 months old and can walk with support or while holding an adult's hand. Her mother is puzzled as Sofie has not fallen, does not have a fever, and does not seem to be experiencing pain elsewhere. She has plans to take the afternoon off to bring Sofie to the family doctor. During the morning, you also notice that Sofie experiences pain in her right leg when being lifted or when attempting to walk. You examined her thoroughly but could not find any bruises or other abnormalities. Despite this, Sofie appears happy and does not seem to have any other issues. | The clinical image shows a toddler who is standing up, supported by an adult. The weight of the child is on the left leg, the right leg seems to be less used. |

**Table 2** : Demographic characteristics of the participants.

| | N = 93 | % |
|---|---|---|
| **Gender** | | |
| **Male** | 2 | 2.2 |
| **Female** | 91 | 97.8 |
| **Age** | (Years) | |
| **19-35 years** | 35 | 37.6 |
| **36-50 years** | 31 | 33.3 |
| **>50 years** | 22 | 23.7 |
| **Missing data** | 5 | 5.4 |
| **Number of children** | (Children) | |
| **0** | 30 | 32.3 |
| **1** | 13 | 14.0 |
| **2** | 34 | 36.6 |
| **3** | 13 | 14.0 |
| **4** | 1 | 1.1 |
| **>4** | 2 | 2.2 |
| **Number of years of work experience** | (Years) | |
| **1-5 years** | 24 | 26.9 |
| **6-10 years** | 15 | 16.1 |
| **11-25 years** | 40 | 43.0 |
| **>25 years** | 13 | 14.0 |
| **Been in contact with suspected child maltreatment** | | |
| **Yes** | 34 | 36.6 |
| **No** | 59 | 63.4 |
| **Total** | 93 | 100 |
| | Mean score (years) | Standard error |
| **Age** | 40.2 | 11.50 |

## Methods

### *Study Design*

This prospective study, using an online survey, received approval from the Research Ethics Committee UZ/KU Leuven (MP023079). The study protocol mirrored a previous research methodology from our group but targeted a different audience (1). An anonymous online survey featuring hypothetical cases with clinical images was used. Participation in the questionnaire was voluntary and contingent upon informed consent. The study design comprised two components: a sociodemographic questionnaire gathering data on gender, age, number of children, years of work experience, and contact with suspected child maltreatment, alongside 16 clinical cases. These hypothetical cases, set within a childcare context, constituted the primary questionnaire content. Each case, depicting potential child maltreatment, was accompanied by a clinical image illustrating the child's signs or injuries (Table 1). Childcare workers evaluated the risk level of each case for child abuse and neglect using a Likert scale ("unsuspicious," "rather not suspicious," "neutral," "rather suspicious," "highly suspicious"). The survey was distributed via Qualtrics, validated by both expert and layperson groups to ensure internal validity and comprehension. Data collection took place from March to June 2023.

### *Statistical Analysis*

Only fully completed questionnaires obtained via Qualtrics were analyzed. IBM SPSS software facilitated all statistical analyses. Categorical variables were presented as frequencies and percentages. Responses were dichotomized for analysis: "unsuspicious" and "rather not suspicious" categorized as "not suspicious," while "rather suspicious" and "highly suspicious" were considered "suspicious," with "neutral" always deemed incorrect. Pediatric experts evaluated each case based on practical experience and medical literature. The scoring of the experts was used to dichotomize the participant's answers into correct or incorrect. Participants' responses were graded accordingly, and an overall score reflecting the ability to distinguish cases indicative of child maltreatment was calculated for each participant. The proportion of correct answers for each case was visualized using a Likert plot. The Chi-Squared test determined statistical correlations between

**Figure 1A** : Overall score on the survey of 16 cases (N=93).

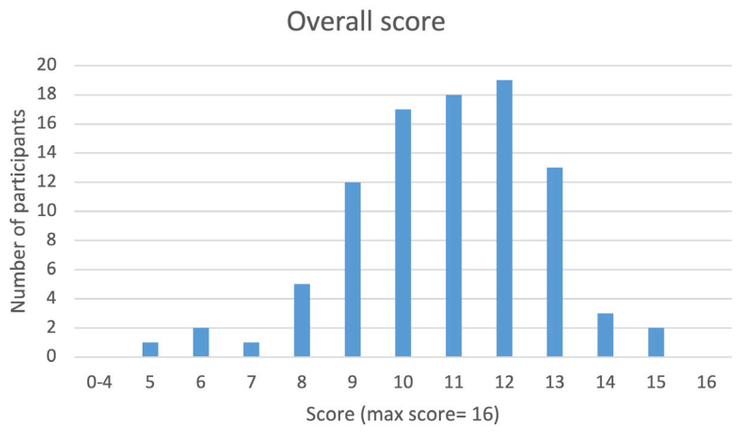



**Figure 1B** : Boxplot of the overall score on the survey and the two subgroups.

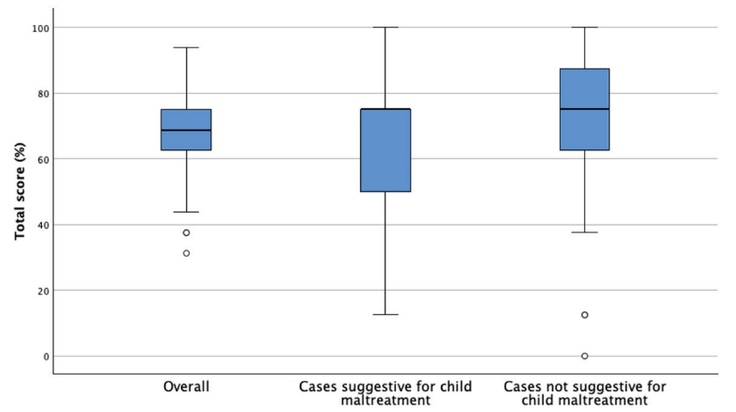



**Table 3** : The proportion of correct answers per case.

| Case | Subject | Correct answers % |
|---|---|---|
| **Case 1** | Congenital dermal melanocytosis | 46.2% |
| **Case 2** | Pulled elbow | 54.8% |
| **Case 3** | Bruise on ear | 41.9% |
| **Case 4** | Diaper rash | 60.2% |
| **Case 5** | Hemangioma | 31.2% |
| **Case 6** | Bite trauma | 84.9% |
| **Case 7** | Infection diaper region | 88.2% |
| **Case 8** | Orbital hematoma | 78.5% |
| **Case 9** | Skin injury behind ear | 74.2% |
| **Case 10** | Bruises on lower leg | 54.8% |
| **Case 11** | Pinch wound | 48.4% |
| **Case 12** | Bite trauma | 92.5% |
| **Case 13** | Forehead hematoma | 89.2% |
| **Case 14** | Slap injury | 98.9% |
| **Case 15** | Burn | 55.9% |
| **Case 16** | Dysfunctional leg | 84.9% |

variables (gender, age, number of children, years of work experience, and contact with suspected child maltreatment) and the overall score, with a significance level set at 0.05.

## Results

### *Participants*

The survey included childcare workers from various daycare centers in Flanders, Belgium. The total number of invited daycare workers remains unknown as invitations were distributed by daycare authorities. Ninety-three respondents completed the questionnaire in full. Participant characteristics are summarized in Table 2. Most participants were women (97.8%) and had at least one child (67.7%). The mean age was 40.2 years (range 19-60 years), with 57% having over 10 years of daycare work experience. Additionally, 36.6% of respondents reported encountering a suspected abuse case.

### *Overall Score*

The survey's overall mean score was 67.8% (Standard Deviation 12.0%) compared to the correction key. Figure 1A presents a histogram illustrating the total scores of all individuals (N=93). The lowest score, 31.3%, was achieved by one respondent who correctly interpreted only 5 of 16 cases, while the highest score, 93.8%, was attained by two respondents (15 of 16 cases answered correctly). Figure 1B displays a boxplot depicting the sensitivity and specificity of detecting child maltreatment, with sensitivity representing the total score on cases suggestive of maltreatment and specificity representing the total score on cases not suggestive of maltreatment.

Furthermore, the proportion of correct responses per case is detailed in Table 3, with a Likert plot visualization in Figure 2A and 2B.

The best-solved case suggestive of maltreatment involved facial linear-shaped hematomas suspected of resulting from a hand slap, with 98.9% correct responses. Conversely, the case concerning a bruise on the ear had the lowest correct response rate (41.9%). Among cases not suggestive of maltreatment, the case involving a bite mark on the face had the highest correct response rate (92.5%), while only 31.2% answered correctly for the case involving a hemangioma. Overall, the percentage of correct answers for cases suggestive and not suggestive of maltreatment was similar, both around 67.8%.

### *Relationship Between Participant Characteristics and Overall Score*

Simple linear regression analysis for age, number of children, years of work experience, and previous contact with suspected maltreatment revealed correlation coefficients (R) of 0.026, 0.130, 0.026, and 0.305, respectively, with coefficients of determination ($R^2$) of 0.001, 0.017, 0.001, and 0.093, respectively. Only previous contact with suspected maltreatment showed a low positive correlation with the outcome, while correlations for other variables were negligible.

Multiple regression analysis incorporating age, gender, number of children, years of work experience, and previous contact with suspected maltreatment yielded an adjusted $R^2$ of 0.073, indicating a low predictive value for this model.

Univariate quadratic regression (Table 4) showed a statistically significant estimate parameter of 0.307 for the variable 'contact with suspected child maltreatment' (P-value 0.005), suggesting that individuals who encountered suspected child maltreatment had greater knowledge in recognizing physical injury due to maltreatment.

**Figure 2A** : Cases suggestive for child maltreatment: ranked from best (upper) to least well (bottom) solved.

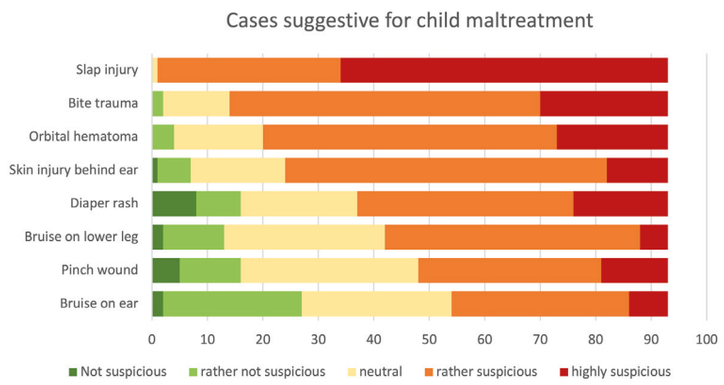



**Figure 2B** : Cases not suggestive for child maltreatment: ranked from best (upper) to least well (bottom) solved.

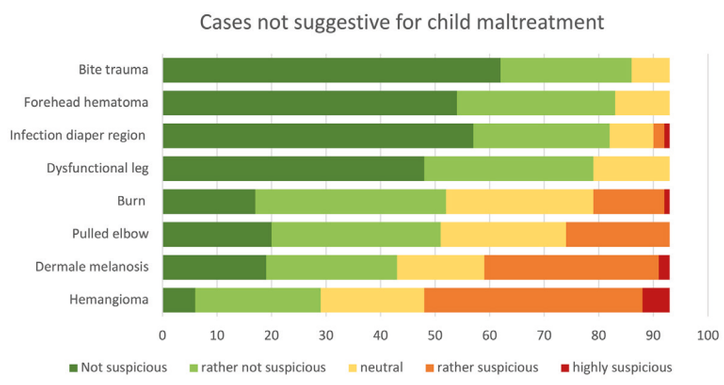



**Table 4** : Relationship between participant characteristics and overall score.

| | Univariate Quadratic regression | | |
|---|---|---|---|
| **Variable** | **Estimate (Standardized coefficients beta)** | **P-value** | **95.0% Confidence interval** |
| **Gender** | | | |
| Female | 0.006 | 0.954 | -17.190;18.228 |
| Male* | - | - | - |
| **Age** | -0.171 | 0.288 | -0.521;0.157 |
| **Number of children** | 0.210 | 0.100 | -0.409;4.563 |
| **Years of work experience** | 0.002 | 0.987 | -3.544;3.602 |
| **Contact with child maltreatment** | 0.307 | 0.005 | 2.430;13.130 |

* Male as reference.

## Discussion

In this study a relevant sample of Flemish daycare workers showed a good appreciation of physical signs of child abuse and neglect.

Out of 93 participants, only 2 respondents were men (2.1%). Due to this low number, the influence of gender on the overall score could not be analyzed. Notably, data on the proportion of men employed in childcare are scarce, but the average proportion in Belgium in 2023 was 1.7% (data supplied by Opgroeien, Flemish Government), aligning with our sample. The average number of children per participant in this study was 2.44 (SD 1.23), notably higher than the average fertility rate in Flanders of 1.53 (data from 2022) (20). This suggests that women working in childcare centers may tend to have more children on average. Additionally, 36.6% of respondents reported prior contact with a suspected case of child abuse.

The average score on the survey was 67.8%, with 89 out of 93 participants scoring at least 8 out of 16 cases correctly. However, there is no established threshold for determining a good result. Interestingly, the proportion of incorrectly assessed cases 'suggestive' and 'not suggestive' of child maltreatment was similar (32.2% and 32.1%, respectively), suggesting equal sensitivity and specificity in detecting maltreatment. This contrasts with a previous study among physicians in training, where cases suggestive of maltreatment were solved better than non-suggestive cases (85.7% [IQR 28.6%] versus 62.5% [IQR 25.0%], $p < 0.001$) (1). While the mean score on suggestive and non-suggestive cases is the same, the boxplot (Figure 1B) reveals that people are more accurate in assessing non-suggestive cases, possibly due to outliers pulling down the mean score for suggestive cases. There is a wider spread of responses within suggestive cases, indicating that childcare workers may struggle more with recognizing typical physical injuries.

Within non-suggestive cases, 68.8% and 55.8% would misjudge a hemangioma and a congenital dermal melanocytosis, respectively, as child maltreatment. These false positives can strain the relationship between parents and childcare workers. Conversely, within cases suspected of maltreatment, 58.1% and 51.6% would consider a bruise on the ear and a pinch wound, respectively, as non-alarming. Overall, the context in which a child presents with a skin injury and the story told by the parents play an enormous role in physical maltreatment cases. Approximately one-third of cases were not interpreted correctly. Additional training on recognizing "mimickers" for child maltreatment may improve results, preventing trauma and false accusations of parents.

We examined if participant's age, number of children, years of work experience, and prior contact with suspected maltreatment could correlate with a higher overall score. However, only previous contact with maltreatment showed statistical significance in relation to the overall score. As age and work experience are not predictors of outcome, we can infer that working in childcare does not inherently increase knowledge, but external education may. Previous studies support this notion, indicating that participants who received formal training displayed significantly higher overall knowledge of recognizing and reporting child abuse and neglect, along with a wider range of individual knowledge items (1,22). A train-the-trainer program promoting knowledge of warning signs of child maltreatment in childcare settings could be an effective strategy, enhancing childcare workers' competence in interventions (23). This approach allows many practitioners to receive relevant information in a short period.

### *Limitations*

The study's invitation was sent to large child daycare centers (with more than 20 children), potentially introducing selection bias, limiting the extrapolation of results to smaller centers. Due to the small sample

size, no subpopulations were defined. The use of written cases in the survey may make judgment more challenging for participants compared to real-life scenarios, where the connection between the childcare worker and the child's family can aid assessment. The scenarios have all been scored by experts, whose answers were not fully identical as the cases were deliberately not designed to be 'black and white'. However all experts scored the cases in the same direction (either suspicious or not suspicious).

## Conclusion

This study is exploratory research that can guide future work in this field. In order to improve overall detection, investments in formal training are necessary since work experience and age are not related to a better detection of child abuse and neglect by the staff in daycare.

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

REFERENCES


1. Jamaer M, Van den Eynde J, Aertgeerts B, Toelen J. Knowledge of Child Abuse and Neglect among General Practitioners and Pediatricians in Training: A Survey. Children (Basel). 2023;22;10(9):1429..
2. Jackson AM, Kissoon N, Greene C. Aspects of abuse: recognizing and responding to child maltreatment. Curr Probl Pediatr Adolesc Health Care. 2015;45(3):58–70.
3. Spector L. Recognizing and Responding to Child Abuse in the Medical Setting. Pediatr Ann. 2020;49(8): e332–3.
4. Stoltenborgh M, Bakermans-Kranenburg MJ, Alink LRA, van Ijzendoorn MH. The Prevalence of Child Maltreatment across the Globe: Review of a Series of Meta-Analyses. Child Abuse Review. 2015;24(1):37–50.
5. Zeanah CH, Humphreys KL. Child Abuse and Neglect. J Am Acad Child Adolesc Psychiatry. 2018;57(9):637-644.
6. Kleinschmidt A. Child Maltreatment Red Flags: Two Cases of Bruising in Premobile Infants. J Pediatr Health Care. 2019;33:92-96.
7. Feng JY, Huang TY, Wang CJ. Kindergarten teachers' experience with reporting child abuse in Taiwan. Child Abuse Negl. 2010;34(2):124–8.
8. Ward MG, Ornstein A, Niec A, Murray CL, & Canadian Paediatric Society. The medical assessment of bruising in suspected child maltreatment cases: A clinical perspective. Paediatr Child Health. 2013;18(8):433–42.
9. Petska HW, Sheets LK. Sentinel injuries: subtle findings of physical abuse. Pediatr Clin North Am. 2014;61(5):923–35.
10. Pomeranz ES. Child Abuse and Conditions That Mimic It. Pediatr Clin North Am. 2018;65(6):1135–50.
11. Schilling S, Christian CW. Child Physical Abuse and Neglect. Child Adolesc Psychiatr Clin N Am. 2014;23(2):309-19.
12. Hindley N, Ramchandani PG, Jones DPH. Risk factors for recurrence of maltreatment: a systematic review. Arch Dis Child. 2006;91(9):744–52.
13. Eurostat. Nederlandse ouders gebruiken vaakst kinderopvang in EU [Internet]. 2016 [cited 2023 Nov 26]. Available from: https://www.cbs.nl/nl-nl/nieuws/2016/34/nederlandse-ouders-gebruiken-vaakst-kinderopvang-in-eu#:~:text=Van%20alle%20kinderen%20tot%20drie,opgevangen%20dan%20in%20Oost%2DEuropa.
14. Kinderopvang baby's en peuters | Opgroeien [Internet]. [cited 2023 Apr 24]. Available from: https://www.opgroeien.be/kennis/cijfers-en-onderzoek/kinderopvang-babys-en-peuters#toc-welk-soort-formele-opvang-gebruiken-kinderen-
15. Vertrouwenscentrum kindermishanndeling. Persbericht - Geïntegreerd jaarverslag vertrouwenscentra kindermishandeling . 2022.
16. Secundair Onderwijs L, Verbond van het Katholiek Secundair Onderwijs V. KINDERZORG 3DE GRAAD BSO SPECIALISATIEJAAR [Internet]. Available from: www.vvkso.be
17. Leerplan OPLEIDING [Internet]. Available from: https://leerplannenso.katholiekonderwijs.vlaanderen/lele/toonleerplan3.asp?Ltsr=189&LTcomplex=1&LTnaam=-Kinderzorg
18. Gün İ, Çopur A, Balcı E. Effect of training about child neglect and abuse to teachers and its effect to awareness. BMC Public Health. 2022;22(1):543.
19. Wurtele SK, Schmitt A. Child care workers' knowledge about reporting suspected child sexual abuse. Child Abuse Negl. 1992;16(3):385–90.
20. Vruchtbaarheid | Vlaanderen.be [Internet]. [cited 2023 Nov 9]. Available from: https://www.vlaanderen.be/statistiek-vlaanderen/bevolking/vruchtbaarheid#gemiddeld-153-kinderen-per-vrouw
21. Aljasser M, Al-Khenaizan S. Cutaneous mimickers of child abuse: A primer for pediatricians. Eur J Pediatr. 2008;167(11):1221-30.
22. Mathews B, Yang C, Lehman EB, Mincemoyer C, Verdiglione N, Levi BH. Educating early childhood care and education providers to improve knowledge and attitudes about reporting child maltreatment: A randomized controlled trial. PLoS One. 2017;12(5):e0177777.
23. Dagenais C, Dutil J. Action in Childcare Settings training programme: development of an evidence-based training programme for the prevention of child maltreatment. Glob Health Promot. 2011;18(1):66–8.

# ENTEROL® 250 mg

*Saccharomyces boulardii* CNCM I-745

| | | | | | |
|---|---|---|---|---|---|
| 10 | 10,32 € | 10 | 10,32 € | 10 | 10,32 € |
| 20 | 19,36 € | 20 | 19,36 € | 20 | 19,36 € |
| 50 | 38,96 € | | | | |


INFORMATIONS ESSENTIELLES. DENOMINATION DU MEDICAMENT Enterol 250 mg, poudre pour suspension buvable. Enterol 250 mg, gélules. *Saccharomyces boulardii* CNCM I-745 COMPOSITION QUALITATIVE ET QUANTITATIVE Enterol 250 mg, poudre pour suspension buvable : Chaque sachet-dose de poudre pour suspension buvable contient 250 mg de *Saccharomyces boulardii* CNCM I-745 sous forme lyophilisée (soit au minimum 6 x $10^9$ cellules reviviscentes au moment de la fabrication et 1 x $10^9$ cellules lyophilisées reviviscentes à la date de péremption). Enterol 250 mg, gélules : Chaque gélule contient 250 mg de *Saccharomyces boulardii* CNCM I-745 sous forme lyophilisée (soit au minimum 6 x $10^9$ cellules reviviscentes au moment de la fabrication et 1 x $10^9$ cellules lyophilisées reviviscentes à la date de péremption). Excipient(s) à effet notoire (voir rubrique 4.4 du RCP) : Enterol 250 mg, poudre pour suspension buvable : fructose, lactose monohydraté, sorbitol. Enterol 250 mg, gélules : lactose monohydraté. Pour la liste complète des excipients, voir rubrique 6.1 du RCP. FORME PHARMACEUTIQUE Enterol 250 mg, poudre pour suspension buvable : Poudre pour suspension buvable. Enterol 250 mg, gélules : Gélule. DONNEES CLINIQUES Indications thérapeutiques • Prévention de la diarrhée associée à l'antibiothérapie à large spectre chez des sujets prédisposés à développer une diarrhée à *Clostridium difficile* ou rechute de diarrhée à *Clostridium difficile*. • Traitement des diarrhées aiguës chez les enfants jusqu'à 12 ans, en complément de la réhydratation orale. Posologie et mode d'administration Posologie : Adulte : 2 à 4 gélules ou 2 à 4 sachets-doses par jour, en 2 prises. Population pédiatrique. Enfant : 2 gélules ou 2 sachets-doses par jour, en 2 prises. Mode d'administration : Gélules : avaler avec un peu d'eau. Sachets-doses : diluer la poudre dans un verre d'eau. Précautions à prendre avant la manipulation ou l'administration du médicament En raison d'un risque de contamination aéroportée, les sachets ou gélules ne peuvent pas être ouverts dans les chambres des patients. Les professionnels de la santé doivent porter des gants durant la manipulation de probiotiques en vue de leur administration, puis les jeter immédiatement après usage et se laver les mains avec soin (voir rubrique 4.4 du RCP). Durée du traitement : Prévention des récurrences ou rechute de diarrhée à *Clostridium difficile* : 4 semaines. Traitement de la diarrhée en complément à la réhydratation orale chez l'enfant : 1 semaine. Contre-indications • Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP. • Patients porteurs d'un cathéter veineux central, patients dans un état critique ou immunodéficients en raison du risque de fongémie (voir rubrique 4.4. du RCP). • Allergie aux levures, spécialement *Saccharomyces boulardii* CNCM I-745. Effets indésirables Les effets indésirables sont classés ci-dessous par système-organe et par fréquence comme définies ci-après : très fréquents (≥ 1/10), fréquents (≥ 1/100, < 1/10), peu fréquents (≥ 1/1.000, < 1/100), rares (≥ 1/10.000, < 1/1.000), très rares (< 1/10.000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Classes de systèmes d'organes Fréquence Infections et infestations Très rares : Fongémie chez des patients porteurs d'un cathéter veineux central, et chez des patients dans un état critique ou immunodéficients (voir rubrique 4.4 du RCP), mycose à *Saccharomyces boulardii* CNCM I-745. Fréquence indéterminée : Sepsis chez les patients de réanimation ou immunodéprimés (voir rubrique 4.4 du RCP) Affections du système immunitaire Très rare : choc anaphylactique. Affections vasculaires Très rare : choc anaphylactique. Affections respiratoires, thoraciques et médiastinales Très rare : dyspnée. Affections gastro-intestinales. Très rares : constipation, épigastralgies, météorisme abdominal (épigastralgies et météorisme abdominal ont été observés lors d'études cliniques). Affections de la peau et du tissu sous-cutané. Très rares : prurit, exanthème, Œdème de Quincke. Troubles généraux et anomalies au site d'administration. Très rares : soif. Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration (Belgique : www.notifieruneffetindesirable.be, adr@afmps.be; Luxembourg : www.guichet.lu/pharmacovigilance). TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE BIOCODEX Benelux NV/SA - Square Marie Curie 20 - 1070 Bruxelles - Belgique - Tél : 0032(0)23704790. NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE Enterol 250 mg, poudre pour suspension buvable : BE269026. Enterol 250 mg, gélules en flacon en verre : BE269035. Enterol 250 mg, gélules en plaquette: BE397896. MODE DE DELIVRANCE Délivrance libre DATE DE MISE A JOUR DU TEXTE Mise à jour : 01/2023. Approbation : 03/2023.

2023_ENT_HCP_007

ENTEROL® 250 mg

*Saccharomyces boulardii* CNCM I-745

| | | | | | |
|---|---|---|---|---|---|
| 10 | 10,32 € | 10 | 10,32 € | 10 | 10,32 € |
| 20 | 19,36 € | 20 | 19,36 € | 20 | 19,36 € |
| 50 | 38,96 € | | | | |


ESSENTIELE GEGEVENS. NAAM VAN HET GENEESMIDDEL Enterol 250 mg poeder voor orale suspensie. Enterol 250 mg harde capsules. *Saccharomyces boulardii* CNCM I-745. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Enterol 250 mg poeder voor orale suspensie: Elk zakje poeder voor orale suspensie bevat 250 mg gelyofiliseerde *Saccharomyces boulardii* CNCM I-745 (hetzij minstens 6 x $10^9$ levensvatbare cellen op het ogenblik van de fabricage en 1 x $10^9$ gelyofiliseerde levensvatbare cellen op de vervaldatum). Enterol 250 mg harde capsules: Elke harde capsule bevat 250 mg gelyofiliseerde *Saccharomyces boulardii* CNCM I-745 (hetzij minstens 6 x $10^9$ levensvatbare cellen op het ogenblik van de fabricage en 1 x $10^9$ gelyofiliseerde levensvatbare cellen op de vervaldatum). Hulpstof(fen) met bekend effect (zie rubriek 4.4 van de SKP): Enterol 250 mg poeder voor orale suspensie: fructose, lactosemonohydraat, sorbitol. Enterol 250 mg harde capsules: lactosemonohydraat. Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de SKP. FARMACEUTISCHE VORM Enterol 250 mg poeder voor orale suspensie: Poeder voor orale suspensie. Enterol 250 mg harde capsules: Harde capsule. KLINISCHE GEGEVENS Therapeutische indicaties • Preventie van diarree bij behandeling met breedspectrumantibiotica van patiënten voorbeschikt tot het ontwikkelen van diarree door *Clostridium difficile* of hervallen in een diarree veroorzaakt door *Clostridium difficile*. • Adjuverende behandeling naast orale rehydratie van acute diarree bij kinderen tot 12 jaar. Dosering en wijze van toediening Dosering: Volwassenen: 2 tot 4 harde capsules of 2 tot 4 zakjes per dag, in 2 innames. Pediatrische patiënten Kinderen: 2 harde capsules of 2 zakjes per dag, in 2 innames. Wijze van toediening: • Harde capsules: de harde capsules met wat water inslikken. • Zakjes: het poeder mengen in een glas water. Te nemen voorzorgen voorafgaand aan gebruik of toediening van het geneesmiddel Vanwege een risico op besmetting via de lucht, mogen zakjes of capsules nooit worden opengemaakt in patiëntenkamers. Beroepsbeoefenaren in de gezondheidszorg moeten tijdens het hanteren en het toedienen van probiotica handschoenen dragen, waarna de handschoenen onmiddellijk moeten worden weggegooid en de handen moeten worden gewassen (zie rubriek 4.4 van de SKP). Duur van de behandeling Preventie van een nieuwe episode of recidief van diarree door *Clostridium difficile*: 4 weken. Behandeling van diarree als aanvulling op orale rehydratie bij het kind: 1 week. Contra-indicaties • Overgevoeligheid voor de werkzame stof of voor één van de in rubriek 6.1 van de SKP vermelde hulpstoffen. • Patiënten met een centrale veneuze katheter, patiënten in kritieke toestand of immuungecompromitteerde patiënten, vanwege een risico op fungemie (zie rubriek 4.4 van de SKP). • Allergie voor gisten, vooral *Saccharomyces boulardii* CNCM I-745. Bijwerkingen De bijwerkingen worden hieronder geklasseerd per orgaansysteem en volgens de frequentie. Die laatste wordt als volgt gedefinieerd: zeer vaak (≥ 1/10), vaak (≥ 1/100, < 1/10), soms (≥1/1.000, < 1/100), zelden (≥ 1/10.000, < 1/1.000), zeer zelden (< 1/10.000), niet bekend (kan met de beschikbare gegevens niet worden bepaald). Systeemorgaanklasse Frequentie Infecties en parasitaire aandoeningen Zeer zelden: fungemie in patiënten met een centraal veneuze katheter en in patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP), mycose door *Saccharomyces boulardii* CNCM I-745. Frequentie niet bekend: sepsis bij patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP) Immuunsysteemaandoeningen Zeer zelden: anafylactische shock Bloedvataandoeningen Zeer zelden: anafylactische shock Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen Zeer zelden: dyspneu Maagdarmstelselaandoeningen Zeer zelden: verstopping, epigastralgie, abdominaal meteorisme (epigastralgie en abdominaal meteorisme werden waargenomen in klinische studies) Huid- en onderhuidaandoeningen Zeer zelden: jeuk, exantheem, Quincke-oedeem Algemene aandoeningen en toedieningsplaatsstoornissen Zeer zelden: dorst Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijk bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem (Website: www.eenbijwerkingmelden.be, e-mail: adr@fagg.be). HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN BIOCODEX Benelux NV/SA - Marie Curiesquare 20 - 1070 Brussel - België Tel: 0032(0)23704790. NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN Enterol 250 mg poeder voor orale suspensie: BE 269026. Enterol 250 mg harde capsules in glazen flesje: BE 269035. Enterol 250 mg harde capsules in blisterverpakking: BE 397896. AFLEVERINGSWIJZE Vrije aflevering DATUM VAN HERZIENING VAN DE TEKST Herziening: 01/2023. Goedkeuring: 03/2023.

2023_ENT_HCP_007

# Recognition of Abusive Head Trauma in Young Children by Emergency Physicians and Paediatricians: A Survey

Annelien Marcelis [a,*], Marjolein Mattheij [b,c,*], Sebastian Schnaubelt [b,d], Wouter Karst [a], Stijn Verhulst [a,e], Berten Ceulemans [a,e], Koenraad G. Monsieurs [b,c]

[*] These authors contributed equally and share first authorship
[a] University of Antwerp, Antwerp University Hospital, Department of Paediatrics, Edegem, Belgium
Dutch National Forensic Medical Expertise Center (LOEF), Leerbroek, The Netherlands"
[b] University of Antwerp, Antwerp University Hospital, Department of Emergency Medicine, Edegem, Belgium
[c] University of Antwerp, Antwerp Surgical Training, Anatomy and Research Centre (ASTARC), Wilrijk, Belgium
[d] Medical University of Vienna, Department of Emergency Medicine, Austria
[e] University of Antwerp, Faculty of Medicine and Health Sciences, Laboratory of Experimental Medicine and Paediatrics, Wilrijk, Belgium

annelienmarcelis@gmail.com ; marjolein.mattheij@uza.be

## Keywords

Abusive head trauma ; inflicted injury.

## Abstract

***Objective***

The aim of our study was to determine the physicians' accuracy in evaluating fictitious cases of young children with high, moderate and low probability of abusive head trauma (AHT), their behaviour in reporting cases to child protection services or legal institutions, and the estimation of their own competence in interpreting injuries in children.

***Methods***

Six hypothetical cases (high, moderate and low probability of AHT, with and without risk factors for abuse) were presented to physicians in a survey. The assigned probability score for AHT was compared with the calculated probability of AHT according to the PediBIRN-7 prediction tool.

***Results***

The majority of physicians underestimated the probability of AHT in the cases with high probability of AHT (especially in the absence of risk factors for abuse), and overestimated the probability of AHT in cases with low probability of AHT (especially in the presence of multiple risk factors for abuse). In cases with high probability of AHT without multiple risk factors for abuse, the majority of physicians would not have reported the case.

***Conclusions***

Our survey showed that the presence or absence of risk factors for abuse seemed to play a more important role in physician's assessment of the aetiology of head injury in young children than the presence of injuries with a high specificity for AHT or accidental head injury. Unawareness of physicians´ lack of competence in evaluating injuries is a potential threat.

## Introduction

Abusive head trauma (AHT) is an injury to the skull or intracranial contents of a child, caused by inflicted blunt impact, shaking, or both (1). AHT is the leading cause of fatal head injuries in children younger than two years (2-4). Survivors show considerable associated morbidity (1). A missed diagnosis leads to an increased risk of further injury or death. A 2016 study found that 25% of the infants with AHT had at least one earlier opportunity to identify abuse (5). However, recognizing AHT is a major challenge, predominantly because of the heterogenous and non-specific clinical findings (vomiting, irritability, feeding difficulties, altered mental status, seizures, increasing head circumference and apnoea) and of further investigations (subdural hematoma, cerebral oedema, skull fracture, spinal changes, complex retinal haemorrhages and rib or other fractures) (1, 2, 6, 7). Although there are known risk factors for abuse such as a low socioeconomical status, a household with unmarried parents or unrelated adults, parental alcohol or substance abuse, or excessive crying of the child, their absence does not rule out abuse: literature shows that AHT was more likely to be unrecognized in white children from intact families (8-12).

Laskey et al found that in 50% of the cases, pathologists and paediatricians did not agree on their categorization (unintentional, undetermined, or inflicted) of hypothetical cases of traumatic brain injury (13). The aim of our study was to determine (a) the accuracy of physicians evaluating fictitious cases of young children with high, moderate and low probability of AHT, (b) to what extent physicians were guided by certain physical injuries and the presence or absence of risk factors for abuse, (c) the behaviour in reporting the cases to child protection services or legal institutions, and (d) if physicians had an accurate idea of their own competence in the interpretation of injuries. Our hypothesis was that the presence or absence of risk factors for abuse would significantly contribute to whether a case would be deemed suspicious and reported to child protection services or legal institutions.

## Methods

The PediBIRN-7 tool is a clinical prediction rule that predicts the likelihood of AHT, based on the presence or absence of seven different clinical variables, being (a) respiratory compromise, (b) bruising involving ear, neck or torso, (c) bilateral or intrahemispheric subdural haemorrhage or fluid collection, (d) a complex skull fracture, (e) fractures on skeletal survey that are suspicious for abuse, (f) moderate to extensive retinal haemorrhages or retinoschisis and (g) brain hypoxia, ischaemia or swelling (14). The tool was designed using prospectively captured data of 500 children aged zero to three years with acute head injury who were admitted to a paediatric intensive care unit. Children with motor vehicle collisions were excluded. Applying a mean probability threshold

of > 0.5 to classify patients as abused, the tool has a sensitivity of 0.73 (95% CI: 0.66-0.79) and a specificity of 0.87 (95% CI: 0.82-0.90). To prevent circular reasoning, the study used definitions of AHT and accidental head trauma without inclusion of the seven variables. Within the group of children with three present variables of the PediBIRN-7 tool, there are three subgroups with a statistical significant different probability of AHT: (a) children with bruising of ear, neck or torso, bilateral or interhemispheric subdural haemorrhage and a suspicious fracture on skeletal survey, with a calculated probability of AHT of 0.91 (CI 0.79-0.97, in our study defined as "high probability of AHT"), (b) children with respiratory compromise, bilateral or interhemispheric subdural haemorrhage and moderate to extensive retinal haemorrhages, with a calculated probability of AHT of 0.55 (CI 0.38-0.70, in our study defined as "moderate probability of AHT") and (c) children with a complex skull fracture, moderate to extensive retinal haemorrhages and brain hypoxia, ischaemia, or swelling with a probability of AHT of 0,17 (CI 0.07-0.37, in our study defined as "low probability of AHT") (14). We incorporated each combination of variables in two hypothetical cases of a young child with traumatic brain injury, one with risk factors for abuse and one without risk factors for abuse. The PediBIRN-7 tool variables and risk factors for abuse that were integrated in the cases can be found in Table 1. Except for the variables that are mentioned above, the content of the hypothetical cases was written by the authors. This strategy led to the development of six cases (high, moderate and low probability of AHT, all with and without risk factors for abuse). We developed an online questionnaire, with introductory questions concerning the education and the employment of the respondent, and a self-evaluation of their competence to interpret injuries in children. After the presentation of each case, the physicians were asked to rate the probability of AHT on a 6-point scale and their decision to report the case.

As emergency physicians, paediatricians and forensic physicians have the highest probability of encountering children with traumatic brain injury, and thus recognition of AHT by these physicians is of great importance, they were the focus of our study. Between February and July 2022 the departments of their specialities at the Antwerp University Hospital and their Flemish professional associations were contacted with a link to the survey, which was forwarded to their members, with a subsequent reminder email. A link was also shared on their social media groups. Participation in the survey was anonymous and voluntary. The Ethics Committee of the Antwerp University Hospital granted a waiver for this study (EC reference number 2023-5426).

An important goal of our study was to evaluate whether the physician´s assigned probability score of abuse was congruent with the calculated probability by the PediBIRN-7 tool (14). In our survey only round numbers from 0 to 5 could be chosen as response options for the probability score for inflicted skull-brain injury ("how likely do you think the option of inflicted skull-brain injury is in this case?" 0 almost non-existent - 1 very unlikely - 2 unlikely - 3 likely - 4 very likely - 5 almost certain). We considered a score of 4 or 5 in the cases with high probability, 2 or 3 in the cases with moderate probability and 0 or 1 in the cases with low probability of AHT as a "correct" assessment, hence a probability score that was congruent with the calculated probability by the PediBIRN-7 tool. Possible differences in correct assessment between the different physician subgroups were evaluated using the Mann-Whitney U-test. The influence of the presence of risk factors for abuse on the assigned probability score for abuse was evaluated using the Wilcoxon Signed Rank test. We assumed that the categories of the AHT probability score were equidistant and described the results as mean and 95% CI of the mean. We also investigated whether physicians who considered themselves more competent in diagnosing inflicted injuries scored better in terms of the total number of correctly assessed cases via the Spearman correlation coefficient.

**Table 1**: The PediBIRN-7 tool variables and risk factors for abuse integrated in the cases of our survey, the number and percentage of the total group of respondents that correctly estimated the probability of abusive head trauma (AHT) based on PediBIRN-7 tool, the elements that the respondents found suspicious for AHT, and information about whether or not the respondents would have reported the case.

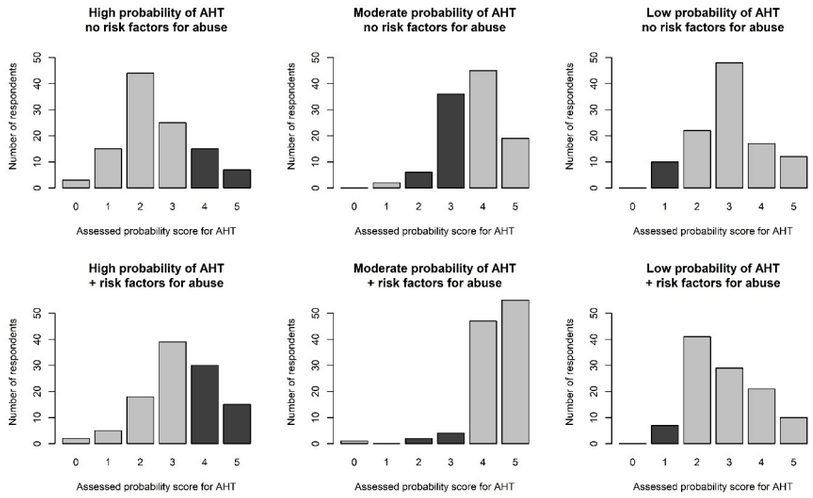
| | PediBIRN-7 variables integrated in the case | Risk factors for abuse integrated in the case | Correct estimation of probability of AHT of total group (n=109) (number, (%)) | Elements suspicious for abuse according to the respondents | Reporting to child protective services or legal institutions |
|---|---|---|---|---|---|
| **Case with high probability of AHT, with risk factors** | Haematoma on thorax<br>Bilateral subdural haemorrhages<br>Rib fracture | Large and reconstituted family<br>Excessive crying | 45 (41%) | Social situation 41%<br>Crying baby 20%<br>Rib fracture 40%<br>Subdural haemorrhage 25% | No 6%<br>Yes 94% |
| **Case with high probability of AHT, without risk factors** | Haematoma on scapula region<br>Bilateral subdural haemorrhages<br>Scapular fracture | None | 22 (20%) | Subdural haemorrhage 27%<br>Scapular fracture 21%<br>Later arrival mother 23%<br>Mother no injuries 13% | No 62%<br>Yes 38% |
| **Case with moderate probability of AHT, with risk factors** | Intrahemispheric subdural haemorrhage<br>Multiple retinal haemorrhages<br>Respiratory compromise | Alcohol abuse parent<br>Aggressive behaviour parent | 5 (5%) | Alcohol and aggression 58%<br>Retinal haemorrhages 76%<br>Subdural haemorrhage 32%<br>Severity of injuries not concomitant with story 42% | No 5%<br>Yes 95% |
| **Case with moderate probability of AHT, without risk factors** | Bilateral subdural haemorrhages<br>Multiple retinal haemorrhages<br>Respiratory compromise | None | 42 (39%) | Retinal haemorrhages 61%<br>Subdural haematoma 31%<br>Late communication fall in nursery 35%<br>Story not congruent with age 11% | No 10%<br>Yes 90% |
| **Case with low probability of AHT, with risk factors** | Frontal skull fracture<br>Brain oedema<br>Multiple retinal haemorrhages | Financial problems<br>Large family | 7 (6%) | Retinal haemorrhage 58%<br>Social situation 18%<br>Financial problems 14% | No 29%<br>Yes 71% |
| **Case with low probability of AHT, without risk factors** | Bilateral parietal skull fracture<br>Brain oedema<br>Multiple retinal haemorrhages | History of prematurity* | 10 (9%) | Skull fracture 17%<br>Retinal haemorrhages 59%<br>Less supervision 19% | No 31%<br>Yes 69% |

*This case was supposed to be a case without risk factors for abuse. The history of prematurity was accidently incorporated in the case, but is indeed a risk factor for abuse. Eight percent of the respondents mentioned the prematurity as a "suspicious element" for AHT in that case

## Results

The survey was sent by email to 193 physicians, and shared through social media. The survey was initiated by 159 physicians. The results of forty-nine respondents who did not fully complete the survey were excluded. One questionnaire had to be excluded due to inconclusive demographical data of the participant, thus eventually 109 questionnaires were included. Participants were paediatricians (n=67; 61%), paediatric residents (n=20; 18%), emergency physicians (n=4; 4%), emergency medicine residents (n=17; 16%), and one forensic physician. Figure 1 shows the assigned probability score for AHT in the different cases. Most physicians underestimated the probability of AHT in the cases with high probability of AHT, and overestimated the probability of AHT in the cases with moderate and low probability of AHT.

**Figure 1**: The assigned probability score for abusive head trauma (AHT) per case. The black columns represent the probability scores that were congruent with the calculated probability according to the PediBIRN-7 study [15] (see section methods for more information).




In the cases with a high probability of inflicted injury, the assigned probability score for AHT in the case with risk factors was significantly higher than in the case without risk factors (with risk factors: mean probability score of 3.24 [95% CI 3.02 - 3.46] vs. without risk factors: mean probability score of 2.48 [95% CI 2.26 - 2.70], p<0.001). For the two cases with the "moderate" probability of AHT, we saw the same effect of the presence of risk factors: the assigned probability score for AHT in the case with risk factors was significantly higher than in the case without risk factors (with risk factors: mean probability score 4.40 [95% CI 4.25-4.55] vs. without risk factors: mean probability score 3.7 [95% CI 3.53-3.86], p<0.001). There was no significant difference in the assigned AHT probability scores between the two cases with "low" probability of abuse (with risk factors: mean probability score 2.88 [2.67-3.09] vs. without risk factors: mean probability score 3.02 [95% CI 2.81-3.22], p 0.179).

The respondents assessed the abuse probability in the high probability case for AHT without risk factors for abuse lower than the abuse probability in all the moderate and low probability cases (p<0.001 for the cases with moderate probability of AHT with and without risk factors; p=0.001 for the case with low probability of AHT without risk factors; p=0.010 for the case with low probability of AHT with risk factors).

Table 2 shows, for each case, the number and percentage of physicians that correctly estimated the probability of AHT. Only 20% correctly

**Table 2**: Number and percentage of four subgroups of respondents (paediatricians, residents paediatrics, emergency physicians and residents emergency medicine) that correctly estimated the probability of AHT based on PediBIRN-7.

| | Correct estimation of probability of AHT - subgroup paediatricians (n=67) (number, (%))* | Correct estimation of probability of AHT - subgroup paediatric residents (n=20) (number, (%))* | Correct estimation of probability of AHT - subgroup emergency medicine residents (n=17) (number, (%))* | Correct estimation of probability of AHT - subgroup emergency physicians (n=4) (number, (%))* |
|---|---|---|---|---|
| **Case with high probability of AHT, with risk factors for abuse** | 30 (45%) | 5 (25%) | 7 (41%) | 2 (50%) |
| **Case with high probability of AHT, without risk factors for abuse** | 14 (21%) | 4 (20%) | 4 (24%) | 0 (0%) |
| **Case with moderate probability of AHT, with risk factors for abuse** | 1 (1%) | 0 (0%) | 4 (24%) | 0 (0%) |
| **Case with moderate probability of AHT, without risk factors for abuse** | 22 (33%) | 15 (75%) | 5 (29%) | 0 (0%) |
| **Case with low probability of AHT, with risk factors for abuse** | 5 (7%) | 2 (10%) | 0 (0%) | 0 (0%) |
| **Case with low probability of AHT, without risk factors for abuse** | 6 (9%) | 0 (0%) | 4 (24%) | 0 (0%) |

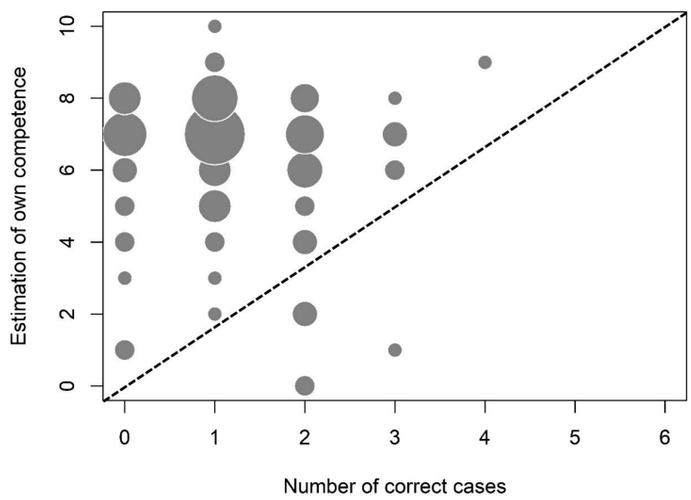
* There was no significant difference between the residents on one hand (paediatrics and emergency medicine, n=37) and the specialists on the other hand (paediatrics and emergency medicine, n=71) (mean number of correctly assessed cases 1.34 (95% CI 1.07-1.62) versus 1.12 (95% CI 0.88-1.35), p-value 0.619), or the paediatric residents and paediatricians on one hand (n=87) and the emergency medicine residents and emergency physicians on the other hand (n=21) (mean number of correctly assessed cases 1.18 (95% CI 0.98-1.39) versus 1.24 (95% CI 0.83-1.64), p-value 0.909).

**Table 3**: Comparison of the assigned probability score for AHT between physicians who would not report the case and physicians who would report the case.

| | Mean probability score for AHT in group physicians that do not report the case (95% CI) (N = number of respondents*) | Mean probability score for AHT in group physicians that report the case (95% CI) (N = number of respondents*) | P-value |
|---|---|---|---|
| **Case with high probability for AHT, with risk factors** | 1.79 (1.22 – 2.35) (N = 14*) | 3.47 (3.27 – 3.68). (N = 93) | p < 0.001 |
| **Case with high probability for AHT, without risk factors** | 1.92 (1.70 – 2.15) (N = 66) | 3.40 (3.11 – 3.70) (N = 42) | p < 0.001 |
| **Case with moderate probability for AHT, with risk factors** | 4.17 (2.94 – 5.39) (N = 6) | 4.42 (4.27 – 4.57) (N = 102) | p = 0.75 |
| **Case with moderate probability for AHT, without risk factors** | 3.00 (2.33 – 3.67) (N = 11) | 3.76 (3.58 – 3.93) (N = 95) | p = 0.010 |
| **Case with low probability for AHT, with risk factors** | 2.00 (1.77 – 2.23) (N = 31) | 3.24 (3.00 – 3.48) (N = 75) | p < 0.001 |
| **Case with low probability for AHT, without risk factors** | 2.18 (1.94 – 2.42) (N = 33) | 3.38 (3.14 – 3.62) (N = 74) | p < 0.001 |

* There was no significant difference between the residents on one hand (paediatrics and emergency medicine, n=37) and the specialists on the other hand (paediatrics and emergency medicine, n=71) (mean number of correctly assessed cases 1.34 (95% CI 1.07-1.62) versus 1.12 (95% CI 0.88-1.35), p-value 0.619), or the paediatric residents and paediatricians on one hand (n=87) and the emergency medicine residents and emergency physicians on the other hand (n=21) (mean number of correctly assessed cases 1.18 (95% CI 0.98-1.39) versus 1.24 (95% CI 0.83-1.64), p-value 0.909).

**Figure 2**: Bubble plot of the correlation between the number of correctly assessed cases of children with acute head injury and the estimation of own competence in child abuse (Spearman correlation 0.12, p = 0.55). The magnitude of the bullets represents the number of respondents. The dotted line in the figure shows the trend of the results if there were to be a correlation.




classified the case with the high probability of AHT without risk factors for abuse, which means that 80% of the respondents underestimated the probability of AHT in this case. When the total number of correctly assessed cases was compared between the four larger subgroups of respondents, we found no significant differences, see Table 2. Belgian law states that reporting cases suspicious of child abuse is not obligated, but that in case of severe and threatening danger professional secrecy can be overruled. In all cases except the case with moderate probability of AHT with risk factors, there was an association between the probability score for AHT and the reporting of the case to child protective services or legal institutions (see Table 3). In other words: when the physician deemed AHT more probable, the threshold to report the case became lower.

In our survey, the respondents were asked to rate their own competence regarding child abuse. Figure 2 shows that there was no correlation between the respondent's number of correctly assessed cases and the estimation of their own competence.

## Discussion

The probability of AHT was underestimated by physicians in the cases with high probability of AHT, and overestimated in cases with moderate and low probability of AHT, when this probability was compared to the calculated probabilities of AHT based on the PediBIRN-7 tool (14). This means that the physicians in our survey tended to give moderate probability scores rather than extreme values. A reason behind these findings could be a lack of knowledge of intra- and extracranial injuries in children with AHT and accidental head trauma. However, it also possibly represents the difficulty for clinicians to handle the uncertainties and nuances of assessing histories, risk factors and concomitant injuries, and the potential risks of a conclusion at either end of the spectrum of accidental or abusive head injury. The four cases with moderate and low AHT probabilities all showed retinal haemorrhages (RH), while the two cases with high probability of AHT did not. It is possible that physicians overestimate the negative and positive predictive value of RH and falsely conclude that "without RH AHT can be ruled out", and "with RH AHT is present". This hypothesis is concomitant with the study by Laskey et al., which showed that the clinicians´ opinion of the aetiology of an injury was affected by the single additional finding of retinal haemorrhages, changing the majority response from undetermined to inflicted traumatic brain injury (13). In our cases with RH, 58-76% of physicians reported the presence of RH as a suspicious factor for AHT. A meta-analysis in children less than three years old with intracranial injury showed that retinal haemorrhages are indeed suspicious for AHT, but that they can

also be the result of accidental trauma (6). The interpretation of the presence or absence of retinal haemorrhages should depend on other injuries or circumstances in the patient, as well as on the different degrees and descriptors of the retinal haemorrhages (6).

The presence of risk factors for abuse effectively increases the probability of abuse; this is of course the consequence of a risk factor. In our survey, the presence of risk factors for abuse increased the physician´s estimation of AHT probability in the cases with a high and moderate probability of AHT, but not in the cases with "low" probability of AHT. This was possibly due to the fact that a risk factor for abuse (prematurity) was accidently incorporated in the low probability case that was supposed to be without risk factors. Although the cases with risk factors had multiple risk factors, it is possible that the presence of the prematurity influenced the physicians: eight percent of the respondents indeed mentioned the prematurity as a "suspicious element" for AHT in that case.

In our survey, AHT was overestimated in cases with risk factors, and underestimated in cases without risk factors for abuse. The case with a high AHT probability without risk factors for abuse was found less suspicious for AHT than the case with moderate (and even low) probability of AHT with risk factors. In other words: the combination of high-risk injuries was not interpreted as high risk in the absence of risk factors. A remarkable finding in our study was that in the cases with a high probability of AHT only 38% of physicians reported the case without risk factors to official authorities, while 94% of physicians reported the case when there were multiple risk factors. This could mean that not only in the assessment of the probability of AHT, but also in the decision of reporting a case, the presence or absence of risk factors for abuse plays a more important role for the physician than the presence of injuries with a high specificity for AHT or accidental head trauma. A recent study indeed showed that biases based on socioeconomic status and social factors may impact the decision to refer to child protective services (15).

Our study has several limitations. The sample size was small. A recent study that was probably performed in the same time frame as our study, that presented four cases of head injury to physicians with interest in the subspecialty of child abuse showed both within and between subspecialty diagnostic variability (16). The original aim of our study to compare the diagnostic variability of paediatricians, emergency physicians, forensic physicians and their residents was not fully possible due to small numbers in certain subgroups. Our survey did not provide information about the training and experience of the respondents, which makes it impossible to examine the possible influence of duration of practice and experience of the physician on the recognition of abuse. Also, the respondents were self-selected, which could be a risk for bias. Furthermore, the artificial surrounding of a survey with fictitious cases and limited information makes its applicability to real life limited: even a slightly different design could yield different judgements. Although the cases were carefully developed and discussed with a co-author of the original PediBIRN-7 tool, they were not internally validated by a broader expert panel, which could have added value (14).

The unvalidated 6-point probability score, and the artificial categorization into a low, intermediate and high risk score for AHT that we used, has its drawbacks, including potential response bias, oversimplification of nuanced opinions, and difficulty in interpreting differences between adjacent score points. However, in a survey as ours, it seems impossible to work without an intuitive score.

Prediction rules such as the PediBIRN-7 tool are developed to provide an estimation of the probability of AHT, based on a certain combination of clinical findings. They should not be considered a sufficient foundation upon which to base expert medical opinion. The PediBIRN-7 tool does not account for the presenting history or familial psychosocial risk factors. History is very important in assessing abuse likelihood, and in our cases the histories varied. It is unknown if the types of trauma that we presented in our survey were representative for the history given in the 500 true cases of the PediBIRN-7 study. Also, different histories have different levels of credibility, and the judged credibility of the history will influence the judgement of the case. It is also unknown whether the social risk factors that we integrated in the cases were present in the PeriBIRN-7 cohort. However, the risk factors that we chose to integrate in our cases are widely present in the community (large and reconstituted family, excessive crying, financial problems, substance abuse, aggressive behaviour), which makes us assume that they were also present in the PediBIRN-7 cohort. Statistically, it was unfortunately impossible to examine which factor weighed heavier in the assessment of the physicians; the history and therefore a certain credibility of the case, the presence or absence of social risk factors, or the potential knowledge of the literature. While it would have been possible to create cases with partly overlapping histories, risk factors for abuse and injures, this would have required at least a doubling of the sample size, which would have presented a challenge.

Overall, our study shows that physicians consider both trauma history and social history while assessing AHT probability, and that the combination of these findings cause them to have substantially different assessments of abuse likelihood than the signs and symptoms considered alone. Paediatrics is a holistic specialty, and considering the social context of the child is crucial. However, we believe it is contributory to realize that the social context of a child with injuries can potentially guide us towards an incorrect interpretation of the injuries. It is clear that both under- and overestimation of child abuse come with risks. Under-estimation causes the risk of continued abuse and harm and delayed intervention, while overestimation leads to loss of the trust relationship between physician and parent, unwarranted investigations, and unnecessary psychological and emotional impact on the children and their families. The question is how to minimize the risk of over- and underestimating child abuse, and how to minimize the bias in the suspicion and reporting of child abuse. Additional training for physicians who could encounter inflicted injuries in children seems recommended. In the United States, there is a specific subspecialisation for paediatricians called Child Abuse Paediatrics. In the Netherlands the subspecialty of social paediatrics exists, where paediatricians focus on the bio-psycho-social determinants as either causes or consequences of health issues. Such trainings or subspecialties do not currently exist in Belgium, for neither paediatricians or emergency physicians.

The existence of a multidisciplinary child abuse team or child abuse paediatrician can also possibly help to minimalize the risk of over- and underestimation of child abuse: a previous study showed that multidisciplinary child abuse teams can reduce unwarranted referral to child protective services or police, or temporary out-of-home placements (17). However, it is not feasible to establish such multidisciplinary teams in every hospital in Belgium. Similar to the Sexual Assault Centres in our country, we would like to advocate for the establishment of a national reference centre for the interpretation of injuries in children in our country, where cases can be presented to a multidisciplinary team with experience regarding child abuse. In the Netherlands the Dutch expertise centre for child abuse prove to be of significant added value in the accurate assessment of inflicted injuries in children (18).

## Conclusion

In cases of young children with brain injury, most paediatricians and emergency physicians underestimated the probability of AHT in cases with a high probability of AHT, especially in the absence of risk factors for abuse, and overestimated the probability of AHT in cases with a moderate or low probability of AHT, especially in the presence of risk factors for abuse. Our survey showed that the presence or absence of risk factors seemed to play a more important role in the assessment of the aetiology of head injury, and possibly also in the referral of possible child abuse cases, than the presence of injuries that have a high specificity for AHT or accidental head injury. We recommend routine child abuse evaluation of all young children with acute brain injury, not only cases that are found suspicious. We believe the results of our study contribute to the need to develop a national reference centre for the interpretation of injuries in children.

## Acknowledgements

We thank K. Wouters, statistician of the University Hospital of Antwerp, for statistical support and for help in designing the figures.

## Funding and competing interests

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript. The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. There are no relevant financial or non-financial interests to disclose.

REFERENCES

1. Greeley CS. Abusive head trauma: a review of the evidence base. AJR Am J Roentgenol. 2015;204(5):967-73.
2. Choudhary AK, Servaes S, Slovis TL, Palusci VJ, Hedlund GL, Narang SK, et al. Consensus statement on abusive head trauma in infants and young children. Pediatr Radiol. 2018;48(8):1048-65.
3. Overpeck MD, Brenner RA, Trumble AC, Trifiletti LB, Berendes HW. Risk factors for infant homicide in the United States. N Engl J Med. 1998;339(17):1211-6.
4. Joyce T, Gossman W, Huecker MR. Pediatric Abusive Head Trauma. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.
5. Letson MM, Cooper JN, Deans KJ, Scribano PV, Makoroff KL, Feldman KW, et al. Prior opportunities to identify abuse in children with abusive head trauma. Child Abuse Negl. 2016;60:36-45.
6. Maguire S, Pickerd N, Farewell D, Mann M, Tempest V, Kemp AM. Which clinical features distinguish inflicted from non-inflicted brain injury? A systematic review. Arch Dis Child. 2009;94(11):860-7.
7. Tiyyagura G, Gawel M, Koziel JR, Asnes A, Bechtel K. Barriers and Facilitators to Detecting Child Abuse and Neglect in General Emergency Departments. Ann Emerg Med. 2015;66(5):447-54.
8. Rebbe R, Mienko JA, Martinson ML. Incidence and Risk Factors for Abusive Head Trauma: A Population-Based Study. Child Abuse Rev. 2020;29(3):195-207.
9. Rosenfeld EH, Johnson B, Wesson DE, Shah SR, Vogel AM, Naik-Mathuria B. Understanding non-accidental trauma in the United States: A national trauma databank study. J Pediatr Surg. 2020;55(4):693-7.
10. Hurme T, Alanko S, Anttila P, Juven T, Svedström E. Risk factors for physical child abuse in infants and toddlers. Eur J Pediatr Surg. 2008;18(6):387-91.
11. Hymel KP, Laskey AL, Crowell KR, Wang M, Armijo-Garcia V, Frazier TN, et al. Racial and Ethnic Disparities and Bias in the Evaluation and Reporting of Abusive Head Trauma. J Pediatr. 2018;198:137-43.e1.
12. Jenny C, Hymel KP, Ritzen A, Reinert SE, Hay TC. Analysis of missed cases of abusive head trauma. Jama. 1999;281(7):621-6.
13. Laskey AL, Sheridan MJ, Hymel KP. Physicians' initial forensic impressions of hypothetical cases of pediatric traumatic brain injury. Child Abuse Negl. 2007;31(4):329-42.
14. Hymel KP, Wang M, Chinchilli VM, Karst WA, Willson DF, Dias MS, et al. Estimating the probability of abusive head trauma after abuse evaluation. Child Abuse Negl. 2019;88:266-74.
15. Zamalin D, Hamlin I, Shults J, Katherine Henry M, Campbell KA, Anderst JD, et al. Predictors of Making a Referral to Child Protective Services Prior to Expert Consultation. Acad Pediatr. 2024;24(1):78-86.
16. Doswell A, Killough E, Zinkus TP, Sherman A, Anderst J. Examining diagnostic variability among pediatric subspecialists using case examples of infant head injury. Child Abuse Negl. 2023;144:106371.
17. Wallace GH, Makoroff KL, Malott HA, Shapiro RA. Hospital-based multidisciplinary teams can prevent unnecessary child abuse reports and out-of-home placements. Child Abuse Negl. 2007;31(6):623-9.
18. van Rijn RR, Affourtit MJ, Karst WA, Kamphuis M, de Bock LC, van de Putte E. Implementation of the Dutch expertise centre for child abuse: descriptive data from the first 4 years. BMJ Open. 2019;9(8):e031008.

Beyfortus®
(nirsévimab)

| Prix Beyfortus® 1 juin 2024 | |
|---|---|
| Prix public, TVA incluse | 777.44 € |
| Prix remboursé (AO) | 12.10 € |
| Prix remboursé (AP) | 8.00 € |

**NOUVEAU**

Beyfortus® est remboursé pour les bébés dans le cadre de la prévention du VRS


# Le pouvoir de réduire le chaos lié au VRS.

Beyfortus® est le **premier** anticorps direct à action prolongée conçu pour **tous les bébés**.[1]

Beyfortus® réduit le risque d'infections des voies respiratoires inférieures et **diminue les hospitalisations** liées au VRS avec un bon profil de **sécurité** et de **tolérance**.[1]

Une seule injection **protège durant toute la saison** de circulation du VRS.[1]

## Scannez le QR code pour plus d'informations sur l'immunisation des bébés avec Beyfortus®.

▼ Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Les professionnels de la santé déclarent tout effet indésirable suspecté. Voir rubrique 4.8 pour les modalités de déclaration des effets indésirables. DÉNOMINATION DU MÉDICAMENT Beyfortus 50 mg solution injectable en seringue préremplie. Beyfortus 100 mg solution injectable en seringue préremplie. COMPOSITION QUALITATIVE ET QUANTITATIVE Beyfortus 50 mg solution injectable en seringue préremplie : Chaque seringue préremplie contient 50 mg de nirsévimab dans 0,5 mL (100 mg/mL). Beyfortus 100 mg solution injectable en seringue préremplie Chaque seringue préremplie contient 100 mg de nirsévimab dans 1 mL (100 mg/mL). Le nirsévimab est un anticorps monoclonal humain de type immunoglobuline G1 kappa (IgG1κ) produit dans des cellules d'ovaires de hamster chinois (CHO) par la technologie de l'ADN recombinant. Pour la liste complète des excipients, voir rubrique 6.1. FORME PHARMACEUTIQUE Solution injectable. Solution limpide à opalescente, incolore à jaune, de pH 6.0. INDICATIONS THÉRAPEUTIQUES Beyfortus est indiqué pour la prévention des infections des voies respiratoires inférieures dues au virus respiratoire syncytial (VRS) chez les nouveau-nés et les nourrissons au cours de leur première saison de circulation du VRS. Beyfortus doit être utilisé conformément aux recommandations officielles en vigueur. POSOLOGIE ET MODE D'ADMINISTRATION Posologie La dose recommandée est une dose unique de 50 mg administré par voie intramusculaire pour les nourrissons dont le poids est <5 kg et une dose unique de 100 mg administré par voie intramusculaire pour les nourrissons dont le poids est ≥5 kg. Beyfortus doit être administré avant le début de la saison d'épidémie à VRS, ou dès la naissance chez les nourrissons nés au cours de la saison d'épidémie à VRS. La posologie chez les nourrissons dont le poids est compris entre 1,0 kg et 1,6 kg est basée sur une extrapolation, aucune donnée clinique n'est disponible. L'administration du traitement chez les nourrissons de moins de 1 kg est susceptible d'entraîner une exposition plus élevée que chez les nourrissons pesant plus de 1 kg. Par conséquent, les bénéfices et les risques de l'utilisation du nirsevimab chez les nourrissons de moins de 1 kg doivent être soigneusement évalués. Les données disponibles sont limitées chez les enfants extrêmement prématurés âgés de moins de 8 semaines (âge gestationnel [AG] < 29 semaines). Il n'y a pas de données cliniques disponibles chez les nourrissons dont l'âge post-menstruel (âge gestationnel à la naissance + âge chronologique) est inférieur à 32 semaines (voir rubrique 5.1). Chez les nourrissons devant subir une chirurgie cardiaque avec circulation extracorporelle, une dose supplémentaire peut être administrée dès que le nourrisson est stable après l'intervention, afin de garantir des taux sériques de nirsévimab adaptés. Si l'intervention a lieu dans les 90 jours suivant l'administration de la première dose de Beyfortus, la dose supplémentaire doit être de 50 mg ou 100 mg selon le poids. Au-delà de 90 jours, la dose supplémentaire peut être une dose unique de 50 mg indépendamment du poids, afin de couvrir le reste de la saison de circulation du VRS. Il n'y a pas de données disponibles sur la sécurité et l'efficacité d'une administration répétée. La sécurité et l'efficacité du nirsévimab chez les enfants âgés de 2 à 18 ans n'ont pas été établies. Aucune donnée n'est disponible. Mode d'administration Beyfortus doit être administré uniquement par voie intramusculaire. Il doit être administré par voie intramusculaire, de préférence dans la partie antérolatérale de la cuisse. Le muscle fessier ne doit pas être utilisé systématiquement comme site d'injection en raison du risque de lésion du nerf sciatique. Instructions relatives à l'administration Beyfortus est disponible sous la forme d'une seringue préremplie de 50 mg et d'une seringue préremplie de 100 mg. Vérifier les étiquettes collées sur l'emballage extérieur et sur la seringue préremplie pour vous assurer d'avoir choisi la présentation correcte requise de 50 mg ou de 100 mg. Seringue préremplie de Beyfortus 50 mg (50 mg/0,5 mL) avec tige de piston violette. Seringue préremplie de Beyfortus 100 mg (100 mg/1 mL) avec tige de piston bleue clair. Étape 1 : En tenant le Luer Lock d'une main (éviter de tenir la tige du piston ou le corps de la seringue), dévisser le capuchon de protection de la seringue en le tournant dans le sens antihoraire avec l'autre main. Étape 2 : Fixer une aiguille sur la seringue préremplie en tournant délicatement l'aiguille, dans le sens horaire sur l'embout Luer Lock de la seringue préremplie, jusqu'à rencontrer une légère résistance. Étape 3 : En tenant le corps de la seringue d'une main, tirer délicatement sur le capuchon protecteur de l'aiguille avec l'autre main pour l'enlever. Ne pas tenir la tige du piston pendant le retrait du capuchon protecteur de l'aiguille, au risque de déplacer la butée en caoutchouc. Ne pas toucher l'aiguille et ne pas la mettre en contact avec une surface. Ne pas remettre le capuchon protecteur sur l'aiguille et ne pas retirer l'aiguille de la seringue. Étape 4 : Administrer tout le contenu de la seringue préremplie en injection intramusculaire, de préférence dans la face antérolatérale de la cuisse. Le muscle fessier ne doit pas être utilisé systématiquement comme site d'injection en raison du risque de lésion du nerf sciatique. CONTRE-INDICATIONS Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1. EFFETS INDÉSIRABLES Résumé du profil de tolérance L'effet indésirable le plus fréquent était les éruptions cutanées (0,7 %) survenues dans les 14 jours suivant l'administration. La majorité des cas étaient d'intensité légère à modérée. De plus, une pyrexie et des réactions au site d'injection ont été rapportées à un taux respectif de 0,5 % et 0,3 % dans les 7 jours suivant l'administration. Les réactions au site d'injection étaient non graves. Liste des effets indésirables La liste ci-dessous présente les effets indésirables rapportés chez 2 966 nourrissons nés à terme et prématurés (AG ≥29 semaines) ayant reçu du nirsévimab dans le cadre d'essais cliniques. Les effets indésirables rapportés au cours des essais cliniques contrôlés sont répertoriés par classe de systèmes d'organes (SOC) MedDRA. Au sein de chaque SOC, les termes préférentiels sont présentés par fréquence décroissante puis par gravité décroissante. La fréquence de survenue de chaque effet indésirable est définie comme suit : très fréquent (≥1/10) ; fréquent (≥1/100 à <1/10) ; peu fréquent (≥1/1 000 à <1/100) ; rare (≥1/10 000 à <1/1 000) ; très rare (<1/10 000) et fréquence indéterminée (ne peut être estimée à partir des données disponibles). Affections de la peau et du tissu sous-cutané • Peu fréquent - Eruptions cutanées1 1 L'éruption cutanée était définie par les termes préférentiels groupés suivants : rash, rash maculopapuleux, rash maculeux. Troubles généraux et anomalies au site d'administration • Peu fréquent - Réaction au site d'injection2 ; Pyrexie 2 La réaction au site d'injection était définie par les termes préférentiels groupés suivants : réaction au site d'injection, douleur au site d'injection, induration au site d'injection, oedème au site d'injection, gonflement au site d'injection. Nourrissons avec un risque plus élevé d'infection sévère par le VRS La sécurité d'emploi a également été évaluée dans l'essai MEDLEY chez 918 nourrissons à risque plus élevé d'infection sévère par le VRS, dont 196 très grands prématurés (AG <29 semaines) et 306 nourrissons porteurs de maladie pulmonaire chronique ou d'une cardiopathie congénitale hémodynamiquement significative pendant leur première saison d'épidémie à VRS, qui ont reçu du nirsévimab (614) ou du palivizumab (304). Le profil de sécurité était comparable à celui du comparateur palivizumab et cohérent avec le profil de sécurité chez les nourrissons nés à terme et prématurés d'AG ≥29 semaines (essais D5290C00003 et MELODY). Immunogénicité Comme avec toutes les protéines thérapeutiques, il existe un potentiel d'immunogénicité. Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via : Belgique: Agence Fédérale des Médicaments et des Produits de Santé – Division Vigilance – Boîte Postale 97 – 1000 Bruxelles Madou – Site internet: www.notifieruneffetindesirable.be – e-mail: adr@afmps.be Luxembourg: Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé – Site internet : www.guichet.lu/pharmacovigilance TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly, France NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ EU/1/22/1689/001 50 mg, 1 seringue préremplie à usage unique EU/1/22/1689/002 50 mg, 1 seringue préremplie à usage unique avec aiguilles EU/1/22/1689/003 50 mg, 5 seringues préremplies à usage unique EU/1/22/1689/004 100 mg, 1 seringue préremplie à usage unique EU/1/22/1689/005 100 mg, 1 seringue préremplie à usage unique avec aiguilles EU/1/22/1689/006 100 mg, 5 seringues préremplies à usage unique DATE DE PREMIÈRE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION Date de première autorisation: 31 octobre 2022 DATE DE MISE À JOUR DU TEXTE Date d'approbation : 11/2023 Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu

**Référence:**
**1.** Beyfortus RCP, nov 2023. Sanofi Belgium - MAT-BE-2400434-1.0-06/2024

sanofi

# A Qualitative Study of the Knowledge of Primary Schoolchildren about Illness Symptoms in Flanders

Anna France [a], Jaan Toelen [b,c,d], Lies Sercu [e]

[a] Faculty of Medicine, KU Leuven, Belgium
[b] Department of Paediatrics, University Hospital Leuven, Belgium
[c] Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[d] KU Leuven Child and Youth Institute, KU Leuven, Leuven, Belgium
[e] Faculty of Arts, KU Leuven, Belgium

Lies.sercu@kuleuven.be

## Keywords

Primary school, language development, health literacy, illness symptoms, patient-centered.

## Abstract

***Objective***

Good physician-patient communication leads to better patient outcomes, but this is less evident when communicating with a child. This investigation aimed to describe primary schoolchildren's perceptions of common illness symptoms in order to establish a baseline for healthcare communication with children.

***Methods***

Data were collected through semi-structured group interviews in ten primary schoolclasses in Flanders, five in the second and five in the sixth year. The interview guide included questions about the definition, causes, symptoms, treatment, and dangerousness of fever, abdominal pain, and cough.

***Results***

Participants from the second and sixth years of primary education gave roughly the same answers. Sixth-year participants did have more specific knowledge and used more details, practical examples, and anecdotes. Second-year participants had more misconceptions, mostly influencing their ideas about the causes and dangers of illnesses.

***Conclusion***

Children do have quite elaborate ideas about fever, cough, and abdominal pain when asked to comment on symptoms, causes, treatments, and dangers. No major differences were found between second-year and sixth-year participants with respect to Piaget's levels of cognitive development. Healthcare professionals working with children can and should consider children's perceptions in their consultations to enhance the effectiveness of care.

## Introduction

When a physician uses an empathetic, patient-centred communication style, this results in a better patient-physician relationship and more engagement of the patient in her/his own therapy, which in turn leads to better patient adherence and health outcomes (1-2). Studies have shown that this also applies to children and that good physician-child communication, educating the child and letting him/her participate in decision-making, results in better compliance and quality of life (3-4).

Patient-centred communication is more complicated when the patient is a child. For one thing, children have a different understanding of health and illness than adults and their understanding changes with the different developmental stages they go through (5-8). For another, physicians may not be familiar with a child's level of cognitive understanding, due to age-related differences (3-5, 9-10). Furthermore, physicians do sometimes underestimate or overestimate their patient's age, leading to potential communication barriers [10]. Based on a study of children's conceptual development of illness, Perrin and Perrin concluded that healthcare professionals are often unaware of children's knowledge about health and illness and that more than half of their age estimates were incorrect (6).

To understand what can be expected of children in terms of their understanding of concepts at a particular age, it is useful to turn to Jean Piaget's seminal theory of cognitive development (5). In his theory of how formal thought develops, Piaget defined four stages of cognitive development in children (5, 11-12). In the sensorimotor stage (birth-age 2), children use their senses to explore the world and they understand object constancy. Children in the preoperational stage (age 2-7) are egocentric and name things with words, but they lack logical reasoning. They start to develop speech and over-focus on visual aspects. Actions are now not only purely motor and perceptual but also mental. In the concrete operational stage (age 7-11), children start to think more logically about concrete events and they develop reflection as they think before acting. They become less egocentric and can dissociate their point of view from that of others. In the final stage, formal operational (age 11+), children can think and reason abstractly.

The aim of this study is to deepen our understanding of the knowledge of primary schoolchildren (ages 7 and 11-12) about the semantics of three health symptoms, namely fever, abdominal pain, and cough. This study is the first to assemble baseline data on children's views of fever, abdominal pain, and cough in Flanders. It not only assesses the children's perspectives of illness aetiology, as was done in previous studies, but also at the broader semantic domain associated with these illnesses (13). Its results want to serve healthcare providers to improve the child-directed nature of their communication. It is only when a child can explain its symptoms well and understand the physician's explanations about the aetiology and pathophysiology of the disease, that patient-centred medical decisions can be made. We anticipate that the participants' understanding of illness will increase with age, and therefore a difference will be seen between the younger and older participants.

## Design and methods

### *Sample*

The target population consisted of two cohorts of Flemish schoolchildren from the second (7-year-olds) and sixth (11-12-year-olds) year of primary education. School principals were invited by e-mail to participate in the study,

**Table 1**: Summary of studies researching the most commonly addressed childhood illnesses/symptoms.

| ARTICLE | COUNTRY OF STUDY | AGES OF PARTICIPANTS | RESEARCH SUBJECT | RESULTS |
|---|---|---|---|---|
| **Workload and management of childhood fever at general practice out-of-hours care: an observational study (18)** | The Netherlands | 0-12 years old | Number of childhood fever related contacts during out-of-hours care | 31.1% |
| **Diagnostic scope in out-of-hours primary care services in eight European countries: an observational study (19)** | Belgium, Denmark, Germany, the Netherlands, Norway, Slovenia, Spain, Switzerland | 0-17 years old | Top five symptoms and diagnoses in out-of-hours primary care | Respiratory, digestive, general and unspecified, ear, skin |
| **The frequency distribution presenting symptoms in children aged six months to six years to primary care (20)** | United Kingdom | 6 months – 6 years | Top five presenting symptoms in primary care organisations | Respiratory, orthopaedics and trauma, skin, gastrointestinal, non-specific symptoms |
| **Everyday symptoms in childhood: occurrence and general practitioner consultation rates (21)** | The Netherlands | 0-14 years old | Top five occurring symptoms | Colds/flu, respiratory, diarrhoea, musculoskeletal, headaches |
| **Medical problems presenting to paediatric emergency departments: 10 years on (22)** | United Kingdom | 0-15 years old | Top six symptoms in the emergency department | Breathing difficulty, febrile illness, diarrhoea and vomiting, rash, cough, abdominal pain |

resulting in the inclusion of two schools. In Belgium, grade and year are equal to each other (second grade is equal to second year). The first school is a public Catholic school located in a village. Of all the schoolchildren, 8% speak another language at home and 1% come from neighbourhoods with delayed education (14). The second school is also a public Catholic school located in a medium-sized city. About 13% of the schoolchildren speak another language at home and 1/3rd of the children come from a neighbourhood with delayed education. 166 participants from ten classes took part in a focus group interview (one per class).

### *Topic selection*

We based the selection of our topics on the frequency of symptoms in paediatric healthcare. As can be seen from Table 1, studies reported that the most frequently returning symptoms include general symptoms (including fever), respiratory symptoms, digestive symptoms, ear problems, skin problems, orthopaedics and trauma, musculoskeletal problems, and headaches (15-19). Since these studies reported that general symptoms, such as abdominal problems and respiratory tract symptoms are frequently recurring symptoms in children, fever, abdominal pain, and cough were chosen as the topics to be addressed in the focus group interviews.

### *Data collection*

Ten semi-structured class interviews, all conducted by the first author, formed the basis of the data collection. The data were collected in April 2023. We decided to use basic questions to get an overview of the children's knowledge and because we had limited time per class. As can be seen from the interview schedule in Appendix A, questions concerned the definition, symptoms, and causes of the illnesses, wether the illness could be dangerous, what the children do when they get sick, what a doctor can do when you are sick, which medications one can take, etc. In all classes, the same preset questions were asked, but there was also room for spontaneous input from the participants' side. Interviews lasted approximately 50 minutes.

Before the start of the interviews, the children and parents received an information letter explaining the purpose of the study, benefits and risks, the anonymity of the participants, voluntary participation, and the purpose of recording the interviews. The parents were required to complete a consent form beforehand. Only children with parental consents were allowed to participate in the interviews. The study was approved by the Research Ethics Committee UZ/KU Leuven (MP023419).

### *Data analysis*

The interviews were transcribed from the recordings, and all transcripts were anonymized. Two researchers (AF, JT) performed independent coding of transcripts. In the first step of the coding process (open coding) the data were summarized, and concepts were constructed into a preliminary coding framework. In the second step (axial coding) general themes were defined based on the identified concepts. The third step (selective coding) confirmed the associations that were made in the first or second step by examining the categories and data that had been included and omitted across all interviews. A 100% interrater reliability was achieved after discussing some minor differences in the initial coding steps. Quotations were matched to the different themes and translated from Dutch into English. To create an overview of the results, a table with the most important findings was drawn up.

## Results

### *Overall findings*

Overall, we found no major differences between the answers from both age groups for the three health symptoms (Table 2). All children had experienced the three symptoms in the past and agreed that everyone can experience those illnesses.

The definitions and causes of the illnesses that the participants from the second and the sixth year of primary education reported were mostly the same, but the children from the older group had more specific knowledge, used more details, and provided more practical examples and anecdotes. The more detailed answers usually came from children who had a close personal (or familial) experience with medical problems. E.g., children and relatives who have had appendicitis, an aunt who is gluten intolerant, a father who has had kidney stones, etc. Another observation from the interviews was the lingering influence of the COVID-19 pandemic: at least one child in nine out of ten classes mentioned COVID-19 as the cause of an illness or a COVID test as one of the things a doctor can do. Illustrative quotes can be found in Table 3.

### *Specific findings*

#### Fever

Knowledge. Both second and sixth-year children came up with the same definition: 'a body temperature higher than normal'. When asked what they felt during a fever, most participants in both age

**Table 2**: Overview of the results of the interviews, second year and sixth year separated.

| | SECOND YEAR | SIXTH YEAR |
|---|---|---|
| **Fever** | | |
| *Knowledge* | | |
| - Definition | A temperature of more than 37°C-40°C | A temperature of more than 37°C-38°C |
| - Symptoms | Alternating hot and cold, headache, abdominal pain, not able to eat, nausea/vomiting, nose bleed, ill feeling, cough, flu, sore throat, being pale, fatigue, stuffed nose | Alternating hot and cold, headache, fatigue, abdominal pain, ill feeling, stuffed nose, nausea/vomiting, muscle pain, sore throat, being pale, shocking |
| - Causes | Not dressing arm enough in cold weather, eating something wrong/raw/mouldy, bacteria, viruses, cancer | Bacteria, not dressing warm enough in cold weather, flu, viruses, cold, eating something wrong, walking barefoot, someone sneezing on you |
| - Actions | Resting, taking medication, drinking soup/water/tea, placing something cold on forehead, measuring fever, going to the doctor | Resting, taking medication, going to the doctor, drinking hot beverages, drinking cola/water, measuring fever, icepack on the forehead, not dressing too hot |
| - Dangerous? | When fever is too high, the elderly, babies, transferable to other people | When fever is too high, the elderly, babies, underlying disease |
| - Medication | Ibuprofen, paracetamol, antibiotics | Ibuprofen, paracetamol, paracetamol-codeine, cough syrup, antibiotics |
| - Doctor visit | Prescribing medication, examining belly, examining throat, listening to heart/lungs, measuring fever, examining ears, measuring blood pressure | Examining throat/ears, listening to heat/lungs, measuring fever, examining belly, prescribing medication, covid test |
| *Misconceptions* | | |
| - Definition | A temperature ranging from 15°C to 70°C | Dressing too hot, a temperature difference between the body and surroundings, eating something you do not like, a big time difference |
| - Causes | Dressing too hot, eating too much candy, not changing your bed sheets | |
| - Dangerous | Suffocation, you could get covid/cancer/burning wounds, you cannot eat anything anymore | |
| - Can everyone get it? | People who eat a lot of vegetables or people who received a shot against it cannot have fever | |
| **Abdominal pain** | | |
| *Knowledge* | | |
| - Definition | Stomach pain, cramps, pressure on the belly, nausea/vomiting, the urge to go to the toilet, the feeling that someone kicked in your belly | Stomach pain, cramps, pressure on the belly, rumbling stomach, vomiting, headache |
| - Causes | Eating too much / too fast / too little / unhealthy, eating something bad / raw / past date, food intolerance, being in the car, drinking too much water, breathing fast, illness, appendicitis, constipation, poisonous spiders, bacteria, viruses, allergies, someone kicking in your belly | Eating too much / too fast / too little / unhealthy, eating something bad / raw / past date, bacteria, stress, allergies, eating things that do not fit together after each other, having it too hot, drinking too much water, viruses, constipation, appendicitis, someone kicking in your belly, taking too much medication, menstruation, tapeworm, flu, animals carrying diseases, giving birth |
| - Actions | Taking medication, resting, going to the doctor, drinking cola, pressing in your belly, going to the toilet | Resting, finding a comfortable position, taking medication, going to the toilet, going to the doctor, drinking water / soup / cola, hot water bottle, vomiting |
| - Dangerous? | If it doesn't go away, the elderly and babies, if you have to go to the hospital, appendicitis, if you cannot eat anymore | If it doesn't go away, if you have to go to the hospital / get surgery, appendicitis, the elderly, tapeworm, kidney stones, underlying disease |
| - Medication | Paracetamol | Paracetamol, macrogol, ibuprofen, antibiotics |
| - Doctor visit | Prescribe medication, examine throat / ears, examine belly / heart / lungs, draw blood | Examine belly / heart / lungs / throat / ears / give medication, examine urine, draw blood, perform ultrasound |
| *Misconceptions* | | |
| - Causes | Eating something you do not like | |
| - Dangerous? | You can get covid and / or cancer from it and die | |
| **Cough** | | |
| *Knowledge* | | |
| - Symptoms | Tremor or itch in the throat, mucus in the throat, sore / dry throat, stuffed nose, a feeling that something is blocking the throat | Tremor or itch in the throat, sore / dry throat, air hitting your throat very hard, air passing over bumps in your throat, swollen and painful tonsils |
| - Causes | Not dressing warm enough in cold weather, allergies, cold, choking, itch in the throat, dirt / mucus / dust in throat, bacteria, viruses, fever, having it too hot, unable to breathe well, fever, smelling something bad | Choking, cold, sore throat, mucus / dust in throat, allergies; viruses, after eating ice cream, after gagging, smelling powder / something bad, itch in the throat, after covid test, asthma, bacteria, dry throat, sharp food, insect stuck in throat, croup / laryngitis, not dressing warm enough in cold weather |
| - Actions | Cough in elbow / hand / tissue / away from others, drink tea / water, honey, take medication | Take medication, drink tea / warm milk / water, take puffer, cough in elbow, hit person coughing on the back |
| - Dangerous? | Suffocation, transferable to other people, the elderly, babies | Suffocation, transferable to other people, the elderly, babies, smokers, asthma, bronchitis, pneumonia, breathing problems, laryngitis, rib fracture |
| - Medication | Cough syrup, paracetamol, ibuprofen | Paracetamol, macrogol, ibuprofen, antibiotics |
| - Doctor visit | Examine throat, prescribe medications, covid test, listen to lungs / heart | Examine belly / heart / lungs / throat / ears / give medication, examine urine, draw blood, perform ultrasound |
| *Misconceptions* | | |
| - Causes | Having it too hot | |
| - Dangerous? | | Fatigue, not brushing teeth<br>Damaging the throat resulting in bleeding or death, damaging lungs causing a hole resulting in bleeding |

**Table 3**: Overview of citations.

| | SECOND YEAR | SIXTH YEAR |
|---|---|---|
| **Fever** | | |
| *Knowledge* | | |
| - Definition | 'If the temperature of your body is too high' | 'If the temperature of your body is higher than normal' |
| - Symptoms | 'That is when your head is so hot and you have an headache and then you can also cough'<br>'Sometimes you are pale and you don't feel well and then you have to go home because you are so ill' | 'I think sometimes you feel warm but then you are cold because you have those chills'<br>'I am also always hot and cold, my throat always hurts, when you lie in your bed and you get up again, your head hurts a lot afterwards' |
| - Causes | 'Because microbes get into your stomach'<br>If you go swimming and you have wet hair and you don't put on your hood, you can also get sick and get fever'<br>'If you eat something mouldy' | 'If someone sneezes in your face you may also get a fever'<br>'Like if you go outside with wet hair when it's freezing'<br>'Eating something wrong' |
| - Dangerous? | Fever can sometimes be so hot that you can die from being too hot'<br>'If your grandfather and grandmother are very old, they can die from it'<br>'Because when you visit older people you can pass that on' | 'if it gets very high'<br>'It can be worse in older people and babies, because they are more sensitive'<br>-People with cancer or people who are already ill because of something' |
| *Misconceptions* | | |
| - Causes | 'If you don't change your bedsheets'<br>'Some people cannot get fever because they eat a lot of vegetables' | 'For example, if you are inside and that takes another 5 minutes and you already put on your coat and your scarf and so on, you are very warm and if you have to go in the car and take it off. Then the environment is colder' |
| - Dangerous | 'If you have it for top long you can choke'<br>Yes, then you can get corona and corona can give you cancer and kill you'<br>'Then you can no longer eat as much because then you become afraid if you eat something hot, you will feel even hotter'<br>'You can get burning wounds from it' | |
| **Abdominal pain** | | |
| *Knowledge* | | |
| - Symptoms | 'It's like having cramps'<br>'Then your stomach hurts and you think you have to throw up' | 'If you get a lot of pain in your stomach, or if you get kicks in your stomach or if you have cramps, and also just really pain' |
| - Causes | 'If you have eaten something bad that your stomach cannot handle very well'<br>'That's because you ate too much, also my stomach hurts when I'm breathing very fast'<br>'I have a stomach ache because there is a lot of poop in my stomach and it hurts and then I have to take something in my water or milk every morning and I find that very disgusting'<br>'If someone who is sick coughs near to you' | I have stomach ache when I am stressed or eat too much, but I also have stomach ache when I have eaten too little, so if I have not eaten for a long time I also get stomach ache' |
| - Dangerous? | 'This is also dangerous for older and younger people'<br>'You can die if the stomach ache is super painful' | 'Yes, if that continues and there are many bacteria and viruses in your stomach, and they continue and then sometimes you may have to go to the hospital'<br>'My dad once had kidney stones and had also a lot of stomach pain, so I also think that can be dangerous. Not fatal, but dangerous'<br>'Appendicitis, I think if it were to explode it would release toxins in our stomach and that could be dangerous' |
| *Misconceptions* | | |
| - Dangerous? | If you have a lot of abdominal pain then you will become very ill or you could get corona or maybe cancer or something. If you get corona from the stomach pain then you might get cancer from corona If you are very ill' | |
| **Cough** | | |
| *Knowledge* | | |
| - Symptoms | 'It vibrates in your throat when you cough, that's when you sneeze or cough' | 'It actually feels like air hitting your throat really hard' |
| - Causes | Sometimes you have mucus in your throat and the you have to cough that mucus away'<br>'Coughing can sometimes be because you may have bacteria in your throat'<br>'I often cough because I have a cold'<br>'If I smell something I'm allergic to I always have to cough'<br>'When the weather was cold and you had been playing outside and you hadn't dressed very well' | 'If food comes in your windpipe then you have to cough to get it out'<br>'If you have a pollen allergy'<br>'When you go outside in the cold without much clothes' |
| - Dangerous? | 'If you cough very hard you can make other people sick'<br>'Because sometimes you can choke and some people can suffocate easily. My sister also had to cough a lot and she had inflamed tonsils and she could hardly breathe'<br>'If you cough on older people, they can die more easily' | 'I think it can suffocate you if you choke or if something is stuck that can suffocate you'<br>'Yes, because you can then pass it on to other people, such as bacteria for example'<br>'It can be dangerous to older people' |
| *Misconceptions* | | |
| - Causes | 'When you are extremely hot, you have to cough' | 'If you haven't brushed your teeth for a long time' |
| - Dangerous? | | 'Yes, because if you cough up your throat, you will die of pain'<br>'If your lungs are damaged and you have to cough, you are coughing blood. Can be dangerous because then there is a hole in it somewhere and you can no longer breathe properly'<br>'If you cough a lot, I think that you can cough open your throat and that the skin in your throat has been coughed away and that a lot of blood flows into your food pipe and that you will then lose too much blood' |

groups mentioned feeling hot and cold, a headache, and fatigue. They also mentioned abdominal pain, being pale, nausea/vomiting, feeling ill, a stuffed nose, etc. One participant mentioned shivering, something she had experienced herself before. Regarding the causes of fever, many participants mentioned: not dressing warm enough in cold weather, eating infected food, and bacteria and viruses (mostly bacteria were mentioned). Most participants rest and take medication when they have a fever. Some drink hot beverages, place something cold on their forehead, or go to the doctor. Sixth-year participants were able to mention more medication names for fever than second-year participants. Most participants in both years agreed that a fever can be dangerous if it becomes too high, and that the elderly and babies are more vulnerable. Two sixth-year classes also mentioned that it can be more dangerous for people with an underlying illness (for example cancer, or a weak immune system). When asked about medical interventions, most of the answers included: measuring the fever, looking in the throat and ears, listening to the lungs and heart, examining the abdomen, and prescribing medications.

Misconceptions. There were more misconceptions in the second-year group. With the definition of fever, many children did not know the cutoff temperature. Most second-year participants guessed between 37°C and 40°C (but with a range of 15°C to 70°C). Another misconception was that a fever is defined as a body temperature not only higher but also lower than normal. Misconceptions about the causes of fever included: a too-warm environment (for example in summer), eating too much candy, and even 'not changing your bedsheets'. They thought a fever could be dangerous for the wrong reasons: you can suffocate, you can get COVID, cancer or burning wounds from a fever, and you cannot eat anything warm because then you will get even warmer. Two participants did not believe that all people can get a fever: some people eat a lot of vegetables, and some have received a vaccine and therefore cannot get a fever.

Sixth-year participants had fewer misconceptions, yet some of them thought that 'dressing too hot,' 'eating something you do not like' and 'a big-time difference' could be causes of fever. Another misconception was thinking that a fever is dangerous when your temperature reaches 45°C.

### Abdominal pain

Knowledge. When asked about the definition, most participants started to explain based on prior experience (what they felt themselves) or gave potential causes. Participants in both years of study described abdominal pain as 'a lot of pain and cramps in their belly.' Some also added: nausea/vomiting, pressure on the belly, and the feeling you need to go to the toilet. The most prevalent cause according to both age groups was food-related: eating too much or too little, eating something wrong or past date, eating something raw, or eating a substance against which one is intolerant (gluten, milk) or allergic. Other causes included stress and being in the car for too long. In most sixth-year classes, bacteria were mentioned. In all classes across both years, viruses were mentioned after more extensive questioning by the interviewer. One participant from each age group mentioned appendicitis, something they or a relative/friend experienced. When asked what the participants do when they have abdominal pain, most answered that they rest, take medication, or go to the doctor. Some go to the toilet or find a comfortable position. Second-year children were not able to mention medication names, sixth-year children mentioned painkillers, antibiotics, and Macrogol. The children think that abdominal pain can be dangerous when it goes on for too long, if you are in too much pain, if you must go to the hospital, if you have appendicitis, if you have kidney stones or an underlying condition (for example cancer). They also mentioned that the elderly and babies are more vulnerable. Both groups gave similar answers to the question 'what can a doctor do?': prescribe medication, examine the abdomen, look in the ears and throat, listen to heart and lungs and take a blood sample. In the sixth-year of primary education, examining the urine and performing an ultrasound were mentioned by two participants, both due to personal experience.

Misconceptions. Second-year participants thought that eating something you do not like' or fatigue are causes of abdominal pain. Two participants thought abdominal pain was dangerous because you could get COVID from it and you could then get cancer from COVID and die.

There were no misconceptions mentioned by the sixth-year classes.

### Cough

Knowledge. Most participants gave a demonstration of a cough when we asked to define a cough. When asked what they felt, most stated that it felt like a tickle in the throat and a sore or dry throat. Three sixth-year participants gave a more detailed explanation: the feeling of air hitting your throat very hard, air passing over bumps in your throat, painful and/or enlarged tonsils. The most common causes in second-year classes included: allergies, a cold, not dressing warm enough in cold weather, and viruses. In the sixth-year class, the most common cause was choking, followed by a cold, sore throat, mucus in the throat, allergies, and viruses. When having a cough, most children took coughing syrup and drank some water or hot beverages. In the younger age group, some participants mentioned that they cough in their elbow or in a tissue. A sixth-year participant with asthma stated she uses her inhaler when she coughs a lot. When we asked which medication the participants took, most answered that they took a cough syrup. Some mentioned pain medication and some sixth-year participants took throat pastilles or antibiotics. Some participants in both age groups did not think a cough could be dangerous, while others thought it could be dangerous because you can pass it on to someone else and because you could suffocate. When asked if certain people are more vulnerable, second-year participants mentioned the elderly and babies. Sixth-year participants also mentioned people with asthma, bronchitis, or pneumonia, and people who smoke a lot or have trouble breathing. One participant mentioned a teacher once broke a rib because of a coughing fit. Their examples of what a doctor can do were more focused on fever and abdominal pain: prescribe medication, look in the throat and listen to the lungs. A sixth-year participant mentioned a laryngoscopy, as he had experienced one before.

Misconceptions. A second-year participant thought you could get a cough if you are too hot. In the sixth- year, misconceptions about the causes of a cough included fatigue and not brushing your teeth for a long time. Three sixth-year participants thought a cough could be dangerous because you can damage your throat resulting in bleeding or death, or because you can damage your lungs by causing a hole in them, which in turn can result in bleeding.

## Discussion

In this study, we did not find major differences between the semantic fields used to describe three frequent medical symptoms in our second- and sixth-year groups (13). Both groups reported similar definitions and symptoms. Both also mentioned many external factors as possible aetiologies of the symptoms. Sixth-year participants were able to mention more medication names, used more specific language, and recounted more anecdotes, suggesting that their mental representations of the illnesses investigated may be more elaborate and different from those of the children in the younger age group. Regarding the pupils' misconceptions, our findings show that the second-year participants had slightly more misconceptions than the sixth-year participants, in the categories of causes and dangers related to illnesses. Common misconceptions among the younger participants included the cut-off temperature for a fever, the belief that one can get cancer from the symptoms, the belief that eating something they do not like can be a cause for the symptoms, and the belief that coughing can cause severe complications in the throat.

In paediatric clinical practice, an explanation from a healthcare professional is more genuinely reassuring for a child when it is framed within the cognitive and psychological or emotional level of the child's understanding of illness. To do so, the professional needs to be aware of the age-related stages of cognitive development of the children under their care. As mentioned in the introduction, Piaget's theory

is an accepted concept to frame our findings. There are studies that further refine the four stages of Piaget in the context of symptoms and disease aetiology (7-8).

These studies confirm that children in the concrete operational stage (the second-year participants in our study) can differentiate internal (self) from external reasons for illness. They use contamination and internalization as explanations of illness. Children in the formal operational stage (the sixth-year participants in our study) use physiological and psychophysiological explanations, as the differentiation between internal and external explanations becomes larger in this stage and they understand that illness can arise from various causes. In this light, our findings corroborate findings from earlier studies, indicating that the situation has not changed much over the years and that today's children appear to process illness symptoms in the same way as children did two or three decades ago (20-21). This is an expected finding when we consider that today's children, like children from previous decades, are cognitively maturing and proceed through the different stages of cognitive development just like children from previous decades. On a more pessimistic note, this suggests that the health literacy of children, and particularly the older children, has not grown much over the years. This may in part be due to the fact that the attainment targets for health education for primary education are quite vague and are not easily translated into a concrete curriculum for younger and older children. Teachers may for example focus on hygiene, and relate hygiene to the prevention of illness, but they may not necessarily also provide information on potential physiological or psychophysiological explanations for illnesses, i.e. information that the older children could grasp given their cognitive developmental stage (formal operational stage with abstract thinking).

Not all children in our two groups behave exactly according to the age-related categories. For example, some sixth-year children display opinions that can be categorized as typical of the concrete operational stage, rather than the formal operational stage where the ability to think abstractly is developing. This became clear in some of the misconceptions that were emerging during the focus group discussions. In other words, Piaget's age ranges may have to be considered loosely rather than strictly with some children being more mature than their age group suggests and others less so. Thus, our findings suggest that the sixth-year children find themselves at a turning point between the concrete operational and the formal operational stage, with some of them already having crossed the line and others not. A possible explanation for this is the fact that the previous studies relied on individual interviews, rather than focus group discussions. It is possible that children behave differently or state different opinions when they are in a group. We did notice that some of the participants made statements that evoked laughter or expressions of amazement in the group. It is unclear if they would have done so in an individual setting as well.

Our findings of congruence between the answers in the two age groups differ from some previous studies of healthy children. One study interviewed three age groups of Icelandic schoolchildren: 6-7 years old, 10-11 years old, and 14-15 years old (22). In individual interviews, the authors asked about the causes, symptoms, prevention, and treatment of illnesses. They found a significant difference between all three age groups. The 6–7-year-old participants were at the beginning of the concrete operational phase and the 10–11-year-old participants were in the formal operational stage. In all age groups, their understanding of the causes of illnesses was higher than their understanding of treatment and prevention. They also mentioned examples of answers the children gave, so we are able to compare those to our results. The 6-7-year-olds mostly associated cold weather and not dressing warm enough with causes of illness, while the 10-11-year-olds mostly mentioned germs. This is in contrast with our results, where both age groups mentioned these causes. For the treatment of illnesses, the second-year group mostly mentioned medical treatment, while the sixth-year group also mentioned self-care. In our study, both age groups mostly mentioned a combination of resting and taking medication. One reason for our non-corroborating findings may lie in the fact that we did not use individual interviews to collect our data, but group interviews. Chances are that when we would have interviewed our participants individually, the individual children would not have been able to come up with the same amount of knowledge as the class as a group could. When interviewed as individuals, we might have seen a clearer distinction between the age groups. As individuals, the younger students from the second-year group might either have been in the preoperational or the concrete operational stage, depending on their degree of maturation. The older children might either have been in the concrete or the formal operational stage as already suggested above.

One interesting and understudied part of the study concerns the children's misconceptions. Even in the older age group, such misconceptions are persistent. When health professionals talk to children about their illnesses, they may have to consider -next to the cognitive developmental stages- the possible misconceptions or lack of information that could burden children with a wrong conception of the causes of their illness or how to treat it. A dialogic approach where the health professional listens to the young patient instead of talking about the young patient is needed to engage the child in the healing process and in a process of health education. Every doctor's appointment could thus become an opportunity for health literacy enhancement in young children, taking away misconceptions and reassuring the child that what it says is meaningful. The doctor's appointment also presents an opportunity to educate the children's parents, since many misconceptions stem from parental influence (23). Fever phobia is prevalent amongst most parents, often caused by poor knowledge and potentially resulting in excessive treatment. Parents may also transfer their own (poor) knowledge about medication usage to their children, since the subject is not covered in school (24). Apart from health professionals, educators can also utilize information about children's misconceptions to design age-appropriate and child-centred learning materials that can take away such misconceptions and help to alter them, perhaps helping the child move to the next stage of Piaget's model of cognitive development and taking away unnecessary fears on the side of the children.

Our study has some limitations. We only interviewed children from the second- and sixth-year group, which does not allow comparisons over a broader age spectrum. To include more children in the study, the interviews were conducted in groups (per classroom) instead of individually. This gave us a broad overview of their general knowledge but made it impossible to see strictly individual differences in knowledge and personal ideas. The interviews were performed in two public catholic primary schools in Flanders, excluding private and special education schools. Both schools were quite similar as they both had a relatively low percentage of schoolchildren who come from a relatively more deprived educational region and/or speak another language at home.

## Conclusion

The aim of this study was to increase our understanding of the knowledge of primary school children about the semantics of health symptoms so that healthcare professionals in Flanders can improve their communication with children.

On the basis of our study and earlier studies, we can conclude that no large differences in describing common illnesses (fever, abdominal pain, cough) exist between children from the second- and sixth-year groups, except for the reasons that children see for having attracted a certain illness. This lack of difference between the age groups is not something we expected, given Piaget's distinct levels of cognitive development and some previous studies that have shown clear distinctions between age groups when inquiring about children's conceptions of causes and symptoms of illnesses.

Based on our overall findings, topic descriptions, and collection of interview quotations taken from the focus group interviews, we recommend that health professionals talking to children take account of children's preconceived ideas and, in particular, their misconceptions

regarding common illnesses and symptoms, such as fever, abdominal pain, and cough. More patient-centred communication should result in better and faster health outcomes, and children's enhanced health literacy. The findings are also relevant for educators who can refine their health curricula to correct and enlarge children's mental representations of common illnesses and assist sixth-year children in achieving Piaget's stage of formal operational thinking.

## Conflict of Interest Statement

The authors declare that there are no conflicts of interest with regards to the acquisition and reporting of the data of the study presented in this manuscript, all procedure were in line with the editorial policy of the Belgian Journal of Paediatrics.

REFERENCES


1. Riedl D, Schüßler G. The Influence of Doctor-Patient Communication on Health Outcomes: A Systematic Review. Z Psychosom Med Psychother. 2017;63(2):131-50.
2. Zolnierek KB, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. Med Care. 2009;47(8):826-34.
3. Pantell RH, Stewart TJ, Dias JK, Wells P, Ross AW. Physician communication with children and parents. Pediatrics. 1982;70(3):396-402.
4. Holzheimer L, Mohay H, Masters IB. Educating young children about asthma: comparing the effectiveness of a developmentally appropriate asthma education video tape and picture book. Child Care Health Dev. 1998;24(1):85-99.
5. Piaget, J. Six psychological studies. New York: Random House; 1967 [consulted on June 16, 2023]. Available via : https://www.worldcat.org/nl/title/six-psychological-studies/oclc/561689379
6. Perrin EC, Perrin JM. Clinicians' assessments of children's understanding of illness. Am J Dis Child. 1983;137(9):874-8.
7. Brewster AB. Chronically ill hospitalized children's concepts of their illness. Pediatrics.1982;69(3):355-62.
8. Bibace R, Walsh ME. Development of children's concepts of illness. Pediatrics. 1980;66(6):912-7.
9. Butz AM, Walker JM, Pulsifer M, Winkelstein M. Shared decision making in school age children with asthma. Pediatr Nurs. 2007;33(2):111-6.
10. Perrin EC, Gerrity PS. There's a demon in your belly: children's understanding of illness. Pediatrics. 1981;67(6):841-9.
11. Vacik HW, Nagy MC, Jessee PO. Children's understanding of illness: students' assessments. J Pediatr Nurs. 2001;16(6):429-37.
12. Newton JT, Harrison V. The cognitive and social development of the child. Dent Update. 2005;32(1):33-4, 37-8.
13. Wierzbicka, A. Is pain a human universal? A cross-linguistic and cross-cultural perspective on pain. Emotion Review. 2012;4(3):307-17.
14. Onderwijs Vlaanderen. Leerlingenkenmerken [internet]. Overzicht leerlingenkenmerken basisonderwijs schooljaar 2022-2023; [consulted on 4 may 2024]. Available via : https://data-onderwijs.vlaanderen.be/documenten/bestanden/Publicaties_Leerlingenkenmerken_Overzicht_2022-2023_bao.pdf
15. de Bont EG, Lepot JM, Hendrix DA, Loonen N, Guldemond-Hecker Y, Dinant GJ, et al.. Workload and management of childhood fever at general practice out-of-hours care: an observational cohort study. BMJ Open. 2015;19:5(5).
16. Huibers LA, Moth G, Bondevik GT, Kersnik J, Huber CA, Christensen MB, et al.. Diagnostic scope in out-of-hours primary care services in eight European countries: an observational study. BMC Fam Pract. 2011;13:12:30.
17. Whitburn S, Costelloe C, Montgomery AA, Redmond NM, Fletcher M, Peters TJ, et al.. The frequency distribution of presenting symptoms in children aged six months to six years to primary care. Prim Health Care Res Dev. 2011;12(2):123-34.
18. Bruijnzeels MA, Foets M, van der Wouden JC, van den Heuvel WJ, Prins A. Everyday symptoms in childhood: occurrence and general practitioner consultation rates. Br J Gen Pract. 1998;48(426):880-4.
19. Sands R, Shanmugavadivel D, Stephenson T, Wood D. Medical problems presenting to paediatric emergency departments: 10 years on. Emerg Med J. 2012;29(5):379-82.
20. Myant KA, Williams JM. Children's concepts of health and illness: understanding of contagious illnesses, non-contagious illnesses and injuries. J Health Psychol. 2005;10(6):805-19.
21. Perrin EC, Sayer AG, Willett JB. Sticks and stones may break my bones ... reasoning about illness causality and body functioning in children who have a chronic illness. Pediatrics. 1991;88(3):608-19.
22. Hansdottir I, Malcarne VL. Concepts of illness in Icelandic children. J Pediatr Psychol. 1998;23(3):187-95.
23. Crocetti M, Moghbeli N, Serwint J. Fever phobia revisited: have parental misconceptions about fever changed in 20 years? Pediatrics. 2001;107(6):1241-6.
24. Hämeen-Anttila K, Bush PJ. Healthy children's perceptions of medicines: a review. Res Social Adm Pharm. 2008;4(2):98-114.

Pampers
premium protection™

# Dubbele bescherming


Dankzij de onmiddellijke absorptie is de huid beschermd en de Stop & Protect pocket helpt lekken aan de achterkant voorkomen.



Baby's veiligheid komt bij ons op de eerste plaats. Ontdek meer op pampers.be/ pampers.nl

OEKO TEX®
STANDARD 100
17.HCH.22181 Hohenstein HTTI
www.oeko-tex.com

Standard 100 gecertificeerd door OEKO-TEX op schadelijke stoffen.

Dermatest
De garantie dat het gebruik absoluut veilig is voor baby's.

Bevatten geen van de EU-parfumallergenen (zoals gereglementeerd in de EU-regelgeving voor cosmetica, nr. 1223/2009).

SKIN HEALTH ALLIANCE

Gecertificeerd door de Skin Health Alliance. Onze Pampers Premium Protection luiers dragen zorg voor de babyhuid. Ze zijn dermatologisch goedgekeurd en gecertificeerd door de dermatologen van de Skin Health Alliance.

# Regional Inequity in 4CMenB Vaccination Coverage in Belgium: A Retrospective Ecological Study

Georgios Nikitas [a], Andrew G. Allmon [b], Anne Meulemans [a], Kathleen Billiaert [a], Florence Strubbe [a], David Magis [c], Christiane Vogel [c], Benoit Brasseur [d], Wesley Mattheus [e], Marc Raes [f]

[a] GSK, Wavre, Belgium
[b] GSK, North Carolina, USA
[c] IQVIA, Zaventem, Brussels, Belgium
[d] Clinique St Pierre, Ottignies, Belgium
[e] Sciensano, Brussels, Belgium
[f] Jessa Hospital, Hasselt, Belgium

georgios.x.nikitas@gsk.com

## Keywords

Neisseria meningitidis ; invasive meningococcal disease ; vaccines ; Belgium.

## Abstract

Invasive meningococcal disease is associated with a high mortality rate and severe long-term health issues. In Belgium, most serogroup-documented invasive meningococcal disease cases are caused by serogroup B. The four-component meningococcal serogroup B vaccine (4CMenB) is recommended in Belgium for certain age groups but is not a publicly funded vaccine. This analysis aimed to estimate 4CMenB coverage and the association between 4CMenB coverage, age and household income at a municipality level in Belgium. 4CMenB vaccinations between November 2022 and October 2023, as well as individuals' age, location and household income level were obtained. Individuals with two to three doses of 4CMenB and municipalities with ≥100 vaccinees were included in this analysis. Of the 16,816 individuals vaccinated, 71% were concentrated within 11% (65/593) of municipalities. 4CMenB coverage was highest amongst the <1 (16%) and 1–2 years (14%) age groups. There was a correlation observed between 4CMenB coverage and age, as well as 4CMenB coverage and household income at a municipality level. This interaction was observed in individuals up to 11 years, with the most statistically significant correlation occurring in age groups <1 and 1–2 years (both $p<0.001$). 4CMenB not being a publicly funded vaccine may contribute to inequity in vaccine access, potentially placing low-income populations in Belgium at increased risk of invasive meningococcal disease. Universal vaccine recommendations and inclusion of 4CMenB into Belgium's regional immunisation programs could reduce potential inequity in vaccine access.

*At the end of the article you will find a graphical abstract that visually summarises the content of the article.*

## Introduction

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, is associated with a high mortality rate and long-term health implications (1, 2). There are twelve types, or serogroups, of this bacterium, six of which can cause epidemics (3). In Europe, the 2022 IMD notification rate rose to 0.3 cases per 100,000 population, after a decline in incidence in 2020 and 2021, potentially caused by COVID-19 pandemic quarantine measures. Incidence in 2022 was highest in infants aged <1 year, followed by those aged 1–4 and 15–24 years. Notably, meningitis caused by meningococcal serogroup B (MenB) accounted for 62% of IMD cases documented with a specific serogroup (4). Looking at 2022 Belgian data, incidence was highest in those aged 0–4 years (1.2 cases per 100,000 population) and <1 year (2.5 cases per 100,000 population) (5). Belgian IMD incidence in 2023 was 0.71 cases per 100,000 population and MenB accounted for 42% of cases (6).

MenB can be prevented through vaccination, with two MenB vaccines currently available in Belgium. The four-component MenB vaccine (4CMenB, Bexsero®; GSK), approved by the European Medicines Agency in 2013 for individuals aged ≥2 months, protects against MenB (7). In Belgium, 4CMenB can be administered to individuals aged ≥2 months on an individual basis, is preferentially recommended on this individual basis for children aged 2 months to 5 years as well as adolescents aged 15–19 years and is universally recommended for high risk groups, at a 2-dose vaccine schedule, followed by a booster dose for those aged <2 years or individuals at high risk (8, 9). 4CMenB is currently the only vaccine in Belgium recommended for infants and young children. The MenB-factor H-binding protein vaccine (MenB-FHbp, Trumenba®; Pfizer), approved by the European Medicines Agency in 2017 for individuals aged ≥10 years, also protects against MenB (10). MenB-FHbp was made available in Belgium in 2019. MenB-FHbp can be administered to individuals in Belgium aged ≥10 years on an individual basis, is preferentially recommended on this individual basis for adolescents aged 15–19 years and is universally recommended for high risk groups, at a 2-dose vaccine schedule, with a booster dose considered for individuals still at risk for IMD and high risk groups (8, 9).

While MenB-FHbp is not included in any regional immunisation programs, 4CMenB is included in the National Immunisation Program of several European countries, including France, Luxembourg, Switzerland, Germany, Portugal, Czech Republic, United Kingdom, Italy, Ireland, Malta, Andora, San Marino and Lithuania (11-15). As 4CMenB is recommended on an individual basis in Belgium, it is not included in regional immunisation programs and is therefore not a publicly funded vaccine. Previous studies, conducted in Australia, France, Spain, United States and United Kingdom, have assessed the association between social deprivation and risk of meningococcal disease, hospitalisation for meningococcal disease or uptake of meningococcal vaccines. These studies show uptake of non-publicly funded vaccines correlates with income, suggesting inequity in access to vaccination, often leaving those most at risk, more vulnerable (16-18). Adding 4CMenB to regional immunisation programs in Belgium could increase vaccine access and immunisation coverage, thereby decreasing social inequity and protecting those at greatest risk of IMD (16).

The relationship between socioeconomic status and meningococcal vaccine coverage in Belgium is not clearly understood. This study aimed to

estimate 4CMenB coverage and evaluate associations between vaccine coverage, age and household income across Belgian municipalities.

## Materials and methods

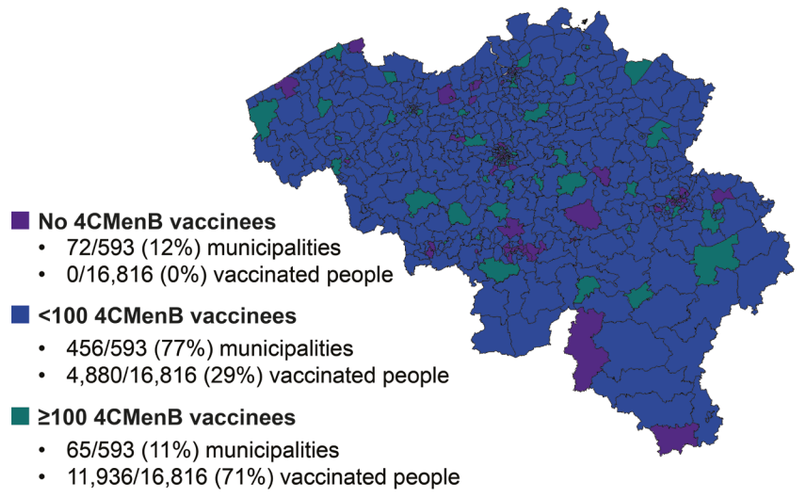
This retrospective, ecological study used data captured in longitudinal prescriptions and sociodemographic databases to obtain information on vaccine uptake, individual's age, location and household income level. Belgium is divided into three regions, 11 provinces (including Brussels) and 589 municipalities. All analyses were performed at a municipality level. Where municipalities are named, general description of municipalities may not align with the formal name due to the municipality granularity level used to map data to territories.

### *Longitudinal prescriptions data panel: Vaccine uptake, age and location*

Vaccine uptake information, along with the age and location of vaccinees, were sourced from a national IQVIA sell-out database. This longitudinal prescriptions data panel contains patient-level information on what is dispensed by pharmacists to patients and collects information on approximately 30% of retail pharmacies (both chain and privately-owned pharmacies) in Belgium.

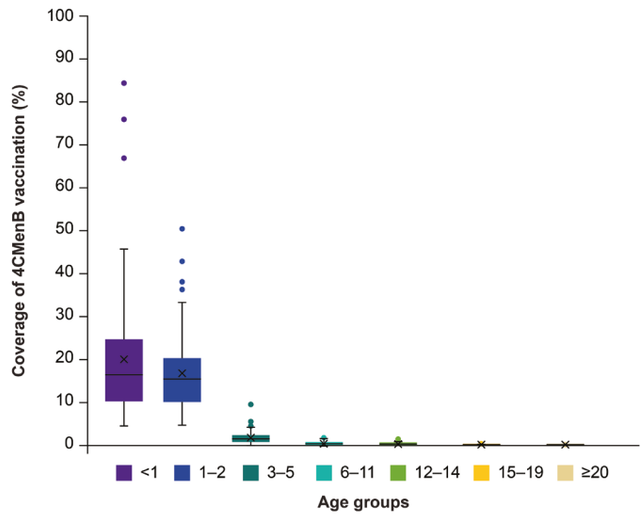
The panel contains metrics on the product, the patient and the prescriber, throughout time, as follows. Metrics on the product, i.e., what is dispensed by pharmacies, informed vaccine uptake data. The age of patients was not available from the database, but individuals' year of birth could be obtained. Posteriori analyses of patients' age range was obtained via a trusted third-party anonymisation process. At least 100 individuals per municipality were required for precise age determination. Age was aggregated to seven age classes based on age at first vaccination: <1 year, 1–2 years, 3–5 years, 6–11 years, 12–14 years, 15–19 years, ≥20 years. Age was rounded to the year (e.g., an individual aged 2.5 years would be classed as 2 years and belong to the 1–2 years age class). The municipality of the vaccination prescriber was used as a proxy to assign a municipality to the vaccinated individual, as an individual's municipality was not provided in the database to maintain data privacy. If an individual had more than one prescriber, the municipality of the first 4CMenB prescription was used.

**Figure 1**: Estimated 4CMenB coverage in Belgium between November 2022 and October 2023.




Municipalities with ≥100 4CMenB vaccinees were further analysed in this study.

**Figure 2**: Distribution of 4CMenB vaccinated population per municipality by age class.




Variation of vaccinated population per municipality, by age group; box plots show mean, median (interquartile range), minimum and maximum 4CMenB vaccination coverage

### *Sociodemographic database: Household income level*

The sociodemographic database contains detailed information regarding the number of inhabitants and households, their distribution by age class and type of household (e.g, household size and property type). It also contains overall indicators (composite scores) of income, age (of the eldest member of a household) and type of housing. These sociodemographic data are obtained via a trusted third-party that aggregated data at a granular level. These aggregated data were then mapped to the Belgian municipality level. The indicator of income is a composite index and was calculated by aggregating wealth and income variables, normalised so that mean (standard deviation) at the municipality level was 100 (10). Income level ranged from 75 (lowest income indicator) to 140 (highest income indicator). The income indicator is a well-established proxy for the actual level of income, which is not directly available from the database.

### *Patient population and municipality selection*

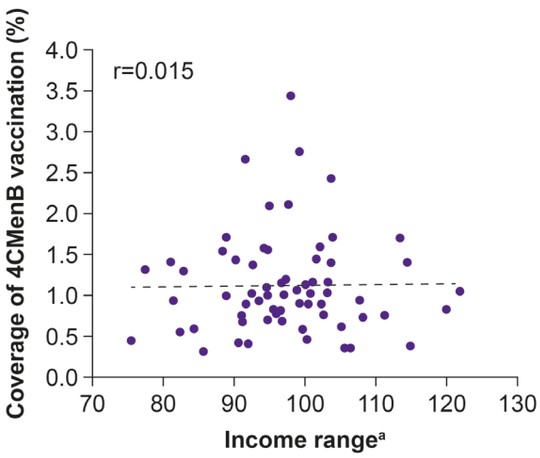
Individuals with either only one or more than three doses of 4CMenB were excluded from this analysis. From November 2022 to October 2023, all individuals with two doses and those aged ≤2 years with three doses within a year were included in the vaccinated population. Due to anonymisation requirements only municipalities with at least 100 vaccinated individuals (two or three doses of 4CMenB) were analysed.

### *Descriptive and statistical analysis*

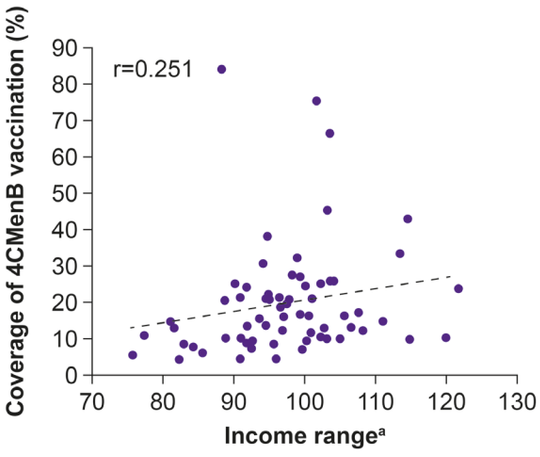
4CMenB coverage at a municipality level was calculated as the percentage of 4CMenB vaccinated individuals out of the total municipality population. Coverage for a specific age class was calculated as the proportion of 4CMenB vaccinated individuals out of the total municipality population in the same age class. 4CMenB coverage per age class and per household income level was assessed via descriptive statistical analysis. A correlation analysis was performed to estimate the association between 4CMenB coverage and household income in the overall population and per age

**Figure 3**: Correlation analysis showing 4CMenB coverage versus household income for different age classes.

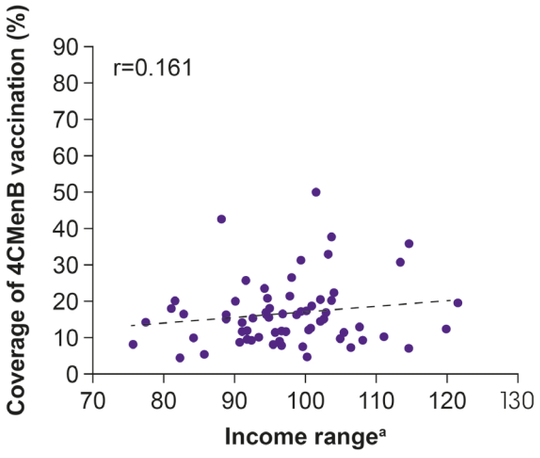
**3A.** All ages




**3B.** Aged <1 year




**3C.** Aged 1–2 years




a: following aggregation at a municipality level, income level was rescaled to have a score of 100 on average, with 75 being the lowest income indicator and 140 being the highest income indicator.

class. A logistic regression modelling approach was implemented to assess the association between 4CMenB coverage by age and household income. Significant effects were measured using the likelihood-ratio test of significance of effects, with a 5% significance level.

### *Objective*

The primary objective of this analysis was to estimate 4CMenB coverage at a municipality level in Belgium – overall, per age class and per income level. The secondary objective of this analysis was to estimate the association between 4CMenB coverage, age and household income level at a municipality level in Belgium.

## Results

### *4CMenB coverage*

Of the 16,816 individuals who had received two to three doses of 4CMenB and were therefore eligible for assessment, 71% (n=11,936) were concentrated within 11% (65/593) municipalities across Belgium. Most municipalities (77%) contained <100 vaccinated individuals and 12% of municipalities contained no individuals vaccinated with 4CMenB (Figure 1). These municipalities were not further analysed. The 65 municipalities further assessed in this study, each containing ≥100 vaccinated individuals, were assessed as representative of all Belgian municipalities according to distribution across Belgium, age and income level. Approximately 50% of analysed municipalities were in Flanders, 40% in Wallonia and 10% in Brussels, which aligns with the regional spread of all municipalities. Average national income level had a composite score of 100 and the analysed municipalities had a similar median composite score of roughly 95.

4CMenB coverage was highest in the two youngest age classes (<1 year: 16%; 1–2 years: 14%), with coverage decreasing significantly with age and reaching <0.5% in those aged ≥12 years. For those aged <1 year and 1–2 years, 4CMenB vaccination coverage varied significantly between the municipalities (Figure 2).

### *Association between 4CMenB coverage, age and household income*

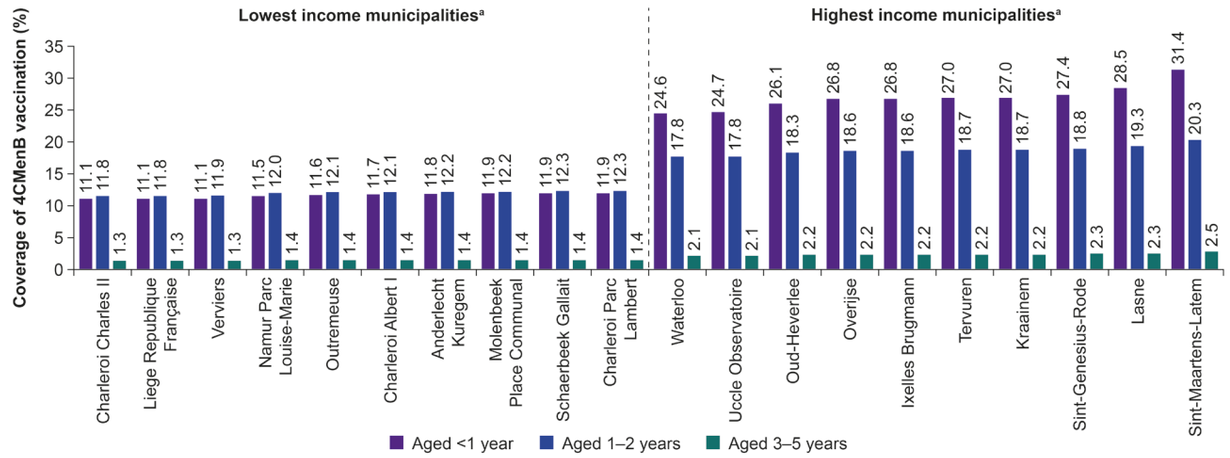
No overall correlation was observed between household income and Belgian 4CMenB coverage across municipalities (r=0.015, 95% CI: -0.230–0.258 for selected municipalities; Figure 3A). However, when analysing the specific age classes, there was a mild positive correlation between 4CMenB coverage and household income for those aged <1 year (r=0.251, 95% CI: 0.008–0.466, p<0.001) and 1–2 years (r=0.161, 95% CI: -0.088–0.388, p<0.001; Figure 3B and 3C) in analysed municipalities. For higher age groups, 4CMenB coverage was not correlated with household income level (r=0.156, 95% CI: -0.092–0.385, p=0.005 for the 3–5 years age class), partially due to low sample size.

When using the logistic regression model within the 65 individual municipalities, both age and income level had a statistically significant effect on 4CMenB coverage (p<0.001). There was also a significant relationship between age (across 0–11 years) and household income, with strong statistical confidence in this result (p=0.002); this association was particularly pronounced in the <1 year and 1–2 years age groups (p<0.001).

Furthermore, vaccine coverage in the 10 lowest income municipalities and the 10 highest income municipalities was estimated. The logistic regression model estimated that 4CMenB coverage for individuals aged <1 year was 11.1–11.9% in the lowest income municipalities and 24.6–31.4% in the highest income municipalities (Figure 4).

When extrapolating data at a national level, the logistical regression model also predicted that 4CMenB coverage among those aged <1 year was lowest in Southern Belgium and in main city centers. 4CMenB coverage was highest in the areas surrounding Brussels, Ghent and Antwerp (Figure 5A), with higher vaccination coverage shown in Figure 5A mapping roughly onto areas of higher income indicator (Figure 5B). The distribution of 4CMenB coverage becomes increasingly uniform as

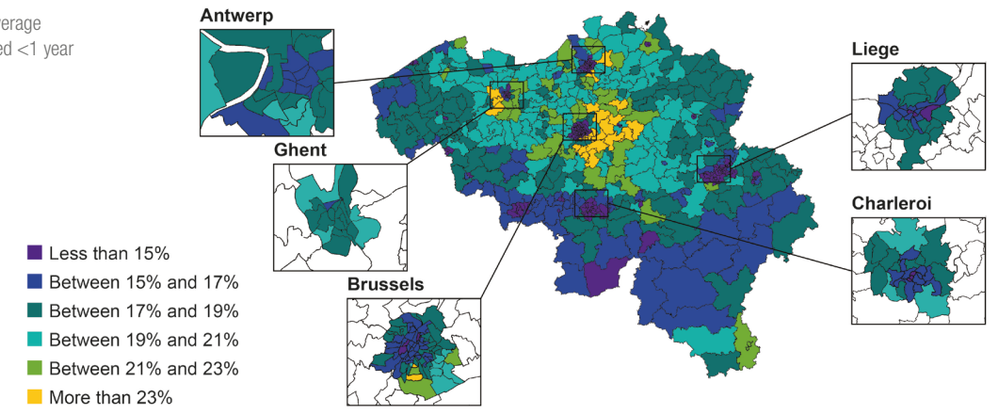
**Figure 4**: Logistical regression analysis estimating 4CMenB vaccination coverage across the 10 lowest and 10 highest income municipalities.



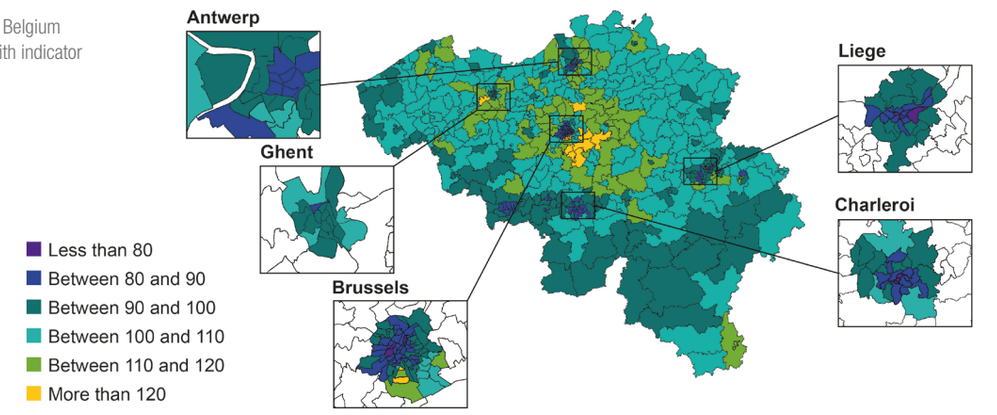

a: General descriptions of municipalities were based on a 593 granularity level, which may not align entirely with formal commune name.

**Figure 5**: Predicted 4CMenB vaccination coverage among those aged <1 year and indicator of income for municipalities.

**5A**: 4CMenB coverage among those aged <1 year




**5B**: Overview of Belgium municipalities with indicator of income




The indicator of income was calculated by aggregating wealth and income variables, normalised so mean (standard deviation) was 100 (10) at the municipality level. Income level ranges from 75 (lowest income indicator) to 140 (highest income indicator).

you move up the age classes, with the 3–5 years age class showing the most even distribution across assessed municipalities.

## Discussion

This is the first study to analyse the correlation between 4CMenB coverage, age and household income level at a municipality level in Belgium. 4CMenB coverage was highest in those aged <1 year and 1–2 years and a statistically significant, positive correlation between 4CMenB coverage and household income was observed for individuals of these ages. This suggests potential inequity in vaccine access at a municipality level in Belgium for those aged <1 year and 1–2 years.

This analysis shows that over 70% of vaccinated individuals are concentrated in just 11% of Belgian municipalities; these municipalities include large cities and so are likely to have higher populations and more vaccinated individuals than other, potentially smaller, municipalities.

In Belgium, the socioeconomic status of families may impact the decision to vaccinate children, particularly with non-publicly funded vaccinations. The positive correlation between MenB coverage and household income observed in this study at a municipality level has also been seen at a provincial level. A study of 2020 vaccination coverage in Flanders showed that children aged 18–24 months from families with an income lower than €3,000 per month were more often incompletely vaccinated against MenB compared with children from families with an income greater than €3,000 (19). A similar trend was also seen with the publicly funded COVID-19 vaccine, with lower uptake of the first dose observed in socioeconomically disadvantaged adults in Belgium (20). Parallels can be seen when looking at the risk of IMD. In France, individuals with a low income are at an increased risk of hospitalisation due to IMD compared with high income individuals, reinforcing the importance of MenB vaccination in populations with a lower income (18).

The higher levels of 4CMenB coverage for the two youngest age classes (<1 year and 1–2 years) compared with the older age classes confirm that paediatricians and general practitioners follow the recommendations of the Belgian Superior Health Council. These recommendations stipulate the best vaccination schedule against MenB is at 8 and 16 weeks, with the third booster dose given between 11 and 14 months, as a high percentage of cases occur before 6 months (8). Despite the recommendations in Belgium, 4CMenB coverage among individuals aged 15–19 years included in this analysis was less than 0.5%. Vaccine uptake and hesitancy in the adolescent population is a known issue and is likely due to a number of reasons, such as adolescents having fewer preventative healthcare visits than infants (21). This holds especially true in non-reimbursed settings and where infrastructure to vaccinate adolescents is lacking. The European Program of Work 2020–2025 of the World Health Organization, which details health priorities for the next five years, has been criticised by the European Academy of Pediatrics for lacking strategies that specifically improve the health of children and adolescents (22, 23). Given adolescent vaccination levels are lower than infant levels and adolescents appear to be overlooked in some policies, universally recommended freely-available vaccination could be key to increasing vaccination coverage and improving the health of all ages. This may also explain why no overall correlation between 4CMenB coverage and household income level was observed. Nearly 80% of individuals in the 65 selected municipalities were aged ≥20 years and 4CMenB coverage in this age group was less than 0.5%. Therefore, the lack of association observed between 4CMenB coverage and household income for older ages is potentially limited by a smaller sample size of vaccinated individuals in these age groups.

Despite the 2019 MenB notification rate in Belgium being similar to or higher than countries where MenB vaccination is publicly funded (United Kingdom and Italy), MenB is not included in any regional immunisation programs in Belgium (24-26). Having 4CMenB as a universally recommended, publicly funded vaccine could reduce inequity in access to 4CMenB and therefore reduce the incidence of MenB in Belgium.

This analysis was associated with some limitations. Firstly, the data panel used for vaccine uptake information represents approximately 30% of Belgian pharmacies and so not all 4CMenB vaccinations were captured. This analysis is also significantly limited by selection bias. Due to anonymisation requirements, only municipalities with ≥100 4CMenB vaccinees were analysed. However, the sample of municipalities used in this study was assessed as representative of the general Belgian population according to distribution across Belgium, age and income level. Thirdly, this analysis only looks at household income as an indicator for socioeconomic status. Factors shown to influence vaccine uptake, such as education and literacy level, were not investigated (20). Additionally, the type and quality of pre-vaccination information provided by healthcare workers, a known key determinant of vaccine uptake, was not assessed. Furthermore, communication regarding vaccine recommendations differs between Belgian regions, which may have independently impacted vaccine coverage. Differences observed between correlation analysis and logistic regression analysis when assessing coverage and age/income level (e.g., effects in older age groups) were caused by the regression analysis testing effects simultaneously, instead of independently. Finally, the location of the prescribing healthcare professional is used as a proxy for patient location, meaning patients may be wrongly allocated to the municipality of their prescriber, while living elsewhere. However, checks prior to this study have shown that such bias is somewhat limited and compensates for each other (i.e., incorrect patient allocation is symmetrical for two municipalities).

## Conclusion

Only a small number of Belgian municipalities contained ≥100 vaccinated individuals and 4CMenB coverage in these municipalities was highest in individuals aged <1 and 1–2 years. For individuals aged 0–11 years, higher household income correlated with higher 4CMenB coverage when looking at the individual municipality level, with a more pronounced effect in the <1 year and 1–2 years age groups. Indeed, in the highest income municipalities analysed, individuals aged <1 year, 1–2 years and 3–5 years were approximately two times more likely to be vaccinated than in the lowest income municipalities. The availability of 4CMenB only in the private sector may contribute to inequity in vaccination access, potentially placing low-income populations in Belgium at an increased risk of IMD. A universal vaccine recommendation, high quality pre-vaccine information from healthcare professionals and inclusion of 4CMenB into Belgium's regional immunisation programs to make the vaccine free of charge could decrease the current inequity in 4CMenB coverage observed in children <2 years of age in Belgium. Although the results of this study indicate inequity in access to 4CMenB vaccination in Belgium, the study has limitations and additional analyses are required to confirm results, such as those investigating additional parameters impacting vaccination uptake. Moreover, conducting a precise cost-effectiveness analysis of the 4CMenB vaccine is crucial to reflect the disease's lifetime impact.

## Data sharing statement

Data used for this publication was generated by IQVIA. For access to anonymised subject level data, please contact IQVIA.


## Acknowledgements

The authors thank Costello Medical for editorial assistance and publication coordination, on behalf of GSK, and acknowledge Hannah Russell, MSci, for medical writing and editorial assistance based on authors' input and direction.

## Funding

This study was sponsored by GSK (VEO-000667). Support for third-party writing assistance for this article, provided by Hannah Russell, Costello Medical, UK and Poppy Wilson, Costello Medical, UK was funded by GSK in accordance with Good Publication Practice (GPP 2022) guidelines (https://www.acpjournals.org/doi/10.7326/M22-1460).


## Conflicts of interest

GN, AGA, AM and FS: employees of and hold financial equities in GSK; KB: employee of GSK; DM and CV: employees of IQVIA; BB: received consultancy fee for the present study; WM: received a research grant from GSK and Pfizer for vaccine coverage of meningococcal B strains; MR: no conflicts of interest reported.

REFERENCES

# Regional inequity in 4CMenB vaccination coverage in Belgium: A retrospective ecological study

Georgios Nikitas, Andrew G. Allmon, Anne Meulemans, Kathleen Billiaert, Florence Strubbe, David Magis, Christiane Vogel, Benoit Brasseur, Wesley Mattheus, Marc Raes

**In Belgium, meningococcal serogroup B is the most common form of invasive meningoccocal disease**

The 4CMenB vaccine, which protects against meningitis B (MenB), is recommended for children aged 2 months to 5 years, adolescents aged 15 years to 19 years and high-risk groups in Belgium

Despite these national recommendations, the 4CMenB vaccine is not a publicly funded vaccine in Belgium

**This study aimed to answer:**

**How 4CMenB vaccination coverage is distributed across Belgian municipalities**

**What the relationship is between 4CMenB vaccine coverage, age and household income**

**Information was sourced from two databases:**

| Sociodemographic database | Longitudinal prescriptions database |
|---|---|
| Level of household income | 4CMenB doses; Year of birth; Municipality (Database granularity level meant data were mapped to 593 municipalities) |

**Individuals with 2 to 3 doses of 4CMenB vaccine were included**

**The following was observed from the 16,816 4CMenB vaccinees identified:**

**Vaccine coverage**

**71%** of vaccinees were concentrated within **65 Belgian municipalities** (11%)

These 65 municipalities were further analysed

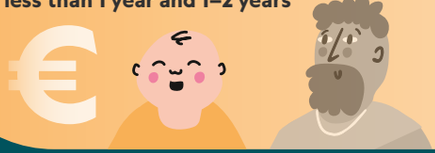
**Vaccine coverage and household income**

**Vaccine coverage and age**

4CMenB vaccine coverage was **highest** in those aged

| <1 year | 1–2 years |
|---|---|
| 16% | 14% |

4CMenB vaccine coverage **correlated with household income** only for those aged **less than 1 year and 1–2 years**



Municipalities with the **lowest average household income** had **lower 4CMenB vaccine coverage** rates than municipalities with the **highest average household income**

| | <1 year | 1–2 years |
|---|---|---|
| ▼ | 12% | 12% |
| ▲ | 27% | 19% |

**4CMenB not being a publicly funded vaccine in Belgium may contribute to inequity in vaccine access**

**The potential inclusion of the 4CMenB vaccine in Belgian regional immunisation programs could help reduce this inequity**

1. Stein-Zamir C, Shoob H, Abramson N, Block C, Keller N, Jaffe J, et al. Invasive meningococcal disease epidemiology and characterization of Neisseria meningitidis serogroups, sequence types, and clones; implication for use of meningococcal vaccines. Hum Vaccin Immunother. 2019;15(1):242-8.
2. World Health Organization. Meningitis. Geneva, Switzerland: WHO; 2023 [cited 2024 July 26]. Available from: https://www.who.int/news-room/fact-sheets/detail/meningitis.
3. World Health Organization. Meningitis 2024 [Available from: https://www.who.int/health-topics/meningitis#tab=tab_1.
4. European Centre for Disease Prevention and Control. Invasive meningococcal disease. Annual Epidemiological Report for 2022; 2024. [cited 2024 July 26]:[12 p.]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/invasive-meningococcal-disease-annual-epidmeiological-report-2022.pdf.
5. Jacquinet S, Mattheus W. Surveillance épidémiologique des infections invasives à méningocoques, Neisseria Meningitidis - 2022; Brussels, Belgium: Sciensano; 2023 [cited 2024 July 26]. Sciensano. [Available from: https://www.sciensano.be/sites/default/files/epidemiologische_surveillance_van_invasieve_meningokokkeninfecties_neisseria_meningitidis_-_2022.pdf.
6. Sciensano. Infoblad Meningokokkeninfecties: Jaar 2023 nr 1, 4de trimester Brussels, Belgium: Sciensano 2023 [cited 2024 July 26]. Available from: https://www.sciensano.be/sites/default/files/t4_2023_sciensano_2.pdf.
7. European Medicines Agency. Bexsero. Amsterdam, The Netherlands: EMA 2018 [cited 2024 July 26]. Available from: https://www.ema.europa.eu/en/documents/overview/bexsero-epar-summary-public_en.pdf.
8. Conseil Supérieur de la Santé. Vaccination contre le méningocoque. Brussels, Belgium: FPS Public Health; 2019 [cited 2024 July 26]. Available from: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/css_9485_vaccination_contre_le_meningocoque_update.pdf.
9. Hoge Gezondheidsraad. Vaccinatie van Personen met Risico op Meningokokkeninfectie. Brussels, Belgium: FPS Public Health; 2023 [cited 2024 July 26]. Available from: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/20231019_hgr-9759_vaccinatie_van_personen_met_risico_op_meningokokkeninfectie_vweb.pdf.
10. European Medicines Agency. Trumenba. Amsterdam, The Netherlands: EMA 2017 [cited 2024 July 26]. Available from: https://www.ema.europa.eu/en/documents/overview/trumenba-epar-summary-public_en.pdf.
11. Sohn WY, Tahrat H, Novy P, Bekkat-Berkani R. Real-world implementation of 4-component meningococcal serogroup B vaccine (4CMenB): implications for clinical practices. Expert Rev Vaccines. 2022;21(3):325-35.
12. Haute Autorité de Santé. Calendrier des vaccinations 2024. Paris, France: Ministère du Travail, de la Santé et des Solidarités; 2024 [cited 2024 July 26]. Available from: https://sante.gouv.fr/IMG/pdf/calendrier_vaccinal_avr2024.pdf.
13. Sante.lu. Meningitis and invasive meningococcal infections. Luxembourg, Luxemburg: Ministère de la Santé; 2023 [cited 2024 July 26]. Available from: https://sante.public.lu/fr/espace-professionnel/recommandations/conseil-maladies-infectieuses/meningite.html.
14. Bundesamt für Gesundheit. Schweizerischer Impfplan 2024. Bern, Switzerland: BAG; 2024 [cited 2024 July 26]. Available from: https://www.bag.admin.ch/bag/de/home/gesund-leben/gesundheitsfoerderung-und-praevention/impfungen-prophylaxe/schweizerischer-impfplan.html.
15. Ständigen Impfkommision. Empfehlung zur Standardimpfung von Säuglingen gegen Meningokokken der Serogruppe B. Epidemiologisches Bulletin [Internet]. 2024 [cited 2024 July 26]; (3):[3-4 pp.]. Available from: https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2024/Ausgaben/03_24.pdf?__blob=publicationFile.
16. Taha M-K, Martinon-Torres F, Köllges R, Bonanni P, Safadi MAP, Booy R, et al. Equity in vaccination policies to overcome social deprivation as a risk factor for invasive meningococcal disease. Expert Rev Vaccines. 2022;21(5):659-74.
17. Carmo M, Callejo D, Pérez A, Vallejo-Aparicio L, García A, Rodríguez R, et al. The relationship between income per capita and access to meningococcal serogroup B vaccination in Spain: an ecological correlation study. Economía de la Salud. 2022;17:35-46.
18. Taha M-K, Weil-Olivier C, Bouée S, Emery C, Nachbaur G, Pribil C, et al. Risk factors for invasive meningococcal disease: a retrospective analysis of the French national public health insurance database. Hum Vaccin Immunother. 2021;17(6):1858-66.
19. Maertens K, Willen L, Van Damme P, Roelants M, Guérin C, de Kroon M, et al. Studie van de vaccinatiegraad in Vlaanderen 2020. Brussels, Belgium: Vlaams Agentschap Zorg en Gezondheid; 2022 [cited 2024 July 26]. Available from: https://www.laatjevaccineren.be/vaccinatiegraadstudie.
20. Cavillot L, Van Loenhout J, Catteau L, Van den Borre L, De Pauw R, Blot K, et al. COVID-19 vaccination uptake in Belgium: socioeconomic and sociodemographic disparities. Eur J Public Health. 2022;32(Supplement_3).
21. English A, Middleman AB. Adolescents, Young Adults, and Vaccine Hesitancy: Who and What Drives the Decision to Vaccinate? Pediat Clin N. 2023;70(2):283-95.
22. World Health Organization. European Programme of Work 2020–2025. Geneva, Switzerland: WHO; 2021 [cited 2024 July 26]. Available from: https://iris.who.int/bitstream/handle/10665/339209/WHO-EURO-2021-1919-41670-56993-eng.pdf?sequence=1&isAllowed=y.
23. Jansen D, Brenner M, Illy K, Dembinski Ł, Del Torso S, Grossman Z, et al. Leave no one behind: why WHO's regional office for Europe should prioritise children and adolescents in their program of work. A position statement from the European academy of paediatrics. Front Pediatr. 2023;11:1184870.
24. Pinto Cardoso G, Lagrée-Chastan M, Caseris M, Gaudelus J, Haas H, Leroy JP, et al. Overview of meningococcal epidemiology and national immunization programs in children and adolescents in 8 Western European countries. Front Pediatr. 2022;10:1000657.
25. Joint Committee on Vaccination and Immunisation. JCVI position statement on use of Bexsero® meningococcal B vaccine in the UK 2024 [cited 2024 July 26]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/294245/JCVI_Statement_on_MenB.pdf.
26. Signorelli C, Chiesa V, Odone A. Meningococcal serogroup B vaccine in Italy: state-of-art, organizational aspects and perspectives. J Prev Med Hyg. 2015;56(3):E125-32.

# 1 BÉBÉ SUR 2 PRÉSENTERA AU MOINS UN TROUBLE GASTRO-INTESTINAL FONCTIONNEL AVANT L'ÂGE DE 6 MOIS.[1]

# UN CHOIX QUI VOUS RESSEMBLE.


**Important:** L'allaitement maternel est l'alimentation idéale pour les bébés. Informations destinées exclusivement au corps (para)médical. Nutrilon® Omneo est une denrée alimentaire destinée à des fins médicales spéciales. Pour les besoins nutritionnels en cas de crampes, coliques, selles dures et régurgitations légères. À utiliser sous supervision médicale.
Nutrilon® A.R. est une denrée alimentaire destinée à des fins médicales spéciales. Pour les besoins nutritionnels en cas de reflux et régurgitations. À utiliser sous supervision médicale.
Référence: 1. Iacono G, et al. Dig Liver Dis. 2005;37:432-8.

Nutrilon®

# Antibiotics Post-Appendectomy in Pediatric Patients

## A Literature Review Leading to Proposition of a New Treatment Protocol

Charlotte Goovaerts [a], Marc Miserez [b], Karen van Hoeve [a], Ilse Hoffman Ilse [a]

[a] Department of Pediatric gastroenterology & Hepatology & Nutrition, University Hospitals Leuven, Leuven, Belgium
[b] Department of Abdominal Surgery, University Hospital Leuven, Leuven, Belgium

charlotte.goovaerts@uzleuven.be

## Keywords

Acute appendicitis ; pediatric population ; children ; postoperative antibiotics ; protocol ; antibiotic treatment.

## Abstract

Although acute appendicitis is a common occurrence in the pediatric population, there is still considerable debate surrounding the optimal postoperative antibiotic treatment. Currently, there is a lack of a clear, evidence-based protocol for postoperative treatment.

The objective of this review is to develop a protocol for postoperative antibiotic treatment in children with acute appendicitis. By introducing this protocol, we aim to establish a more straightforward policy and avoid overtreatment with antibiotics.

## Introduction

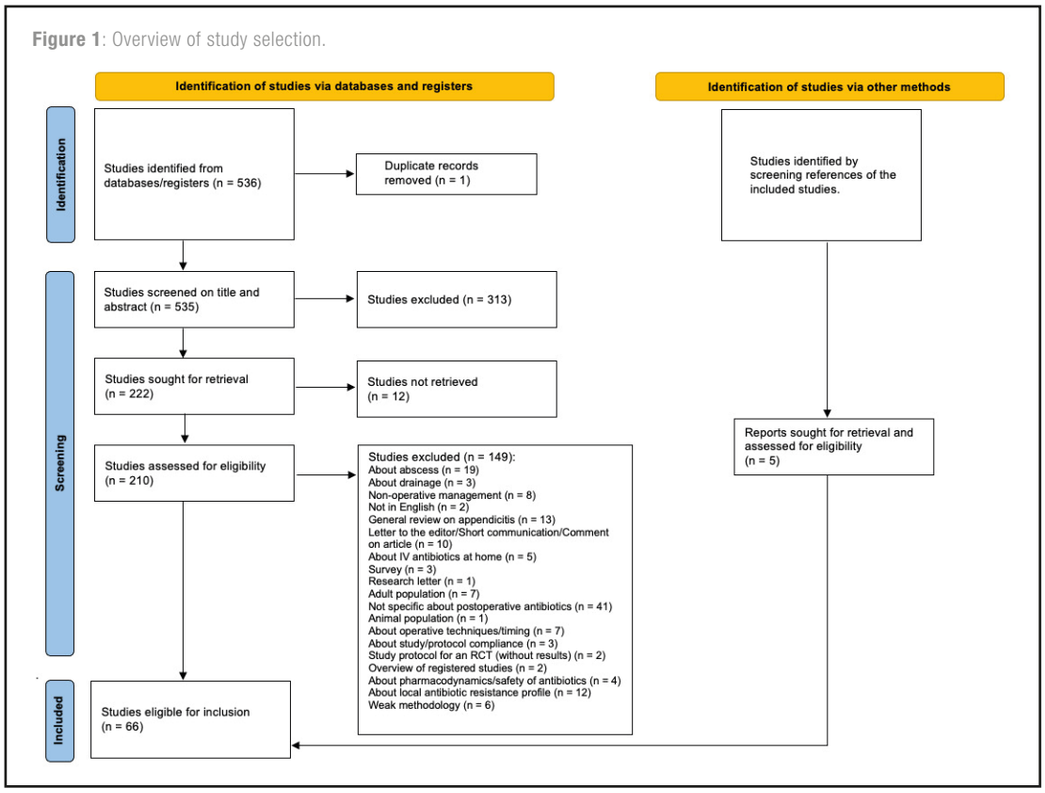
Acute appendicitis (AA) is a common surgical presentation with a lifetime incidence of 9% (1). Despite being one of the most common reasons for abdominal surgery in pediatric patients, there is a wide variation management. In general, AA is treated with appendectomy, followed by antibiotics in the case of complicated appendicitis.

The indication and the optimal duration of postoperative antibiotics for AA still pose significant ambiguity, as described in the 2015 European Association of Endoscopic Surgery (EAES) consensus document, where the duration of antibiotic treatment varied between 3, 5, 7, and 10 days. They also stated that the evidence regarding the duration of postoperative antibiotic treatment is limited (2).

The World Society of Emergency Surgery (WSES) recommends transitioning to oral administration of postoperative antibiotics after 48 hours, advocating for a total treatment duration of less than 7 days (3). However, they do not provide specific guidance on duration based on classification or define parameters for discontinuation.

Experience has shown that treatment is often based on the preference of the treating physician. Therefore, we aimed to create a protocol for antibiotic use after appendectomy in the pediatric population based on the most recent literature.

**Figure 1**: Overview of study selection.




## Methods

### *Exclusion and inclusion criteria*

Only studies reporting on postoperative antibiotic treatment of acute appendicitis in children (< 18 years) written in Dutch or English were included. Randomized controlled trials, pro- and retrospective studies, (systematic) reviews and international guidelines were included. Articles describing planned postoperative treatment were included whereas studies describing

prolonged treatment due to postoperative complications (such as surgical site infections) were excluded.

We excluded letters to the editor, comments on articles, surveys or research letters.

Studies describing a conservative antibiotic treatment approach without appendectomy were not included. Patients with an appendicular mass at first presentation were also excluded, since in these cases different approaches are possible depending on disease duration and clinical signs (appendectomy, conservative treatment with antibiotics, percutaneous drainage) and this was beyond the scope of this review.

### *Literature search*

To identify potential studies and guidelines, a literature search was performed according to the PRISMA guidelines in Pubmed (Figure 1) using the Medical Subject Heading (MeSH) terms 'acute appendicitis AND (pediatric OR children OR child) AND (antibiotics OR antibiotic) AND (postoperative OR appendectomy OR surgery).

To include the most recent literature, we decided to review publications from the last 11 years from 01/08/2012 to 01/03/2024. Duplicates were removed using Covidence.

An overview of the study selection is shown in Figure 1.

Our literature search identified 61 studies eligible for inclusion. By screening references of the included studies, 5 additional articles were added. Details of these studies are provided in the supplementary table.

## Results

### *Classification*

By reviewing the literature, we noted a great variability in the classification of AA. In general, everyone agrees that AA is a continuum from an inflamed appendix to perforated appendicitis with generalized peritonitis.

An inflamed appendix is classified as simple or uncomplicated/noncomplicated appendicitis and perforated appendicitis as complex or complicated appendicitis. However, the so-called intermediate forms, such as gangrenous appendicitis (GA), are perceived differently by different studies.

The WSES updated the Jerusalem Guidelines on diagnosis and treatment of AA in 2020. They recommend using an intra-operative grading system for AA. A grading system can help to identify homogeneous groups of patients and assist in determining the optimal postoperative management according to the grade of the disease (3).

Two validated classifications systems are available: the grading system proposed by Gomes and the Anatomic Severity of Disease Grading System for Acute Appendicitis by the American Association for the Surgery of Trauma (AAST) (4,5). Both grading systems are based on clinical, imaging and operative findings and have been validated in prospective, observational studies. An overview of these classifications is shown in Table 1.

Gomes further divides AA in non-complicated AA, grade 0 and grade 1, and complicated AA, grades 2 to 4 (4). The AAST does not make this distinction but remarks an increasing complication rate associated with the severity grade (5).

The classification systems proposed by Gomes and the AAST do not specifically take into account the purulent/suppurative appendix lacking signs of perforation, which we believe warrants inclusion. A multicenter analysis by Cramm showed that presence of gangrenous, suppurative or exudative changes of a nonperforated appendix was associated with an increased risk of organ space infections and prolonged postoperative length of stay (6). Do-Wyeld also describes advanced appendicitis as gangrenous or suppurative appendicitis without perforation (7).

To address this gap, we suggest the classification outlined in Table 2.

We decided not to divide AA into uncomplicated and complicated appendicitis because of the heterogeneous definitions of (un)complicated appendicitis. We will use the grading classification described in Table 2 since it clearly describes the surgical findings and the continuum of severity of AA.

As mentioned before, in this paper we will not discuss appendicitis presenting with a phlegmon or abscess (grade 4) since this was beyond the scope of this review. We do acknowledge that for a complete treatment protocol, a specific literature search on these subtypes should be done.

### *Duration and administration of antibiotics*

Based on the aforementioned literature review, we made a proposition for duration for antibiotic therapy for the different subtypes of AA. An overview of the protocol is shown in Figure 2.

#### Grade 1: Simple, acutely inflamed appendix

While there was one article suggesting that 2 postoperative doses of antibiotics can reduce postoperative wound infections, there exists a widespread consensus supporting a single preoperative dose of prophylactic antibiotics, with no indication for postoperative antibiotic administration (8). Antibiotics should be administered within 60 minutes prior to skin incision (2,3,9,10). Hospital discharge should be scheduled within 24 hours after surgery.

#### Grade 2: Purulent appendicitis

Our comprehensive literature review unveiled a paucity of articles addressing this particular type of AA, with treatment protocols varying from no intervention to a total duration of 7 days (7,11,12). Although suppurative changes in a nonperforated appendix were associated with

**Table 1**: Overview of the grading systems by Gomes (4) and the AAST (5).

| | Grading by Gomes (4) | AAST Grading System (5) |
|---|---|---|
| **Grade 0** | Normal looking appendix (Endoappendicitis/Periappendicitis) | |
| **Grade 1** | Inflamed appendix (hyperemia, edema, ± fibrin without or little pericolic fluid) | Intact but acutely inflamed appendix |
| **Grade 2** | Necrosis<br>A – Segmental necrosis (without or small amount of pericolic fluid)<br>B – Base necrosis (without or small amount of pericolic fluid) | Intact but gangrenous appendix |
| **Grade 3** | Inflammatory tumor<br>A – Phlegmon<br>B – Abscess less than 5 cm without peritoneal free air<br>C – Abscess over 5 cm without peritoneal free air | Perforated appendix with local contamination |
| **Grade 4** | Perforated – Diffuse peritonitis with or without peritoneal free air | Perforated appendix with peri-appendiceal phlegmon or abscess |
| **Grade 5** | | Perforated appendix with generalized peritonitis |

**Table 2**: Classification of subtypes of appendicitis.

Our classification on which we further base our treatment protocol. It is based both on the grading system of Gomes (4) and the AAST (5) with inclusion of suppurative appendicitis.

| | |
|---|---|
| **Grade 1** | Simple – inflamed appendicitis: intact, hyperemic, edemic appendix |
| **Grade 2** | Purulent appendicitis with or without purulent fluid: thickened, yellowish discoloration of the appendix, no signs of perforation, with or without purulent liquid adjacent to the appendix, not extending to other intra-abdominal quadrants |
| **Grade 3** | Gangrenous appendicitis: appendiceal wall necrosis, no signs of macroscopic perforation |
| **Grade 4** | Inflammatory tumor<br>• A – Phlegmon<br>• B – Abscess |
| **Grade 5** | Perforated appendicitis: visible hole in the appendix, intraperitoneal faecolith<br>• A - With localized peritonitis: peritonitis/contamination in the right lower quadrant and/or pelvis<br>• B – With generalized peritonitis: peritonitis/contamination outside the right lower quadrant and pelvis |

an increased risk of organ space infection and prolonged hospital stay in a large retrospective study, the complication rate after withdrawal or limiting of postoperative antibiotics to 24 hours from the clinical pathway remained the same even in two prospective studies with gangrenous appendicitis (6,13,14).

Most studies try to facilitate discharge and minimize resource usage, yet some set ambitious treatment goals, as seen in the approach of Do-Wyeld et al., who treated all the advanced forms of AA, including suppurative AA, for a duration of 7 days (7). This seems however largely overshooting since this is a longer treatment duration compared to the treatment of some patients with a perforated appendicitis, which we will discuss below. Contrary to this, a retrospective study showed that adhering to 48 hours of postoperative antibiotics for purulent appendicitis, did not increase the risk of infectious complications in comparison to longer treatment durations (11) . Also, Cunningham subdivides suppurative appendicitis as uncomplicated appendicitis and thereby implies to not treat it with antibiotics (12). This is in line with recent literature where a propensity-matched study showed that postoperative antibiotics could be omitted. The study could not show a significant difference rate of surgical site infections (both incisional surgical site infections as organ space infections) between patients who did or did not receive postoperative antibiotics (15).

Since postoperative antibiotics were not associated with a clinically meaningful reduction in rates of surgical site infections, nor omitting of postoperative antibiotics results in an increase of surgical site infections, we decided to not treat this subgroup of appendicitis with postoperative antibiotics. We aim for discharge within 24hours after surgery as for the simple, acutely inflamed appendix.

### Grade 3: Gangrenous appendicitis (GA)

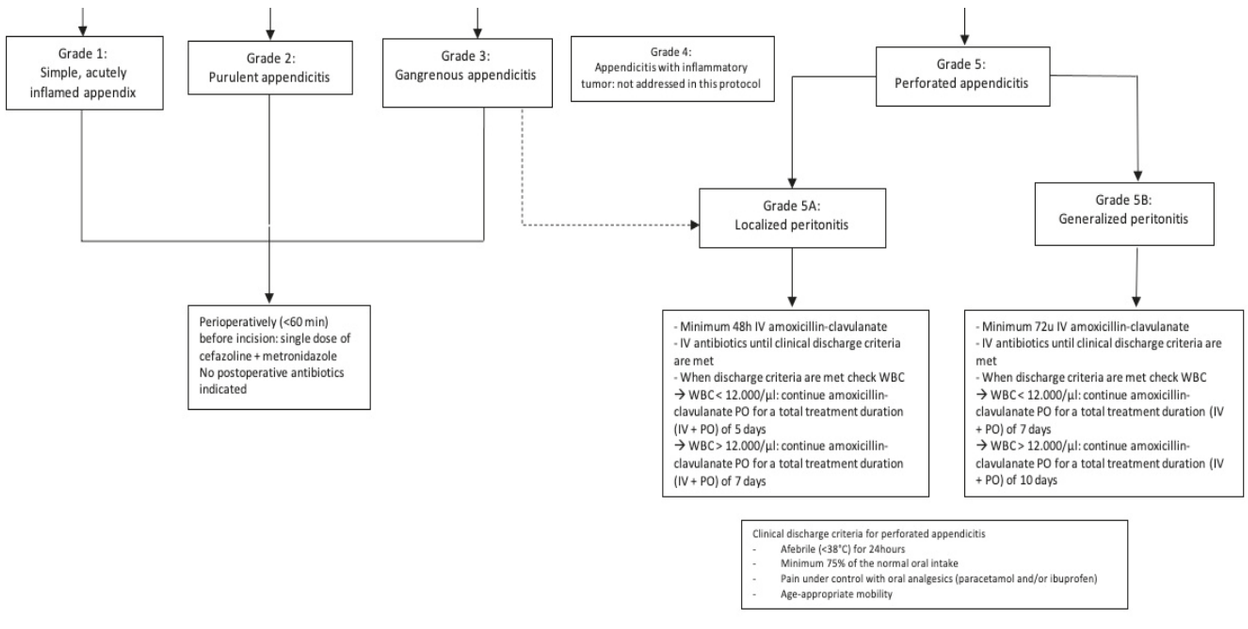
Considerable heterogeneity exists regarding the classification of GA, with debates whether it should be categorized as uncomplicated or complicated appendicitis or even a separate identity, leading to varying treatment protocols (9,12,13,14,16,17,18–28,29). Some studies even omit a distinct description of this subtype, inadvertently suggesting the treatment of GA as if it were uncomplicated (30–35).

Similar to purulent appendicitis, the presence of GA correlates with an increased risk of surgical site infections (6). However, adopting the same treatment strategy for GA as for perforated appendicitis may lead to unnecessary overtreatment. Evidence supporting postoperative antibiotic use often relies on postoperative complication rates after altering the standard of care, highlighting persistent issues of broad-spectrum antibiotic overuse and prolonged therapy durations in surgical settings. Local guidelines for GA management vary, ranging from two single postoperative doses to 3-5 days in some centers (13,36) . Others advocate for administering intravenous (IV) antibiotics until clinical discharge with or without leukocyte count checks before discharge (29,37) .

Cramm demonstrated that for both suppurative and GA there is no difference in rates of surgical site infections whether antibiotics are administered or not (15). We therefore advice to not administer postoperative antibiotics for GA and treat GA identical to suppurative and simple appendicitis.

Peroperatively a GA with in addition a local peritonitis (i.e. seropurulent or

**Figure 2**: Protocol for postoperative antibiotic treatment in acute appendicitis.
Abbreviatons: AB = antibiotics, IV = intravenous treatment, PO = Per Os = oral treatment, WBC = white blood cell.
The dotted line is meant to show that gangrenous appendicitis is only treated with postoperative antibiotics if it is associated with local peritonitis.



fecal contamination of the peritoneum) can be seen. A microperforation is expected in this case. We could not deduct a clear advice on how to treat this subtype based on the literature review. We decided to treat a GA with local peritonitis similarly to macroscopic perforated appendicitis with local peritonitis, but we do acknowledge that this approach is expert-based. It is therefore debatable and should be prospectively analyzed.

### Grade 5: Perforated appendicitis

In our literature review we found opposing recommendations on the duration of antibiotic treatment for perforated appendicitis and on the decision whether or not oral antibiotic treatment after discharge is necessary and, if so, whether a white blood cell (WBC) count at discharge is necessary to define if switch to oral antibiotics is possible.

The WSES guidelines from Jerusalem recommends transitioning from intravenous to oral antibiotics after 48 hours in perforated appendicitis, with a total treatment duration shorter than 7 days (3). However, they do not specify criteria for determining the timing of this switch. It's important to note that this recommendation is based largely on expert opinion and only supported by a limited number of studies. Whereas the consensus statement of the SPIGC in 2021 from Italy advices to treat complicated appendicitis (defined as a grade 4-5 AA according to table 2) for minimum of 3-5 days and to discontinue IV antibiotics depending on WBC count, fever and normalization of bowel function (10).

We decided to divide the management of perforated appendicitis in localized and generalized peritonitis because the more extensive the contamination, the higher the risk of postoperative complications and increased use of resource utilization (longer duration of antibiotics, narcotic analgesia, parenteral nutrition, postoperative imaging) is seen (38–40).

The subtypes of perforated appendicitis require different duration of antibiotic treatment, but the same clinical discharge criteria apply for both localized and diffuse peritonitis.

The four clinical discharge parameters, that each patient must meet before discharge, are (16,24,28,33,41–43):

1. Afebrile (<38°C) for 24hours
2. Minimum 75% of the normal oral intake
3. Pain under control with oral analgesics (paracetamol and/or ibuprofen)
4. Age-appropriate mobility

### Grade 5A - Localized peritonitis

We found 4 studies advocating for intravenous (IV) antibiotic treatment until meeting clinical discharge criteria, without continuation of oral antibiotics at home or leukocyte count assessment before discharge (1,12,44,45). However, most other studies utilize leukocyte count as a discharge criterion (17,22,23,38,43,46–52). Depending on the study, an elevated leukocyte count may result in continuation of IV antibiotics, discontinuation of antibiotics or guide the duration of oral antibiotics after discharge.

Even though an analysis suggests that post-discharge organ space infections may not reliably predicted by routine WBC counts before discharge, we have opted to include leukocyte count assessment at discharge to determine antibiotic duration in children with perforated appendicitis given the prevalence of articles using leukocyte count as a discharge criterion and alignment with the SPIGC consensus statement (53). For localized peritonitis, we recommend initiating IV antibiotic treatment for a minimum of 48 hours, following the WSES guidance. Transitioning to oral antibiotics is done after 48 hours if clinical discharge criteria are met (3).

Although 2 other studies advice that not all patients with complicated appendicitis should be discharged with antibiotics after appendectomy we suggest a minimum total treatment duration of 5 days (IV plus oral treatment) which is largely in line with the SPIGC consensus statement (10,(54,55). In particular, two studies noted a potential trend toward undertreatment in children receiving less than 5 days of treatment, leading to increased intra-abdominal abscess rates (48,56). Regarding the total duration of postoperative antibiotic treatment, we differentiate between 5 and 7 days based on the leukocyte count at discharge. A normal leukocyte count (<12,000/µL) allows discharge with a total treatment duration of 5 days total (IV and oral antibiotics combined).

An elevated leukocyte count (>12,000/µL) allows discharge but requires a total treatment duration of 7 days, consistent with various study protocols (22,23,33,49,50).

### Grade 5B - Generalized peritonitis

WSES guidelines recommends a switch to oral therapy after 48 hours, but multiple treatment protocols still treat at least 72hours IV for perforated appendicitis with localized or generalized contamination (3,17,23,49,57).

Wakeman et al. more specifically saw a reduction of surgical site infections when they created a clinical practice guideline in which they advise IV therapy for at least 72hours postoperatively and they continue IV therapy until the WBC count is normalized before transitioning to oral antibiotics (17). This latter practice is confirmed by Fallon et al, showing that an elevated WBC count is associated with intra-abdominal abscess formation. In particularly, 50% of patients with an WBC count over 14,000/µL developed an intra-abdominal abscess. But even then there is ambiguity considering treatment duration as they do not continue antibiotics at home if normalization of WBC count occurred (43).

Although not based on clear evidence, WSES guidelines advice to use an overall length of therapy shorter than 7 days. However, there are still different studies and treatment protocols advising a longer treatment duration of 10 days.

Theodorou et al. apply a treatment duration of 10 days for patients with an elevated WBC count at discharge (42). Wakeman et al. treat all complicated appendicitis for a total of 10 days (17). Simó et al. treat an appendicular peritonitis for 7 to 10 days without further specification (36). Lastly Lam et al. successfully studied the effect of implementing a standardized care pathway in the Alberta Children's Hospital in Calgary. Their guideline makes a differentiation between perforated and diffuse peritonitis. Diffuse peritonitis is treated with IV antibiotics until clinical discharge criteria are met and a normalization of WBC is reached. Subsequently they switch to oral antibiotics to finish a course for a total of 7-10 days. The final duration of the antibiotic therapy, varying between 7 and 10 days, is based on clinical judgement, without further definition of what this implies (37,58).

Considering the higher risk of postoperative complications with more diffuse peritonitis, we decided to treat this category more strictly by advising at least 72hours of IV treatment. After 72hours a transition to oral antibiotics can be made when clinical discharge criteria are met. To avoid further treatment duration based on clinical judgment, we decided to use the WBC count as a decisive parameter. If the WBC count at discharge is <12.000/µl, we recommend a total treatment duration of 7 days. If the WBC count is elevated (>12.000/µl) a total treatment duration of 10 days is applied.

## *Type of antibiotics*

The most common bacterial species isolated from peritoneal cultures are *Escherichia coli*, *Streptococcus milleri/anginosus*, *Bacteroides fragilis* and *Pseudomonas Aeruginosa* (26,59,60).

For prophylactic antibiotic administration in the case of uncomplicated appendicitis cefazoline with metronidazole is used.

For postoperative antibiotic treatment, we use amoxicillin-clavulanate as first choice of antibiotics, both for IV as oral treatment of perforated appendicitis, according to our local antibiotic guidance.

In case of penicillin allergy, we recommend the combination of ciprofloxacin and metronidazole (17,28). While amoxicillin-clavulanate adequately covers E. coli (except for *Extended-spectrum beta-lactamase*), *B. fragilis* and *S. anginosus/milleri,* it does not treat infections with *P. aeruginosa*. However, studies investigating the use of broad-spectrum antibiotics covering *P. aeruginosa*, such as piperacillin-tazobactam, could not demonstrate a beneficial effect of broad-spectrum treatment compared to narrower treatment. Narrower treatment mostly consisted of

ceftriaxone combined with metronidazole (31,35,61–66). We decided to follow our local antibiotic guidance and treat with amoxicillin-clavulanate.

## Discussion

We created a treatment protocol for postoperative antibiotic treatment after appendectomy in the pediatric population since this was in our opinion still missing in literature. An overview of the treatment protocol can be seen in in Figure 2. Our aim is primarily to implement a straightforward policy and to avoid further treatments based on a physician's preference. We opted for a transparent and evidence-based yet safe protocol taking into account the clinical evolution of the patient and implemented the use of WBC counts to guide antibiotic duration trying to avoid unnecessary overtreatment based on the physician's preference.

Certain limitations in this study warrant acknowledgment. The studies identified from the literature search varied in quality, encompassing both prospective and retrospective analyses, often centered around modifications in local treatment protocols without randomization. In addition, the criteria guiding the establishment of these protocols remained unclear in many instances. The inherent ambiguity surrounding the topic prompted the inclusion of articles expressing divergent opinions and advice regarding antibiotic treatment, complicating the delineation of a definitive protocol. For some aspects of our protocol, such as addressing purulent appendicitis, decisions had to be made with reliance on scarce evidence.

## Conclusion

Based on an extensive literature search, we made a proposition of a treatment protocol for planned postoperative antibiotic treatment after appendectomy. We plan to prospectively evaluate our treatment protocol by evaluating surgical site infections in the first month postoperatively. In addition, a prospective analysis of peritoneal cultures will be performed to re-evaluate whether a change in type of antibiotic use is necessary.

## Disclosure

The authors have no financial interest to declare in relation to the content of this article. We have no conflict of interest to disclose.

REFERENCES


1. Ketha B, Stephenson KJ, Dassinger MS, Smith SD, Burford JM. Eliminating Use of Home Oral Antibiotics in Pediatric Complicated Appendicitis. J Surg Res [Internet]. 2021;263:151–4. Available from: https://doi.org/10.1016/j.jss.2020.12.059
2. Gorter RR, Eker HH, Gorter-Stam MAW, Abis GSA, Acharya A, Ankersmit M, et al. Diagnosis and management of acute appendicitis. EAES consensus development conference 2015. Surg Endosc. 2016;30(11):4668–90.
3. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg. 2020;15(1):1–42.
4. Gomes CA, Sartelli M, Di Saverio S, Ansaloni L, Catena F, Coccolini F, et al. Acute appendicitis: Proposal of a new comprehensive grading system based on clinical, imaging and laparoscopic findings. World J Emerg Surg [Internet]. 2015;10(1):1–6. Available from: http://dx.doi.org/10.1186/s13017-015-0053-2
5. Mouch CA, Cain-Nielsen AH, Hoppe BL, Giudici MP, Montgomery JR, Scott JW, et al. Validation of the American Association for the Surgery of Trauma grading system for acute appendicitis severity. J Trauma Acute Care Surg. 2020;88(6):839–46.
6. Cramm SL, Lipskar AM, Graham DA, Kunisaki SM, Griggs CL, Allukian M, et al. Association of Gangrenous, Suppurative, and Exudative Findings with Outcomes and Resource Utilization in Children with Nonperforated Appendicitis. JAMA Surg. 2022;157(8):685–92.
7. Do-Wyeld M, Cundy TP, Court-Kowalski S, Dandie L, Cooper C, Burgoyne L, et al. Improving quality and efficiency of care for advanced appendicitis in children. ANZ J Surg. 2021;91(7–8):1497–503.
8. Mennie N, Panabokke G, Chang A, Tanny ST, Cheng W, Pacilli M, et al. Are Postoperative Intravenous Antibiotics Indicated after Laparoscopic Appendicectomy for Simple Appendicitis? A Prospective Double-blinded Randomized Controlled Trial. Ann Surg. 2020;272(2):248–52.
9. Devin CL, D'Cruz R, Linden AF, English S, Vinocur CD, Reichard KW, et al. Reducing resource utilization for patients with uncomplicated appendicitis through use of same-day discharge and elimination of postoperative antibiotics. J Pediatr Surg [Internet]. 2020;55(12):2591–5. Available from: https://doi.org/10.1016/j.jpedsurg.2020.04.003
10. Guaitoli E, Gallo G, Cardone E, Conti L, Famularo S, Formisano G, et al. Consensus Statement of the Italian Polispecialistic Society of Young Surgeons (SPIGC): Diagnosis and Treatment of Acute Appendicitis. J Investig Surg [Internet]. 2021;34(10):1089–103. Available from: https://doi.org/10.1080/08941939.2020.1740360
11. Surlemont J, Lecuelle D, Courbier G, Haraux E, Delforge X. Antibiotic therapy in pediatric acute appendicitis: Compliance with local protocol to reduce antibiotic overuse. Arch Pediatr [Internet]. 2020;27(5):261–4. Available from: https://doi.org/10.1016/j.arcped.2020.04.001
12. Cunningham ME, Zhu H, Hoch CT, DeMello AS, Gusman ND, Fallon SC, et al. Effectiveness of a clinical pathway for pediatric complex appendicitis based on antibiotic stewardship principles. J Pediatr Surg [Internet]. 2020;55(6):1026–31. Available from: https://doi.org/10.1016/j.jpedsurg.2020.02.045
13. Shbat L, Emil S, Elkady S, Baird R, Laberge JM, Puligandla P, et al. Benefits of an abridged antibiotic protocol for treatment of gangrenous appendicitis. J Pediatr Surg [Internet]. 2014;49(12):1723–5. Available from: http://dx.doi.org/10.1016/j.jpedsurg.2014.09.039
14. Nordin AB, Diefenbach K, Sales SP, Christensen J, Besner GE, Kenney BD. Gangrenous appendicitis: No longer complicated. J Pediatr Surg [Internet]. 2019;54(4):718–22. Available from: https://doi.org/10.1016/j.jpedsurg.2018.10.064
15. Cramm SL, Graham DA, Blakely ML, Kunisaki SM, Chandler NM, Cowles RA, et al. Postoperative Antibiotics, Outcomes, and Resource Use in Children with Gangrenous Appendicitis. JAMA Surg. 2024;1–7.
16. Khan S, Siow VS, Lewis A, Butler G, Srinivasan S, Michaels M, et al. An Evidence-Based Care Protocol Improves Outcomes and Decrease Cost in Pediatric Appendicitis. J Surg Res. 2020;390–6.
17. Wakeman D, Livingston MH, Levatino E, Juviler P, Gleason C, Tesini B, et al. Reduction of surgical site infections in pediatric patients with complicated appendicitis: Utilization of antibiotic stewardship principles and quality improvement methodology. J Pediatr Surg [Internet]. 2022;57(1):63–73. Available from: https://doi.org/10.1016/j.jpedsurg.2021.09.031
18. Kwok CPD, Tsui SYB, Chan KWE. Updates on bacterial resistance and empirical antibiotics treatment of complicated acute appendicitis in children. J Pediatr Surg [Internet]. 2021;56(7):1145–9. Available from: https://doi.org/10.1016/j.jpedsurg.2021.03.027
19. Van Rossem CC, Schreinemacher MHF, Van Geloven AAW, Bemelman WA, Van Acker GJD, Akkermans B, et al. Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. JAMA Surg. 2016;151(4):323–9.
20. Sorooshian P, Ward R, Sandison AJP. A simple intervention to improve the use of postoperative antibiotics and intra-abdominal drains in appendicectomy patients. Ann R Coll Surg Engl. 2022;104(3):210–5.
21. van Coller R, Arnold M, le Roux H, Tootla H, Dix-Peek S, Nuttal J, et al. Amoxycillin/Clavulanic acid monotherapy in complicated paediatric appendicitis: Good enough? J Pediatr Surg [Internet]. 2022;57(6):1115–8. Available from: https://doi.org/10.1016/j.jpedsurg.2022.01.032
22. Bonasso PC, Dassinger MS, Wyrick DL, Smith SD, Burford JM. Evaluation of white blood cell count at time of discharge is associated with limited oral antibiotic therapy in children with complicated appendicitis. Am J Surg [Internet]. 2019;217(6):1099–101. Available from: https://doi.org/10.1016/j.amjsurg.2018.12.071
23. Lansdale N, Fryer S, Stockdale M, Bancroft J, Orr J, Corbett H, et al. Prospective evaluation of a clinical response directed pathway for complicated appendicitis. J Pediatr Surg [Internet]. 2019;54(2):272–5. Available from: https://doi.org/10.1016/j.jpedsurg.2018.10.082
24. Do-Wyeld M, Rogerson T, Court-Kowalski S, Cundy TP, Khurana S. Fast-track surgery for acute appendicitis in children: a systematic review of protocol-based care. ANZ J Surg. 2019;89(11):1379–85.
25. Litz CN, Asuncion JB, Danielson PD, Chandler NM. Timing of antimicrobial prophylaxis and infectious complications in pediatric patients undergoing appendectomy. J Pediatr Surg [Internet]. 2018;53(3):449–51. Available from: https://doi.org/10.1016/j.jpedsurg.2017.05.005
26. Aiyoshi T, Masumoto K, Tanaka N, Sasaki T, Chiba F, Ono K, et al. Optimal First-Line Antibiotic Treatment for Pediatric Complicated Appendicitis Based on Peritoneal Fluid Culture. Pediatr Gastroenterol Hepatol Nutr. 2021;24(6):510–7.
27. Fallon SC, Hassan SF, Larimer EL, Rodriguez JR, Brandt ML, Wesson DE, et al. Modification of an evidence-based protocol for advanced appendicitis in children. J Surg Res [Internet]. 2013;185(1):273–7. Available from: http://dx.doi.org/10.1016/j.jss.2013.05.088
28. Willis ZI, Duggan EM, Gillon J, Blakely ML, Di Pentima MC. Improvements in Antimicrobial Prescribing and Outcomes in Pediatric Complicated Appendicitis. Pediatr Infect Dis J. 2018;37(5):429–35.
29. Emil S, Gaied F, Lo A, Laberge JM, Puligandla P, Shaw K, et al. Gangrenous appendicitis in children: A prospective evaluation of definition, bacteriology, histopatholo-

gy, and outcomes. J Surg Res [Internet]. 2012;177(1):123–6. Available from: http://dx.doi.org/10.1016/j.jss.2012.03.010

30. Kashtan MA, Graham DA, Melvin P, Cameron DB, Anandalwar SP, Hills-Dunlap JL, et al. Ceftriaxone Combined with Metronidazole is Superior to Cefoxitin Alone in the Management of Uncomplicated Appendicitis in Children: Results from a Multicenter Collaborative Comparative Effectiveness Study. Ann Surg. 2021;274(6):E995–1000.
31. Kashtan MA, Graham DA, Melvin P, Hills-Dunlap JL, Anandalwar SP, Rangel SJ. Ceftriaxone with Metronidazole versus Piperacillin/Tazobactam in the management of complicated appendicitis in children: Results from a multicenter pediatric NSQIP analysis. J Pediatr Surg [Internet]. 2022;57(10):365–72. Available from: https://doi.org/10.1016/j.jpedsurg.2021.11.009
32. Loux TJ, Falk GA, Burnweit CA, Ramos C, Knight C, Malvezzi L. Early transition to oral antibiotics for treatment of perforated appendicitis in pediatric patients: Confirmation of the safety and efficacy of a growing national trend. J Pediatr Surg [Internet]. 2016;51(6):903–7. Available from: http://dx.doi.org/10.1016/j.jpedsurg.2016.02.057
33. Munoz-Abraham AS, Osei H, Kazmi S, Damle R, Zemela MS, Badru F, et al. Protocolized management of pediatric complicated appendicitis leads to improved outcomes. Pediatr Surg Int [Internet]. 2022;38(6):891–7. Available from: https://doi.org/10.1007/s00383-022-05124-z
34. Hurst AL, Olson D, Somme S, Child J, Pyle L, Ranade D, et al. Once-daily ceftriaxone plus metronidazole versus ertapenem and/or cefoxitin for pediatric appendicitis. J Pediatric Infect Dis Soc. 2017;6(1):57–64.
35. Cameron DB, Melvin P, Graham DA, Glass CC, Serres SK, Kronman MP, et al. Extended Versus Narrow-spectrum Antibiotics in the Management of Uncomplicated Appendicitis in Children. Ann Surg. 2018;268(1):186–92.
36. Simó S, Velasco-Arnaiz E, Ríos-Barnés M, López-Ramos MG, Monsonís M, Urrea-Ayala M, et al. Article effects of a paediatric antimicrobial stewardship program on antimicrobial use and quality of prescriptions in patients with appendix-related intraabdominal infections. Antibiotics. 2021;10(1):1–12.
37. Lam JY, Beaudry P, Simms BA, Brindle ME. Impact of implementing a fast-track protocol and standardized guideline for the management of pediatric appendicitis. Can J Surg. 2021;64(4):E364–70.
38. Yousef Y, Youssef F, Dinh T, Pandya K, Stagg H, Homsy M, et al. Risk stratification in pediatric perforated appendicitis: Prospective correlation with outcomes and resource utilization. J Pediatr Surg [Internet]. 2018;53(2):250–5. Available from: https://doi.org/10.1016/j.jpedsurg.2017.11.023
39. Anandalwar SP, Cameron DB, Graham DA, Melvin P, Dunlap JL, Kashtan M, et al. Association of Intraoperative Findings with Outcomes and Resource Use in Children with Complicated Appendicitis. Vol. 153, JAMA Surgery. 2018. p. 1021–7.
40. Feng C, Anandalwar S, Sidhwa F, Glass C, Karki M, Zurakowski D, et al. Beyond perforation: Influence of peritoneal contamination on clinical severity and resource utilization in children with perforated appendicitis. J Pediatr Surg [Internet]. 2016;51(11):1896–9. Available from: http://dx.doi.org/10.1016/j.jpedsurg.2016.08.002
41. Robinson JR, Avritscher EBC, Gay JC, Willis ZI, Putnam LR, Anglemyer A, et al. Measuring the Value of a Clinical Practice Guideline for Children with Perforated Appendicitis. Ann Surg. 2017;266(1):195–200.
42. Theodorou CM, Lee SY, Lawrence Y, Saadai P, Hirose S, Brown EG. The Utility of Discharge Antibiotics in Pediatric Perforated Appendicitis Without Leukocytosis. J Surg Res. 2022;275:48–55.
43. Fallon SC, Brandt ML, Hassan SF, Wesson DE, Rodriguez JR, Lopez ME. Evaluating the effectiveness of a discharge protocol for children with advanced appendicitis. J Surg Res [Internet]. 2013;184(1):347–51. Available from: http://dx.doi.org/10.1016/j.jss.2013.04.081
44. Russell KW, Skarda DE, Jones TW, Barnhart DC, Short SS. Cessation of Antibiotics for Complicated Appendicitis at Discharge Does Not Increase Risk of Post-operative Infection. J Pediatr Surg [Internet]. 2024;59(1):91–5. Available from: https://doi.org/10.1016/j.jpedsurg.2023.09.023
45. Rossidis AC, Brown EG, Payton KJ, Mattei P. Implementation of an evidence-based protocol after appendectomy reduces unnecessary antibiotics. J Pediatr Surg [Internet]. 2020;55(11):2379–86. Available from: https://doi.org/10.1016/j.jpedsurg.2020.07.001
46. Planas Díaz I, Díaz Menéndez L, Cabello Laureano R, Molina M. Beneficios de la estandarización en el manejo de la apendicitis aguda. Cir Pediatr. 2024;37(1):5–10.
47. Pérez Costoya C, Gómez Farpón A, Enríquez Zarabozo E, Granell Suárez C, Vega Mata N, Amat Valero S, et al. Analysis of a clinical guideline for treatment and early discharge in complicated acute appendicitis. Cirugía Pediátrica. 2023;36(3):122–7.
48. Ferguson DM, Parker TD, Arshad SA, Garcia EI, Hebballi NB, Tsao KJ. Standardized Discharge Antibiotics May Reduce Readmissions in Pediatric Perforated Appendicitis. J Surg Res [Internet]. 2020;255:388–95. Available from: https://doi.org/10.1016/j.jss.2020.05.086
49. Pennell C, Meckmongkol T, Arthur LG, Ciullo S, Prasad R, Lindholm E, et al. A Standardized Protocol for the Management of Appendicitis in Children Reduces Resource Utilization. Pediatr Qual Saf. 2020;5(6):E357.
50. Lee J, Garvey EM, Bundrant N, Hargis-Villanueva A, Kang P, Osuchukwu O, et al. IMPPACT (Intravenous Monotherapy for Postoperative Perforated Appendicitis in Children Trial): Randomized Clinical Trial of Monotherapy Versus Multi-drug Antibiotic Therapy. Ann Surg. 2021;274(3):406–10.
51. Gordon AJ, Choi JH, Ginsburg H, Kuenzler K, Fisher J, Tomita S. Oral Antibiotics and Abscess Formation After Appendectomy for Perforated Appendicitis in Children. J Surg Res [Internet]. 2020;256:56–60. Available from: https://doi.org/10.1016/j.jss.2020.05.082
52. Slusher J, Bates CA, Johnson C, Williams C, Dasgupta R, Von Allmen D. Standardization and improvement of care for pediatric patients with perforated appendicitis. J Pediatr Surg [Internet]. 2014;49(6):1020–5. Available from: http://dx.doi.org/10.1016/j.jpedsurg.2014.01.045
53. Cramm SL, Graham DA, Allukian M, Blakely ML, Chandler NM, Cowles RA, et al. Predictive Value of Routine WBC Count Obtained Before Discharge for Organ Space Infection in Children with Complicated Appendicitis: Results from the Eastern Pediatric Surgery Network. J Am Coll Surg. 2023;236(6):1181–7.
54. Anderson KT, Bartz-Kurycki MA, Kawaguchi AL, Austin MT, Holzmann-Pazgal G, Kao LS, et al. Home Antibiotics at Discharge for Pediatric Complicated Appendicitis: Friend or Foe? J Am Coll Surg [Internet]. 2018;227(2):247–54. Available from: https://doi.org/10.1016/j.jamcollsurg.2018.04.004
55. Liu Q, Hao F, Chen B, Li L, Liu Q, Guo C. Multi-Center Prospective Study of Restrictive Post-Operative Antibiotic Treatment of Children with Complicated Appendicitis. Surg Infect (Larchmt). 2020;21(9):778–83.
56. Desai AA, Alemayehu H, Holcomb GW, St. Peter SD. Safety of a new protocol decreasing antibiotic utilization after laparoscopic appendectomy for perforated appendicitis in children: A prospective observational study. J Pediatr Surg [Internet]. 2015;50(6):912–4. Available from: http://dx.doi.org/10.1016/j.jpedsurg.2015.03.006
57. Somers KK, Eastwood D, Liu Y, Arca MJ. Splitting hairs and challenging guidelines: Defining the role of perioperative antibiotics in pediatric appendicitis patients: Perioperative antibiotics in children with appendicitis. J Pediatr Surg [Internet]. 2020;55(3):406–13. Available from: https://doi.org/10.1016/j.jpedsurg.2019.07.004
58. Clinical Guidance Viewer P. Provincial Clinical Knowledge Topic. 2018;(September):1–33. Available from: https://extranet.ahsnet.ca/teams/policydocuments/1/klink/et-klink-ckv-appendicitis-pediatric-inpatient.pdf
59. Bhaskar K, Clarke S, Moore LSP, Hughes S. Bacterial peritonitis in paediatric appendicitis; microbial epidemiology and antimicrobial management. Ann Clin Microbiol Antimicrob [Internet]. 2023;22(1):1–8. Available from: https://doi.org/10.1186/s12941-023-00591-1
60. Gerber F, Joseph JM, Crisinel PA, Andrey V. Evidence-based optimisation of empirical antibiotic regimens in paediatric complicated appendicitis: A retrospective study of 94 patients. Swiss Med Wkly. 2022;152(3536).
61. Seddik TB, Rabsatt LA, Mueller C, Bassett HK, Contopoulos-Ioannidis D, Bio LL, et al. Reducing Piperacillin and Tazobactam Use for Pediatric Perforated Appendicitis. J Surg Res [Internet]. 2021;260:141–8. Available from: https://doi.org/10.1016/j.jss.2020.11.067
62. Hamdy RF, Handy LK, Spyridakis E, Dona D, Bryan M, Collins JL, et al. Comparative effectiveness of ceftriaxone plus metronidazole versus anti-pseudomonal antibiotics for perforated appendicitis in children. Surg Infect (Larchmt). 2019;20(5):399–405.
63. Zeineddin S, Pitt JB, Linton S, De Boer C, Hu A, Carter M, et al. Postoperative Antibiotics for Complicated Appendicitis in Children: Piperacillin/Tazobactam Versus Ceftriaxone with Metronidazole. J Pediatr Surg [Internet]. 2023;58(6):1128–32. Available from: https://doi.org/10.1016/j.jpedsurg.2023.02.027
64. Cramm SL, Graham DA, Feng C, Allukian M, Blakely ML, Chandler NM, et al. Use of Antipseudomonal Antibiotics is not Associated with Lower Rates of Postoperative Drainage Procedures or More Favorable Culture Profiles in Children with Complicated Appendicitis. Ann Surg. 2023;
65. Skarda DE, Schall K, Rollins M, Andrews S, Olson J, Greene T, et al. Response-based therapy for ruptured appendicitis reduces resource utilization. J Pediatr Surg [Internet]. 2014;49(12):1726–9. Available from: http://dx.doi.org/10.1016/j.jpedsurg.2014.09.012
66. Theodorou CM, Stokes SC, Hegazi MS, Brown EG, Saadai P. Is Pseudomonas infection associated with worse outcomes in pediatric perforated appendicitis? J Pediatr Surg. 2021;56(10):1826–30.

**Supplementary Table**:

An overview with more detailed information of the included articles.

| Title | 1st Author | Year | Type of study | Number of patients | Aim of the study |
|---|---|---|---|---|---|
| Acute appendicitis: Proposal of a new comprehensive grading system based on clinical, imaging and laparoscopic findings. (4) | C. Gomes | 2015 | Literature Review | Not applicable | The goal is review and update the laparoscopic grading system of acute appendicitis and to provide a new standardized classification system to allow more uniform patient stratification. |
| Amoxycillin/clavulanic acid monotherapy in complicated paediatric appendicitis: good enough? (21) | Rochelle van Coller | 2022 | Retrospective review | 455 patients with acute appendicitis | We examined the transition to single antimicrobial agent (amoxiclav) with respect to clinical consequences |
| Analysis of a clinical guideline for treatment and early discharge in complicated acute appendicitis (47) | C. Pérez Costoya | 2023 | Retrospective analytic study | 314 patients with complicated appendicitis | The objective of this study was to assess the results in terms of infectious complications and hospital stay of applying a clinical guideline introduced in June 2018 for the treatment of acute appendicitis in our department and aimed at standardizing its management. |
| An evidence-based care protocol improves outcomes and decreases cost in pedatric appendicitis (16) | Sidrah Khan | 2020 | Prospective and retrospective observational study | 1289 patients with acute appendicitis | We aim to examine the outcomes of these patients with a specific focus on length of stay (LOS), healthcare cost, the type and course of antibiotic use, and postoperative complications. We hypothesized that the introduction of an evidence-based clinical care protocol would decrease LOS and health care cost in the post-intervention group without compromising clinical outcomes. |
| Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis (19) | Charles C. van Rossem | 2016 | Multicenter, prospective, observational cohort study | 415 patients with acute complicated appendicitis | The objectives of this prospective study were to investigate the relation of antibiotic duration and infectious complications and to identify possible risk factors for a postoperative infectious complication after laparoscopic appendectomy for acute complicated appendicitis. |
| Antibiotic therapy in acute appendicitis: compliance with local protocol to reduce antibiotic overuse (11) | J. Surlemont | 2020 | Retrospective study | 142 patients with acute appendicitis | The primary objective was to assess the concordance between the antibiotic therapy defined by the ATBP, and the antibiotic therapy actually received by the patients. The efficacy of the ATBP was also evaluated by assessing whether the intended antibiotic was adapted to the bacteria isolated from intraoperative samples. Infectious complication rates were compared between patients receiving antibiotics according to the ATBP and patients receiving non-recommended antibiotic therapy. |
| Are postoperative Intravenous antibiotics indicated after laparoscopic appendicectomy for simple appendicitis? A prospective double-blind randomized controlled trial (8) | Nicole Mennie | 2020 | Prospective double blind RCT | 243 patients with simple appendicitis | Our aim was to perform a prospective double-blinded randomized controlled trial (RCT) comparing 2 postoperative intra- venous doses of Abx to placebo to ascertain the incidence of postoperative WI after a laparoscopic pediatric appendicectomy. |
| A simple intervention to improve the use of postoperative antibiotics and intra-abdominal drains in appendicectomy patients (20) | P. Sorooshian | 2022 | Retrospective study | 130 patients | Assess whether the simple intervention of an educational poster can improve the appropriate use of postoperative antibiotic and intra-abdominal drain use in appendicectomy patients |
| Association of Gangrenous, Suppurative, and Exudative Findings With Outcomes and Resource Utilization in Children With Nonperforated Appendicitis (6) | Shannon L. Cramm | 2022 | Retrospective, multicenter cohort study using NSQIP-P database | 867 patients with appendicitis with GSE findings | The goal of this multi-center study was to evaluate whether the presence of GSE findings in patients with nonperforated appendicitis is associated with increased risk of surgical site infections (SSIs) and resource utilization |
| Association of Intraoperative Findings With Outcomes and Resource Use in Children With Complicated Appendicitis (39) | Seema P. Anandalwar | 2018 | Retrospective cohort study | 1333 patients with complicated appendicitis | the goal of this study was to examine the association of different combinations of intraoperative findings with resource use and rates of adverse events in children with complicated appendicitis. |
| A standardized protocol for the management of appendicitis in children reduces resource utilization (49) | Christopher Pennell | 2020 | Prospective and retrospective cohort study | 699 children with acute appendicitis | Determine whether delivering uniform and protocolized care to children with appendicitis would improve healthcare resource utilization and clinical outcomes |
| Bacterial peritonitis in paediatric appendicitis; microbial epidemiology and antimicrobial management (59) | Keir Bhaskar | 2023 | Retrospective observational analysis | 530 patients with appendectomy | This retrospective study aims to determine the microbial epidemiology of paediatric appendicitis from intra-operative cultures in order to assess the appropriateness of empirical antimicrobial prophylaxis during surgery. |
| Benefits of an abridged antibiotic protocol for treatment of gangrenous appendicitis (13) | Layla Shbat | 2014 | Prospective cohort study | 58 patients with gangrenous appendicitis (38 patients prolonged antibiotics, 20 patients abridged antibiotics) | Determine if shortening the duration of postoperative antibiotics for children with gangrenous appendicitis can decrease the length of stay without increasing complications |

| Title | 1st Author | Year | Type of study | Number of patients | Aim of the study |
|---|---|---|---|---|---|
| Benefits of standardization in the management of acute appendicitis (46) | I. Planas Díaz | 2023 | Observational, retrospective cohort study | 771 patients with acute appendicitis | The objective of this work was to present our results following the optimization of this protocol in our institution, while establishing professionals' adhesion, efficacy in terms of number of postoperative intra-abdominal infectious complications, and use of financial resources (control tests and HS). |
| Beyond perforation: Influence of peritoneal contamination on clinical severity and resource utilization in children with perforated appendicitis (40) | Christina Feng | 2016 | Retrospective analysis of prospectively collected data | 417 patients with appendicitis | The goal of this study was to investigate the relationship between degree of peritoneal contamination in complicated appendicitis and its influence on resource utilization in the postoperative period. |
| Ceftriaxone combined with metronidazole is superior to cefoxitin alone in the management of uncomplicated appendicitis in children (30) | Mark A. Kashtan | 2021 | Multicenter retrospective cohort analysis (using data from NSQIP-Pediatric Appendectomy Pilot database and PHIS database | 846 patients with uncomplicated appendicitis | Compare the clinical effectiveness of ceftriaxone + metronidazole versus cefoxitin alone in preventing SSIs after appendectomy for uncomplicated appendicitis |
| Ceftriaxone with metronidazole versus piperacillin/ tazobactam in the management of complicated appendicitis in children: results from a multicenter pediatric NSQIP analysis (31) | Mark A. Kashtan | 2021 | Multicenter retrospective cohort analysis using data from the NSQIP-Pediatric Appendectomy Pilot Collaborative database merged with PHIS database | 654 patients with complicated appendicitis | Leverage data from a collaborative of 14 hospitals participating in the NSQIP-Pediatric to compare outcomes associated with CM and PT in children with complicated appendicitis |
| Cessation of Antibiotics for Complicated Appendicitis at Discharge Does Not Increase Risk of Post-operative Infection (44) | Katie W. Russell | 2024 | Retrospective study (NSQIP-P database) | 306 patients with complicated appendicitis | We sought to evaluate our outcomes following this protocol change. We hypothesized that the elimination of home antibiotic therapy did not increase our rate of post-operative deep organ space infection or other complications in our patient population. |
| Comparative effectiveness of ceftriaxone plus metronidazole versus anti-pseudomonal antibiotics for perforated appendicitis in children (62) | Rana F. Hamdy | 2019 | Retrospective cohort study | 353 patients with perforated appendicitis | Compare the clinical outcomes of children with perforated appendicitis who were treated with ceftriaxone + metronidazole versus a broader-spectrum, anti-pseudomonal regimen (cefepime, ceftazidime, pip/tazo, cipro, imipinem or meropenem) |
| Consensus statement of the Italian polispecialistic society of young surgeons (SPIGC): diagnosis and treatment of acute appendicitis (10) | Eleonora Guatioli | 2020 | Consensus statement based on literature search | | Consensus statement was built in relation to the most recent evidence for AA with the aim of summarizing evidence from the last published guidelines and latest studies on this topic. |
| Diagnosis and management of acute appendicitis. EAES consensus development conference 2015 (2) | Ramon R. Gorter | 2016 | Guideline based on best available evidence and expert opinions | | The aim of this consensus meeting was to develop practical guidelines based on the available evidence combined with the expertise of a selected panel of EAES surgeons. The findings are reported in this manuscript. |
| Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines (3) | Salomone Di Saverio | 2020 | WSES Guidelines – consensus conference | | WSES decided to convene an update of the 2016 Jerusalem guidelines. |
| Early transition to oral antibiotics for treatment of perforated appendicitis in pediatric patients: Confirmation of the safety and efficacy of a growing national trend (32) | Tara J. Loux | 2016 | Prospective and retrospective study | 259 patients with perforated appendicitis | Analysis of a new protocol. We instituted a new protocol, expecting that the regimen would prove equally safe, more efficient and more cost effective for perforated appendicitis than the PICC line/IV protocol employed previously. |
| Effectiveness of a clinical pathway for pediatric complex appendicitis based on antibiotic stewardship principles (12) | Megan E. Cunningham | 2020 | Interrupted time series | 465 patients with complex appendicitis | To evaluate the safety and efficacy of a complex appendicitis discharge protocol based on clinical parameters alone, limiting antibiotic prescription at discharge. We hypothesized that this simplified, antibiotic-limiting protocol would not have inferior postoperative outcomes with regards to postoperative LOS, readmission rates, and rates of intra-abdominal abscess formation when compared to a more traditional resource-intensive regimen |
| Effects of a paediatric antimicrobial stewardship program on antimicrobial use and quality of prescriptions in patients with appendix-related intraabdominal infections (36) | Silvia Simo | 2020 | Pre-post intervention study | 2021 admissions for appendix-related intraabdominal infections | We aimed to describe and evaluate the results on antibiotic use, LOS and quality of prescriptions of the first 3 years of an ASP intervention directed to children admitted for appendix-related intra-abdominal infections in a European referral paediatric university hospital |
| Eliminating the use of home oral antibiotics in pediatric complicated appendicitis (1) | Bavana Ketha | 2021 | Retrospective study (pre- and post-protocol change) | 170 patients with perforated appendicitis | Our aim with this study was to evaluate a further protocol change to eliminate a WBC check and oral antibiotics if patients were discharged before post- operative day 7. We hypothesized that this protocol change would further decrease our overall antibiotic use without an increase in our readmission rate or abscess rate. |

| | | | | | |
|---|---|---|---|---|---|
| Evaluating the effectiveness of a discharge protocol for children with advanced appendicitis (43) | Sara C. Fallon | 2013 | Retrospective review | 450 patients with advanced appendicitis | The purpose of this study is to assess the effectiveness of laboratory parameters as part of discharge criteria in a clinical pathway for the treatment of advanced appendicitis. |
| Evaluation of white blood cell count at time of discharge is associated with limited oral antibiotic therapy in children with complicated appendicitis (22) | Patrick C. Bonasso | 2019 | Retrospective review | 179 patients with complicated appendicitis | The purpose of our study was to investigate the impact of WBC at discharge on oral antibiotic therapy, abscess rate, and readmission rate. We hypothesized that evaluation of WBC at the time discharge criteria were met would decrease use of home oral antibiotics and total length of antibiotic treatment. |
| Evidence-based optimisation of empirical antibiotic regimens in paediatric complicated appendicitis: a retrospective study of 94 patients (60) | Filippo Gerber | 2022 | Retrospective study | 94 patients with complicated appendicitis | This study's primary objective was to describe and analyse microorganisms' microbiology and antibiotic susceptibility in complicated appendicitis since 2017. Secondary objectives included evaluating the change of EAR on the rate of postoperative infectious complications in complicated appendicitis and identifying possible determinants of postoperative infectious complications in our population |
| Extended versus narrow-spectrum antibiotics in the management of uncomplicated appendicitis in children (35) | Danielle B. Cameron | 2018 | A Propensity-matched Comparative Effectiveness Study | 1389 patients with uncomplicated appendicitis | The purpose of this study was to compare the relative effectiveness of extended and narrow-spectrum antibiotics in preventing SSIs and hospital revisits in children undergoing appendectomy for uncomplicated appendicitis. |
| Fast-track surgery for acute appendicitis in children: a systematic review of protocol based care (24) | Montgommery Do-Wyeld | 2019 | Systematic Review | 33 studies included | The aim of this systematic review is to evaluate the current evidence for standardization of care in childhood appendicitis and to identify future directions in this field. |
| Gangrenous appendicitis in children: a prospective evaluation of definition, bacteriology, histopathology, and outcomes (29) | Sherif Emil | 2012 | Prospective observational study | 38 patients with gangrenous appendicitis | Our primary goal was to determine if the clinical and economic outcomes of gangrenous appendicitis can be further improved by decreasing length of stay without increasing complications. |
| Gangrenous appendicitis: no longer complicated (14) | Andrew B Nordin | 2019 | Prognosis study | 1007 patients who underwent laparoscopic appendectomies | We sought to reduce inpatient length of stay and antibiotic utilization for patients with gangrenous appendicitis, and hypothesized that treating these patients according to the simple pathway would accomplish these goals without adversely increasing postoperative abscess rates or readmissions. |
| Home Antibiotics at Discharge for Pediatric Complicated Appendicitis: Friend or Foe? (54) | K Tinsley Anderson | 2017 | Retrospective review | 6412 patients with complicated appendicitis | The purpose of this study was to evaluate the postdischarge outcomes of pediatric complicated appendicitis patients discharged with or without antibiotics, stratified by presence of a predischarge surgical site infection (SSI) and LOS. |
| Impact of implementing a fast-track protocol and standardized guideline for the management of pediatric appendicitis (37)<br>Guideline available online: (58) | Jennifer Y. Lam | 2020 | Retrospective review | 276 patients with acute appendicitis included | Study to determine the impact of implementation of the guideline at our institution on length of stay (LOS), antibiotic stewardship efforts and costs. |
| Implementation of an evidence-based protocol after appendectomy reduces unnecessary antibiotics (45) | Avery C. Rossidis | 2020 | Retrospective review | 1562 patients with acute appendicitis | We hypothesized that the implementation of this protocol would result in reduced antibiotic usage and shorter lengths of hospital stay without increasing the incidence of surgical site infection (SSI) or other complications. |
| IMPPACT (Intravenous Monotherapy for Postoperative Perforated Appendicitis in Children Trial) (50) | Justin Lee | 2021 | Randomized Clinical Trial | 162 patients with perforated appendicitis enrolled | We conducted a prospective randomized clinical trial comparing a broad- spectrum, single-drug regimen of PT versus a 2-drug regimen of CM. |
| Improvements in antimicrobial prescribing and outcomes in pediatric complicated appendicitis (28) | Zachary I. Willis | 2018 | Prospective + retrospective study | 313 patients with complicated appendicitis | We evaluated the effects of 2 successive interventions, an antimicrobial stewardship program (ASP) and a condition- specific clinical practice guideline (CPG), on antimicrobial utilization and patient outcomes in these patients. |
| Improving quality and efficiency of care for advanced appendicitis in children (7) | Montgommery Do-Wyeld | 2021 | Case-control study (pro+retrospective) | 44 patients with advanced appendicitis enrolled | Study aims to design, implement and evaluate a clinical protocol for a proposed intermediate pathology cohort termed ‘advanced’ appendicitis in children based on a number of intra-operative and patient characteristics. The goal of our enhanced recovery pathway (ERP) is to facilitate discharge and reduce resource utilization for this targeted patient group with ‘advanced’ appendicitis without increasing existing post-operative complication or readmission rates. |
| Is Pseudomonas Infection Associated with Worse Outcomes in Pediatric Perforated Appendicitis? (66) | Christina M. Theodorou | 2021 | Single-center retrospective review | 255 patients with perforated appendicitis | Given that Pseudomonas is a common gastrointestinal microbe that is not covered by our empiric antibiotic regimen, we hypothesized that post-operative outcomes of children with Pseudomonas identified on intraoperative cultures would be worse than children without Pseudomonas. |

| Title | 1st Author | Year | Type of study | Number of patients | Aim of the study |
|---|---|---|---|---|---|
| Measuring the value of a clinical practice guideline for children with perforated appendicitis (41) | Jamie R. Robinson | 2017 | Analysis before and after implementation of CPG | 122 patients with perforated appendicitis | Determine if a CPG is costeffective for preventing adverse events (AEs) in children undergoing treatment for perforated appendicitis at a tertiary referral children's hospital. |
| Modification of an evidence based protocol for advanced appendicitis in children (27) | Sara C. Fallon | 2013 | Prospective + retrospective study | 50 patients with advanced appendicitis | We prospectively studied peritoneal fluid microbial cultures at the time of appendectomy in children with perforated appendicitis in order to update our hospital's clinical pathway guidelines for advanced appendicitis. |
| Multi-center prospective study of restrictive post-operative antibiotic treatment of children with complicated appendicitis (55) | Qianyang Liu | 2020 | Randomized, controlled, parallel group, multi-center analysis | 685 patients with complex appendicitis | The purpose of our study was to assess the effect of limiting a course of post-operative antibiotic treatment for complex appendicitis in term of abscess, incision infection rate, and re-admission rate. We hypothesized that restrictive post-operative antibiotic administration is equivalent to the standard regimen after surgery for complicated pediatric appendicitis. |
| Once-Daily Ceftriaxone Plus Metronidazole Versus Ertapenem and/or Cefoxitin for Pediatric Appendicitis (34) | Amanda L. Hurst | 2017 | Retrospective review | 841 patients with acute appendicitis | Because we changed from a historical regimen of ERT (for perforated and abscessed at presentation cases) and cefoxitin ([CFX] for nonperforated cases) to a current regimen of CTX plus MTZ for all appendicitis, we were presented with a unique opportunity to evaluate and compare these regimens for clinical efficacy and cost in a retrospective manner |
| Optimal first line antibitoic treatment of pediatric complicated appendicitis based on pertioneal fluid culture (26) | Tsubasa Aiyoshi | 2021 | Retrospective study | 86 patients with complicated appendicitis | this study aimed to determine the appropriate first-line antibiotic treatment for pediatric CA. |
| Oral antibiotics and abscess formation after appendectomy for perforated appendicitis in children (51) | Alex J. Gordon | 2020 | Retrospective study | 253 patients with perforated appendicitis | We sought to further assess the safety of discharging patients without oral antibiotics using a multicenter retrospective pre implementation/ postimplementation study design |
| Postoperative Antibiotics for Complicated Appendicitis in Children: Piperacillin/Tazobactam Versus Ceftriaxone with Metronidazole (63) | Suhail Zeineddin | 2023 | Retrospective comparative study | 29.015 patients with complicated appendicitis | The aim of this retrospective, cross sectional analysis is to describe the relationship between antibiotic regimen and postoperative outcomes using a large administrative database. |
| Postoperative Antibiotics, Outcomes, and Resource Use in Children With Gangrenous Appendicitis (15) | Shannon L. Cramm | 2024 | Retrospective multicenter propensity-matched cohort study using NSQIP-P database | 958 patients with appendicitis with GSE findings | The goal of this analysis was to evaluate whether use of postoperative antibiotics was associated with improved outcomes in children with nonperforated appendicitis with GSE findings |
| Predictive Value of Routine WBC Count Obtained Before Discharge for Organ Space Infection in Children with Complicated Appendicitis: Results from the Eastern Pediatric Surgery Network (53) | Shannon L Cramm | 2022 | Retrospective multicenter cohort study (using data from NSQIP-P) | 1264 children with complicated appendicitis (of which 348 had a WBC) | The goal of this multicenter analysis was to evaluate the predictive value of RPD-WBC data to identify children at risk of post discharge OSI after appendectomy for complicated appendicitis. |
| Prospective evaluation of a clinical response directed pathway for complicated appendicitis (23) | Nick Lansdale | 2019 | Prospective + retrospective cohort study | 264 patients with acute appendicitis | The aim of this study was to assess whether a new response-based post-operative pathway was safe and effective and whether or not it offered benefit. |
| Protocolized management of pediatric complicated appendicitis leads to improved outcomes (33) | Armando Salim Munoz- Abraham | 2022 | Retrospective review | 246 patients with complicated appendicitis | For this study, our aim was to evaluate the effectiveness of our evidence-based complicated appendicitis management protocol at a stand-alone children's hospital. We set out to compare outcomes and resource utilization for complicated appendicitis treated with early versus interval appendectomy. We hypothesized that patients presenting with complicated appendicitis with or small abscess (≤ 3 cm) would most likely benefit from an early appendectomy. |
| Reducing Piperacillin and Tazobactam Use for Pediatric Perforated Appendicitis (61) | Talal B. Seddik | 2021 | Single center, retrospective cohort study | Forty children before and 109 after intervention were included | We aim to determine the efficacy of this intervention to decrease PT use for perforated appendicitis and whether this led to any differences in clinical outcomes. |
| Reducing resource utilization for patients with uncomplicated appendicitis through use of same-day discharge and elimination of postoperative antibiotics (9) | Courtney L. Devin | 2020 | Retrospective comparative study. | 575 patients who underwent appendectomy for un-complicated appendicitis | Our goal was to create a standardized perioperative pathway in the treatment of acute, uncomplicated appendicitis that would reduce variability among surgeons and increase compliance with evidence-based practices. We then compared our pre- versus post-pathway outcomes. |

| | | | | | |
|---|---|---|---|---|---|
| Reduction of surgical site infections in pediatric patients with complicated appendicitis: Utilization of antibiotic stewardship principles and quality improvement methodology (17) | Derek Wakeman | 2022 | Pre- and post-implementation cohort study | 104 patients with complicated appendicitis | We hypothesized that implementing clinical practice guidelines to standardize post-operative care would improve clinical outcomes for CA and reduce healthcare utilization. Our aim was to reduce surgical site infection after appendectomy for CA by 25% in 1 year. |
| Response-based therapy for ruptured appendicitis reduces resource utilization (65) | David E. Skarda | 2014 | Prospective and retrospective query of a database | 306 patients with ruptured appendicitis | We sought to evaluate the differences in patient out- comes and resource utilization between a previously implemented fixed-duration IV antibiotic therapy protocol that included Pseudomonas coverage vs. our newer patient response-based IV antibiotic therapy protocol that did not include Pseudomonas coverage and utilized home oral antibiotics in potentially high-risk patients. |
| Risk stratification in pediatric perforated appendicitis: prospective correlation with outcomes and resource utilization (38) | Yasmine Yousef | 2018 | Prospective cohort study | 122 patients with perforated appendicitis | We prospectively validated the ability of a grading system for perforated appendicitis to predict outcomes and resource utilization associated with treatment of the disease. We believe such a grading system can finally standardize outcomes reporting, and accurately reflect the resource burden across the disease spectrum. |
| Safety of a new protocol decreasing antibiotic utilization after laparoscopic appendectomy for perforated appendicitis in children: A prospective observational study (56) | Amita A. Desai | 2015 | Prospective + retrospective observational study | 540 patients with perforated appendicitis | In order to progress the protocol further, we conducted a prospective observational study in the next 270 patients admitted in which patients could be discharged home early without PO antibiotics if a leukocytosis is not identified at time of discharge prior to completion of a 5 day IV antibiotic course. |
| Splitting hairs and challenging guidelines: defining the role of perioperative antibiotics in pediatric appendicitis patients (57) | Kimberly K Somers | 2019 | Prospective, observational, cohort study | 988 patients with AA and 561 patients with CA | This study asked questions relevant to the impact of timing and duration of pre- and postoperative antibiotics on SSIs in AA and CA |
| Standardized discharge antibiotics may reduce readmissions in pediatric perforated appendicitis (48) | Dalya M. Ferguson | 2020 | Retrospective cohort study | 617 patients with acute and perforated appendicitis | Given the paucity of high-quality evidence available on the ideal duration of postoperative antibiotics, we aimed to assess patient outcomes before and after our institutional CPG was modified. We hypothesized that receiving an additional 7 d of oral antibiotics after discharge would be associated with a reduced risk of IAA in children with perforated appendicitis. |
| Standarization and improvement of care for pediatric patients with perforated appendicitis (52) | Joyce Slusher | 2014 | Prospective and retrospective chart review | Retrospective 119 patients with perforated appendicitis, prospective 134 patients | By standardizing care, we hoped to reduce variation in practice and in turn reduce consumption of health care resources while maintaining excellent patient outcomes. |
| The Utility of Discharge Antibiotics in Pediatric Perforated Appendicitis Without Leukocytosis (42) | Christina M Theodorou | 2022 | Pre- and post-cohort study | 210 patients with perforated appendicitis | As part of a quality improvement initiative, our institutional pediatric perforated appendicitis clinical practice guideline was modified to discontinue antibiotics on discharge in the presence of a normal white blood cell count (WBC) without neutrophilia. We aimed to assess the effect of this practice change on rates of discharge antibiotics. We hypothesized that patients would receive fewer antibiotics without increased adverse events. |
| Timing of antimicrobial prophylaxis and infectious complications in pediatric patients undergoing appendectomy (25) | Cristen N. Litz | 2018 | Retrospective cohort study | 478 patients with acute appendicitis | The purpose of this study was to determine the impact of administering antibiotics within one hour prior to incision on infectious complications in pediatric patients with acute appendicitis who are started on parenteral antibiotics upon diagnosis. |
| Updates on bacterial resistance and empirical antibiotics treatment of complicated acute appendicitis in children (18) | Chun Pong Daniel Kwok | 2021 | Retrospective Historical Comparative Study | 257 children with acute appendicitis | We aim to provide updates on bacterial resistance and evidence-based recommendation on choice of empirical antibiotics over the decade. |
| Use of Antipseudomonal Antibiotics is not Associated with Lower Rates of Postoperative Drainage Procedures or More Favorable Culture Profiles in Children with Complicated Appendicitis: Results from a Multicenter Regional Research Consortium (64) | Shannon L Cramm | 2023 | Multicenter cohort study (using NSQIP-P data) | 1268 patients included with complicated appendicitis | The goal of this analysis was to compare rates of postoperative drainage procedures and microbiological culture profiles between children treated with PT or CM at 15 children's hospital |
| Validation of the American Association for the Surgery of Trauma grading system for acute appendicitis severity (5) | Charles A. Mouch | 2020 | Retrospective cross-sectional analysis of prospectively collected | 734 patients with acute appendicitis | Our objective was to conduct a retrospective cross-sectional analysis of prospectively collected data to determine the relationship between AAST grade and clinical outcomes in acute appendicitis. We hypothesized that prospectively collected AAST grades for appendicitis would be associated with clinical outcomes such as complications and hospital length of stay. By conducting this study, we provide support for use of the AAST grading scale as a valid and optimal measure for risk-adjustment in clinical benchmarking and outcomes research. |

# Infant regurgitation? Opt for Nutrilon® A.R.!

**Regurgitation is very common in infants, and can affect up to a third of them. It generally diminishes around 6 months, and usually ceases around 1 year. All too often, however, regurgitation is treated with medication, while scientific societies advocate the use of thickeners for formula feeding. Among these thickeners, locust bean gum has proved its worth, a benefit recently confirmed by two studies.**[9,10]

Regurgitation is a frequent, physiological and transient manifestation of gastro-oesophageal reflux disease (GERD) in infants. Its prevalence is around 30%, making it one of the most common functional digestive disorders in early childhood [1]. It often goes hand in hand with other gastrointestinal symptoms (78% also present with additional gastrointestinal disorders such as colic, flatulence or constipation) [2], which increase the risk of the child gaining insufficient weight and/or taking unnecessary medication. Regurgitation also reduces the quality of life of the child and its parents, for whom it is often a source of great anxiety, leading to many too rapid or inappropriate changes in milk formula [3]. With a view to reducing these risks, the European ESPGHAN and the American NASPGHAN have jointly issued recommendations to provide information on prevention (e.g. limiting the volume of feeding bottles), to reassure that the symptom is benign [4] and tends to disappear with time [5], and to suggest thickening milk before any other form of treatment [4].

## Thickening milk: the most sensible solution

Locust bean gum (LBG) has long proven its efficacy and safety, including in infants [6]. A natural product, this galactomannan polysaccharide is highly viscous and very low in calories. It also has the advantage of thickening directly in the bottle (rather than in the stomach as is the case for starch). What's more, this thickening occurs independently of the pH of its environment [7], and has a significant effect in reducing the frequency (down 78%) and severity (61% score reduction) of regurgitation episodes in otherwise healthy children [8].

These benefits translate into a significant improvement in the quality of life of infants and their families, marked by a 50% reduction in sleep disorders in infants, and a 54% reduction in their agitation. In addition, 58% of parents report less worry, anxiety and stress [7].

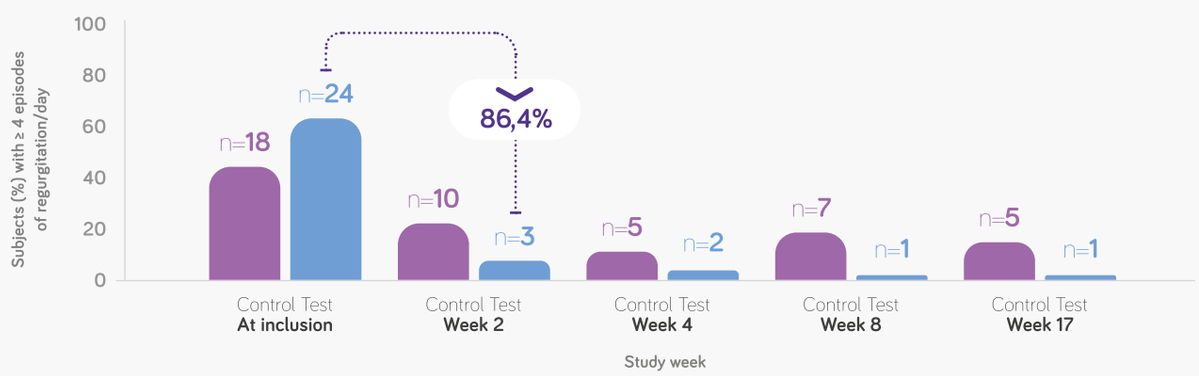
## New evidence presented at the ESPGHAN congress

### Improved stool consistency and significantly reduced frequency of regurgitation episodes [9]

The main aim of the study presented by Silvia Salvatore (Varese) was to assess the non-inferiority of an anti-regurgitation formula thickened with LBG in terms of stool consistency in infants with regurgitation. The study also analysed stool frequency, changes in the Infant Gastrointestinal Symptom Questionnaire (IGSQ) score, adverse events, child growth and severity of regurgitation.

This prospective randomised controlled trial enrolled 103 full-term infants aged 21 to 63 days with regurgitation diagnosed according to Rome IV criteria (presence of ≥ 2 episodes of regurgitation per day for ≥ 7 days). After randomisation, these infants received either the formula containing

Figure 1: **Decrease in regurgitation severity over time [9].**
In 2 weeks, the number of subjects with ≥ 4 regurgitations/day decreased by 86.4% in the test group versus 44.5% in the control group.



locust bean gum (0.4g/100ml), short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides (scGOS/lcFOS 9:1; 0.4g/100ml) as well as postbiotics (bioactive compounds derived from the Lactofidus™ fermentation process), or the control formula without LBG, but containing scGOS/lcFOS (0.8g/100ml) and postbiotics.

93 infants completed the study. The results showed non-inferiority in the test group in terms of stool consistency, which was also numerically better. Growth was similar in both groups, as was the incidence of diarrhea (3.9% vs. 3.8%) and flatulence (2.0% vs. 1.9%), which was low. No cases of constipation were reported. The total IGSQ score decreased comparably in both groups. Finally, the frequency of regurgitation was significantly lower in the test group at all time points after inclusion. Thus, after 2 weeks, the number of subjects presenting ≥ 4 regurgitations/day decreased by 86.4% in the test group versus 44.5% ($p < 0.028$) in the control group *(Figure 1)*, enabling the authors to infer the non-inferiority of the formula containing locust bean gum versus the control formula with regard to associated gastrointestinal symptoms. The frequency of regurgitation was significantly lower.

## Improved quality of life [10]

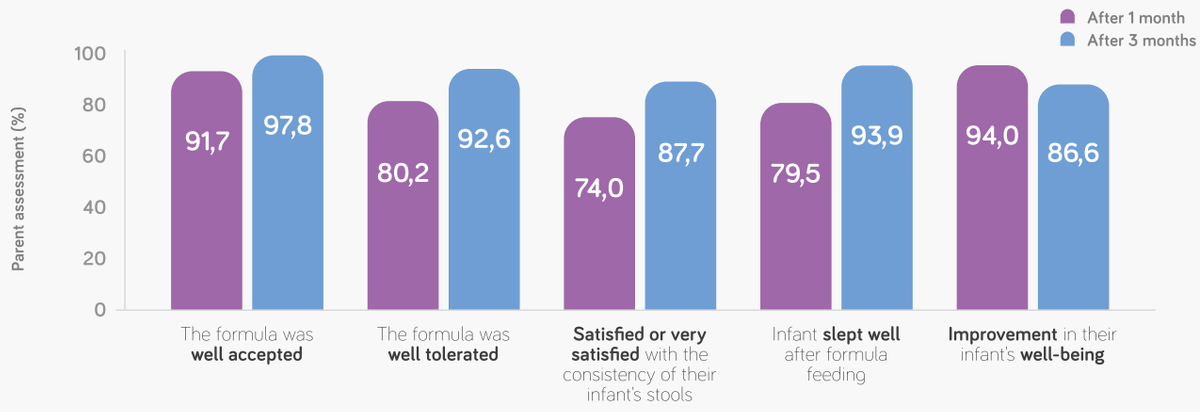
The study presented by Marc Bellaiche (Hôpital Robert Debré, Paris) presented the safety, tolerance and efficacy of the same anti-reflux milk as in the previous study in real-life situations. Efficacy was assessed in terms of stool consistency and frequency, prevalence of colic, constipation and diarrhea, severity of regurgitation and child growth. This 3-month, multicentre, observational study included 190 full-term infants with a mean age of 1.9 months, with regurgitation requiring prescription of anti-regurgitation infant milk in accordance with usual clinical practice. Parental ratings of infant crying, well-being and sleep quality, as well as parental satisfaction with stool consistency were also analysed.

Regurgitation severity was significantly reduced in 83.4% of infants at 1 month, and in 92.6% of infants at 3 months, compared with baseline values. Furthermore, stool frequency and consistency assessed at 3 months remained within the normal physiological range (82.7% of infants had 1 or 2 stools per day and 90.4% had soft or formed stools), with no significant increase in the number of infants suffering from diarrhea, and with a significant reduction at 1 month in constipation and at 1 and 3 months in the frequency of colic. Furthermore, quality of life was expressed by an increase in the number of infants crying less than one hour per 24 hours, from 29.3% at baseline to 74.9% at 1 month and 88.9% at 3 months. Parent assessment scores (intensity and frequency of crying, sleep quality) were all high (>85%) at 3 months, while growth remained adequate. The data also testify to the safety of this well-accepted formula *(Figure 2)*.

## Summary

All these studies show that the anti-regurgitation formulation containing LBG is an effective strategy for managing infant regurgitation and the commonly associated symptoms of intestinal discomfort. It also offers a significant improvement in quality of life for both child and parents.

Figure 2: **Acceptability of the Nutrilon® AR formula and impact on quality of life and infant well-being, as reported by parents [10].**




REFERENCES

1. Vandenplas Y, et al. J Pediatr Gastroenterol Nutr. 2015;61(5):531-7.
2. Bellaiche M, et al. Acta Paediatr. 2018;107(7):1276-82.
3. Vandenplas Y, et al. Pediatr Gastroenterol Hepatol Nutr. 2019;22(3):207-16.
4. Rosen R, et al. J Pediatr Gastroenterol Nutr. 2018;66(3):516-54.
5. Hegar B, et al. Acta Paediatr Int J Paediatr. 2009;98(7):1189-93.
6. Meunier L, et al. Regul Toxicol Pharmacol. 2014;70(1):155-69.
7. Tounian P, et al. Pediatr Gastroenterol Hepatol Nutr. 2020;23(6):511-20.
8. Wenzl TG, et al. Pediatrics 2003;111(4 Pt 1):e355-9.
9. Salvatore S, et al. J Pediatr Gastroenterol Nutr. 2023;76(S1):499.
10. Bellaiche M, et al. Pediatr Gastroenterol Hepatol Nutr. 2023 Sep;26(5):249-65.

**Any questions about our NUTRILON products?**
**Our dieticians are happy to help you on workdays from 8:30 a.m. to 5 p.m. (Fridays 4 p.m.).**
Telephone (freephone): 0800 16 685 - Whatsapp: +32 471 13 43 00 - Email: www.nutriciababy.be

NUTRICIA

# Gonadal Mosaicism in Rhabdoid Tumor Predisposition Syndrome

An-Sophie Lemoine [a], Marleen Renard [b,c], Eric Legius [d], Hilde Brems [d], Heidi Segers [b,e]

[a] Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium
[b] Department of Pediatric Oncology, University Hospital Leuven, Leuven, Belgium
[c] Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[d] Department of Human Genetics, KU Leuven and University Hospitals Leuven, Leuven, Belgium
[e] Department of Oncology – Pediatric Oncology, KU Leuven, Leuven, Belgium

ansophielemoine@hotmail.com

## Keywords

Rhabdoid tumor predisposition syndrome ; gonadal mosaicism.

## Abstract

Rhabdoid tumor (RT) is a malignant tumor occurring in children with a peak incidence between 1-4 years of age. The tumor exhibits diverse subtypes: atypical teratoid rhabdoid tumor (ATRT), malignant rhabdoid tumors in the kidney (MRTK) and extrarenal tumors (MRT). These malignancies are associated with a pathogenic variant in *SMARCB1* (98%) or *SMARCA4* (2%). Within 25-35% there is a germline pathogenic variant leading to rhabdoid tumor predisposition syndrome (RTPS). These variants can be inherited in an autosomal dominant mode, but most occur de novo. Even with a multimodal treatment the prognosis is poor. We report on a family with 2 siblings diagnosed with RT due to a germline nonsense pathogenic variant in *SMARCB1* caused by gonadal mosaicism. This germline variant was found in the 9-month-old brother who presented with metastatic MRTK and was absent in the parents. However familial recurrence of an RT occurred when a newborn sister presented with an ATRT. Both patients died from the disease. SNP haplotyping identified maternal gonadal mosaicism. Only seven families affected by RTPS due to gonadal mosaicism have been reported in the literature. The current new and more extensive genetic tests will probably identify more families with RTPS due to gonadal mosaicism. However, most germline pathogenic variants in children of healthy parents arise de novo, making it challenging to predict the risk of RT development in siblings. Therefore, extensive genetic testing in families with a child affected by RTPS is necessary to rule out gonadal mosaicism and to more accurately predict the possible recurrence risk of RT in siblings.

## Introduction

Rhabdoid tumor (RT) is a rare malignant tumor that occurs mostly in young children and infants with a peak incidence between 1 and 4 years (1). These RTs are divided into different groups according to their location. The most frequent is an atypical teratoid rhabdoid tumor (ATRT) which occurs in the central nervous system (65%). Furthermore, there are malignant RTs in the kidney (MRTK) (9%) and in extrarenal tissues (MRT) (26%). The extrarenal sites encompass the head and neck, liver, lungs, and almost all soft tissues and viscera (2). In more than 50% of the cases, metastases are present at diagnosis, the most frequent sites being the lungs, liver, lymph nodes and brain (3). Approximately 10% of the tumors present as synchronous tumors (4).

In 98% of the RTs, immunohistochemistry shows loss of INI-1 protein expression due to a *SMARCB1* deletion or a pathogenic inactivating variant in the *SMARCB1* gene on chromosome band 22q11.2, also referred to as the *SMARCB1* (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1) /INI1/BAF47/hSNF5 locus (4,5). In 2% the *SMARCA4* gene is involved. Both genes are tumor suppressor genes and give rise to subunits of the SWI/SNF (mammalian switch/sucrose non-fermentable) or BAF (BRG1/BRM-Associated Factor) ATP-dependent chromatin-remodeling complex (4–6). This complex controls the chromatin structure and is responsible for regulating gene transcription (1,7). It facilitates DNA replication, selective gene transcription, DNA repair and recombination (8). Dysregulation of the SWI/SNF complex in cancer can result in either loss-of-function of tumor suppressors and/or gain-of-function of oncogenic mechanisms (8). Their tumor-suppressing effects are likely due to the disruption of multiple coordinated pathways, rather than a single downstream target pathway. This is because the complex interacts with a large number of proteins and active enhancers, suggesting a broader impact on lineage-specific signaling pathways (9). Inactivation of the *SMARCB1* gene is also described within other tumors, for example, schwannomas, meningiomas, myeloid sarcoma, chondrosarcoma, ganglioglioma etc. (5,6,10). Inactivation of *SMARCA4* can also cause small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) and *SMARCA4*-deficient undifferentiated thoracic tumors (1,8).

Pathogenic variants in *SMARCB1* and *SMARCA4* can be somatically acquired, but 25-35% of the patients have a germline pathogenic variant in these genes which gives rise to the rhabdoid tumor predisposition syndrome (RTPS). A germline pathogenic variant in *SMARCB1* is causing RTPS1, while RTPS2 is caused by a germline pathogenic variant in *SMARCA4* (12). From these germline pathogenic variants, the majority originate de novo, however some cases of autosomal dominant inheritance and gonadal mosaicism are described in literature (2,5). Patients with RTPS follow Knudson's two-hit hypothesis, requiring besides the germline a second hit such as a somatic pathogenic variant or loss of the wild-type allele in the tumor, to develop an RT (6,9,11,12). They usually develop tumors at a median age of 4-7 months (sometimes even in the prenatal period), compared to children with sporadic RTs with a median age of 18 months. In addition, RTPS is characterized by aggressive and often synchronous tumors at diagnosis and by metachronous tumors. All these factors contribute to a worse prognosis in patients with this germline pathogenic variant (4,6,13).

Treatment options depend on several parameters, such as the age at diagnosis, the tumor location and the presence of metastasis. The EU-RHAB protocol proposes multimodal treatment including complete chirurgical resection, chemotherapy (also intraventricular in case of ATRT) and radiotherapy (4). In 58% of the children with RTPS who developed an RT, progression during chemotherapy occurs. Thereby most children die of progressive disseminated disease (2,14). Despite intensive multimodal therapy, 5-year overall survival rates of only 17% to 36% are reported by several studies (15,16).

The goal of this review is to give an overview of published families affected by RTs due to gonadal mosaicism. Moreover, we want to raise awareness of the possible recurrence of an RT in siblings of patients with an RT that seems to be caused by a 'de novo' pathogenic variant but in reality, is an RTPS due to gonadal mosaicism, emphasizing the importance of extensive genetic testing and counseling.

## Case report

A 9-mont-old presented to the emergency department with an acute abdomen. Radiographic evaluation showed a renal mass suspicious for nephroblastoma, as well as lung metastases. Preoperative chemotherapy (vincristine, actinomycin D and doxorubicin) was started according to SIOP-WT 2001 protocol (17). He had surgery with a right-sided nephrectomy, partial colectomy and para-aortic lymphadenectomy. Anatomic-pathological examination shows an MRTK local stage III because of positive lymph nodes. The postoperative chemotherapy was changed to EU-RHAB protocol (18). Nevertheless, tumor progression occurred with locoregional relapse and the development of liver metastases. Together with the parents we decided to stop chemotherapy and start palliative care. The patient died at the age of 15 months.

The subsequent results of the germline genetic analysis showed a heterozygote nonsense pathogenic variant NM_003073.5: c.601C>T p.(Arg201*) in the *SMARCB1* gene confirming the diagnosis of RTPS1. The parents also underwent genetic testing for this specific variant on white blood cells. This *SMARCB1* variant was absent by Sanger sequencing. It was therefore concluded to be a de novo mutation, keeping in mind that gonadal mosaicism could not be ruled out. Following the identification of the germline pathogenic variant in the boy, the parents were genetically counseled, but the mother was already pregnant at that time. At the same time, the non-affected 6-year-old brother and the 4-year-old sister of the boy were tested. The *SMARCB1* variant was absent in these two children.

A girl was born and there were no pre- and perinatal problems. At the age of 2 weeks, she presented with drinking difficulties and failure to thrive. A comprehensive diagnostic work-up showed a fossa posterior mass in the right cerebellopontine angle most compatible with ATRT based on MRI and the familial history. No biopsy was performed. Urgent germline genetic analysis in the girl confirmed the presence of the same *SMARCB1* pathogenic variant as her brother. Together with the parents it was decided to start palliative care and she died at the age of 5 weeks.

Because of two cases of malignant rhabdoid tumor in the same family with the same germline *SMARCB1* pathogenic variant, more extensive genetic analyses were performed in both parents as we were unable to detect this variant with Sanger sequencing in their white blood cells. To verify the presence of gonadal mosaicism, Sanger sequencing for the *SMARCB1* variant was negative on the spermatocytes of the father. In addition, deep next-generation sequencing for this variant (>345 000 reads) did not identify the *SMARCB1* variant. Thereafter, deep next-generation sequencing for this variant (>134 000 reads) did not identify the *SMARCB1* variant in the blood of the mother. As a next step, to evaluate whether the *SMARCB1* variant was present on the maternal allele, a haplotyping study was performed using the Human CytoSNP v1.2.-Infinium protocol. Single nucleotide polymorphism (SNP) array data from all family members were generated. The Human CytoSNP v1.2 is a streamlined panel designed for whole-genome scanning, enabling high-throughput analysis of genetic and structural variations. This panel is a product of the Infinium, which offers high sensitivity and specificity and it is particularly useful for identifying mosaicism, crucial for diagnosing genetic disorders (19,20).

To summarize the results of the mutation analysis and SNP haplotyping, a two-generation family of 6 people is presented, two parents and 4 children (Figure 1). The two younger affected children carry the same maternal allele with the *SMARCB1* pathogenic variant and a different paternal allele. The two older non-affected children carry a different maternal allele without the *SMARCB1* pathogenic variant. The non-affected son carries the same maternal allele as the 2 affected children; however, the only difference is that the pathogenic *SMARCB1* variant is not present. The non-affected children carry a different paternal allele. This haplotyping study determined that the variant is inherited from the mother, resulting from a mutation in mosaicism in the oocytes, probably occurred during oogenesis. This finding supports the suspicion of gonadal mosaicism.

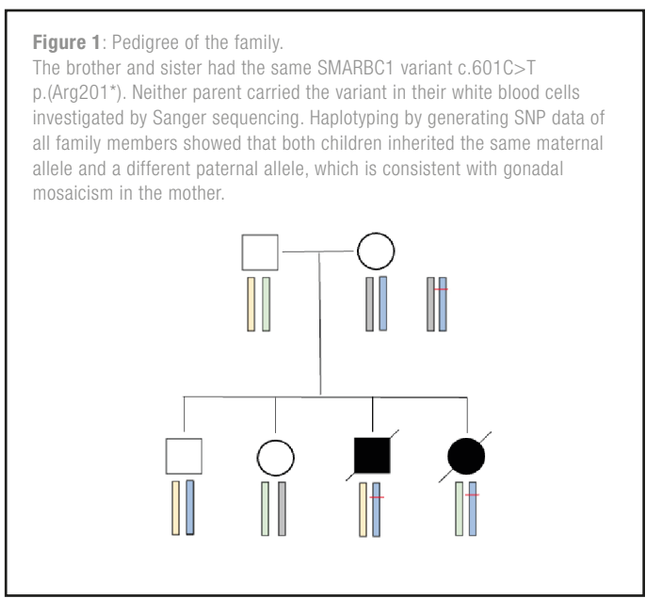


**Figure 1**: Pedigree of the family.
The brother and sister had the same SMARBC1 variant c.601C>T p.(Arg201*). Neither parent carried the variant in their white blood cells investigated by Sanger sequencing. Haplotyping by generating SNP data of all family members showed that both children inherited the same maternal allele and a different paternal allele, which is consistent with gonadal mosaicism in the mother.

## Methods

The PubMed databases were accessed from November 2021 until October 2023 for case studies, case series and reviews. The following medical subject headings (MeSH) terms were used: "rhabdoid tumor", "rhabdoid tumor predisposition syndrome", "rhabdoid tumor predisposition syndrome" AND "gonadal mosaicism, "gonadal mosaicism'. All the resulting titles were manually screened. Subsequently, an assessment of the abstracts was performed, followed by the review of the full texts as the basis for inclusion. Subsequently, the references of all retained papers were examined for relevant studies. In total 26 articles were retrieved. Informed consent was obtained from both parents to publish this case report.

## Literature review and discussion

We described a new family consisting of 4 children of whom 2 siblings were diagnosed with an RT caused by a germline pathogenic variant in *SMARCB1* due to maternal gonadal mosaicism. A review of the literature only reports 7 families with RTPS due to gonadal mosaicism, as summarized in Table 1. Regarding sex, results confirm the known slight male predominance; a 1.3-1.5 male-to-female ratio, by the occurrence of a malignancy in 9 boys and 7 girls (10). In all cases the RT diagnosis was made at a very young age, with the oldest only 12 months old. Although ATRT is reported as the most prevalent type, germline pathogenic variants do not increase the chance of a certain tumor location (21). In all reported families except for one, the diagnosis of RTPS due to gonadal mosaicism was only made after a recurrence of an RT in another sibling (22). This was also the case in our family.

We will provide a discussion regarding (i) why and for whom genetic testing is crucial to perform; (ii) the possibility and difficulties to make predictions for other family members based on genetic testing; (iii) current general recommendations for clinical surveillance in RTPS.

Literature rarely reports large pedigrees with transmission of the germline pathogenic variant across generations due to the diagnosis of RT at a very young age and the often fatal outcome. Germline pathogenic variants are mostly found in patients with congenital presentation or early-onset RT, advanced stage of RT at diagnosis, synchronous RTs and a family history of RT or RTPS (6). However, the European Society of Pediatric Oncology Host Genome working group (SIOP-HGWG) strongly advises to offer all patients with an RT genetic counseling and testing for a *SMARCB1* and *SMARCA4* germline pathogenic mutation (13). In case of the presence of a germline pathogenic variant in the affected child, parents and also siblings, need to be offered genetic counseling and testing. This regardless

of the parents' results due to the possibility of gonadal mosaicism. Patients with an SCCOHT should be tested for a germline *SMARCA4* pathogenic variant and if present, first-degree relatives should also be offered genetic counseling and testing. The purpose of genetic testing and counseling in case of a pathogenetic variant is to offer the possibility of a surveillance program for family members. A surveillance program aims to detect and treat tumors in an early stage thereby possibly improving survival rates. Besides the possibility of following a surveillance program, the presence of a pathogenic variant also implies the possibility of performing prenatal genetic testing or preimplantation genetic testing (PGT) (13). The decision to undergo PGT is a complex and personal one, but given the severity of the disease, its use is justified (22–24). In general, genetic counseling and testing are important to help affected family members make informed decisions whether or not to follow a surveillance program, to perform prenatal testing or PGT.

There are multiple reasons why predicting the risk of developing an RT within siblings of families with RTPS is difficult.

First, most germline *SMARCB1* and *SMARCA4* pathogenic variants within RTPS appear de novo. Therefore, besides routine genetic testing, no other genetic tests are performed when parents don't carry the pathogenic mutation in their white blood cells, especially when it is the first child in the family with an RT. Nonetheless, recurrence in siblings of healthy parents is possible due to gonadal mosaicism and may be more common than previously believed (2,6,23). When patients and their families undergo genetic counseling for a presumed de novo mutation, they are informed about the estimated 1% recurrence risk due to gonadal mosaicism. Unfortunately, no good data on the prevalence of apparent de novo mutations due to gonadal mosaicism within RTPS are available. This, among others, because the most exact method to detect gonadal mosaicism involves direct examination of germ cells for the pathogenic mutation. Paternal gonadal mosaicism is relatively easy to detect by collecting sperm cells and examining them by routine genetic tests for the presence or absence of the pathogenic mutation. In contrast, to identify maternal gonadal mosaicism a biopsy to evaluate oocytes is necessary. This is an invasive procedure that is almost never done in clinical practice. Moreover, there are currently no molecular diagnostic tests available that are routinely performed in daily clinical practice to detect maternal gonadal mosaicism, estimating there is an ever-higher underrepresentation in the literature of maternal gonadal mosaicism. This is also reflected in the data available from the reported families with RTPS due to gonadal mosaicism (see Table 1): 4 were paternal, 1 maternal and 2 not further specified (maternal or paternal). Taken together, gonadal mosaicism may be more common than previously believed, but it is imperceptible in routine genetic testing on blood samples (2,6,23). In case gonadal mosaicism is proven, it remains challenging to estimate the risk of recurrence in siblings, as it depends on the proportion of germ cells that carry this variant which is, even more in the case of maternal gonadal mosaicism, difficult to estimate (23,24).

Secondly, when a germline pathogenic variant in *SMARCB1* is confirmed, there is a high penetrance >90% by 5 years, but this is an incomplete and estimated penetrance (13). Only some small studies are available that report a few unaffected carriers such as the study of Eaton et al. reporting 22 cases of RTPS1 of whom 7 cases had an unaffected parent that carried the pathogenic variant (5,25). The reason for this incomplete penetrance is unknown. The current high estimated penetrance in patients with RPTS1 could be influenced by selection bias emphasizing the need to perform larger studies involving systematically screened trios (parents and affected offspring) to accurately define penetrance. There is even less data on the penetrance within RTPS2, making it at the moment almost impossible at the moment to make predictions (13).

Thirdly, as outlined in cases by Bourdeaut et al., there is no clear genotype-phenotype correlation. The same germline pathogenic variant may lead to the development of different types of RT at various ages. Furthermore, distinct tumor types may differently impact family members who carry the same variant in an unpredictable manner (21). This difficulty in predicting the phenotype linked with a certain genotype is also a concern in genetic counseling. Additionally, other tumors can occur in individuals who have been successfully treated for an initial RT, as alterations in SMARBC1/*SMARCA4* are not specific to RT (26,27). With RTPS1 there is a chance of developing late-onset schwannomas and meningiomas, particularly associated with splice site and missense mutations in *SMARCB1* (2,21). Females, 5-46 years of age, with RTPS2 have a higher risk of developing SCCOHT. This tumor can be regarded as a special type of MRT, given its close clinical, histologic and (epi)genomic resemblance to RTs (12). So, the presence of a germline pathogenic *SMARCA4* variant makes it necessary to offer genetic counseling and testing for women until 45 years of age in that family (13,28).

To date, there are no official recommendations for surveillance of carriers of germline *SMARCB1* or *SMARCA4* pathogenic variants. In 2020 the SIOP-HGWG organized a panel discussion with pediatric oncologists and genetics. They drafted a proposal outlining a surveillance program targeting unaffected carriers of *SMARCB1* or *SMARCA4* pathogenic variants and long-term survivors of RT (13). Among other sources, the article of Foulkes et al. was the basis for their recommendations (12). For carriers of a

**Table 1** : Clinical and molecular features of cases reported with *SMARCB1* gonadal mosaicism

| Reference | Gender | Age (months) | Type of malignancy | SMARCB1 pathogenic variant NM_003073.3 | Inheritance | Method to identify genetic origin of mutated allele |
|---|---|---|---|---|---|---|
| **Sévenet *et al.* (27) (Pedigree 2)** | M | 3 | Medulloblastoma | Unknown | Paternal mosaicism | Segregation and LOH analyses |
| | M | / | RT soft tissues of the neck | c.472C>T, p.(Arg158*) | | |
| **Sévenet *et al.* (27) (Pedigree 3)** | M | 4 | Choroid plexus carcinoma | c.591del, p.(Gln198Argfs*11) | Maternal mosaicism | Segregation and LOH analyses |
| | F | 2 | ATRT | c.591del, p.(Gln198Argfs*11) | | |
| | M | 12 | ATRT | c.591del, p.(Gln198Argfs*11) | Maternal mosaicism | |
| **Lee *et al.* (28)** | M | 7 | MRTK | c.472C>T, p.(Arg158*) | Gonadal mosaicism | |
| | F | 5 | ATRT | c.472C>T, p.(Arg158*) | Gonadal mosaicism | / |
| **Eaton *et al.* (5)** | F | 5 | Bladder sarcoma | c.20_43delinsT, p.(Ser7Ilefs*56) | Paternal mosaicism | Chromosome 22q microsatellite analysis |
| | F | 2 | ATRT | c.20_43delinsT, p.(Ser7Ilefs*56) | Paternal mosaicism | |
| **Bruggers *et al.* (14)** | M | 0 | ATRT | Unknown | | Single-nucleotide polymorphism array and multiplex ligation-dependent probe amplification |
| | F | 5 | ATRT | c.(362+1)_(363-1)_(c.628+1_629-1) | Paternal mosaicism | |
| | M | 0.5 | ATRT | c.(362+1)_(363-1)_(c.628+1_629-1) | Paternal mosaicism | |
| **Bourdeaut *et al.* (19)** | M | 3 | ATRT | c.472C>T, p.(Arg158*) | Paternal mosaicism | |
| | F | 8 | Spinal ATRT | c.472C>T , p.(Arg158*) | Paternal mosaicism | / |
| **Gigante *et al.* (20)** | M | 9 | MRT and ATRT | Deletion, LOH 22q | Paternal mosaicism | Chromosome 22q microsatellite analysis |
| | F | prenatal | / | Deletion, LOH 22q | Paternal mosaicism | |

M: Male; F: Female; RT: rhabdoid tumor; MRT, malignant rhabdoid tumor; ATRT, atypical teratoid rhabdoid tumor; MRTK, malignant rhabdoid tumor in the kidney; MRT malignant rhabdoid tumor; LOH 22q: Loss of heterozygosity of the long arm of chromosome 22

*SMARCB1* or *SMARCA4* pathogenic variant who have not yet developed a tumor, clinical monitoring should be started as soon as possible. The proposed surveillance program by the SIOP-HGWG includes extensive clinical examination every 4-6 weeks and an MRI of the brain together with an ultrasound of the abdomen and kidneys every 3 months during early infancy through the age of 5 years (7,13). The likelihood of experiencing a new onset of RT significantly diminishes after 5 years of age. Nonetheless, it remains advisable to continue follow-up, not only for MRT but also for other potential manifestations such as schwannomas and meningiomas (6). Here the SIOP-HGWG proposes a physical examination every 6 months and a yearly whole-body MRI (13). But for how long can a long-term follow-up program be justified? Some case reports suggest a lifelong threat, but the risk of an RT in unaffected carrier parents is not thoroughly assessed. Thus, it is essential to properly educate patients to seek medical advice when symptoms occur so that imaging can be done in a timely manner. The SIOPS-HGWG proposes the same surveillance program for children with RTPS who were treated for an RT, on top of their own specific follow-up schedule for their treated tumor type hereby also keeping in mind the risk of secondary tumors. For all females who carry a *SMARCA4* pathogenic variant, it is recommended to continue surveillance from 5 through the age of 45 with a gynecological ultrasound due to the increased risk of SCCOHT. On a case-by-case basis, preventive oophorectomies can be discussed considering factors such as the patient's age and pregnancy wish, family history and, ideally, new studies to better estimate the risk (12,13,28). Finally, it remains unclear what to do with parents of children with RTPS due to gonadal mosaicism. To date, no studies are available reporting RT or other related tumors in parents with *SMARCB1* or *SMARCA4* gonadal mosaicism.

## Conclusion

We described a family with 2 successive siblings diagnosed with RT due to a germline nonsense pathogenic variant in *SMARCB1* caused by maternal gonadal mosaicism. It is important to be aware of the possible recurrence of an RT in siblings of patients with an RT that appears to be caused by a 'de novo' pathogenic variant but is actually RTPS caused by gonadal mosaicism. Literature review only described seven other families affected by RTPS due to gonadal mosaicism. With the advent of new and more extensive genetic tests, more families with RTPS due to gonadal mosaicism will likely be identified. However, most germline *SMARCB1* and *SMARCA4* pathogenic variants in children of healthy parents arise de novo, making it challenging to predict the risk of RT development in siblings. Therefore, extensive genetic testing in families with a child affected by RTPS is crucial to rule out gonadal mosaicism and to predict more accurately the possible recurrence risk of RT within siblings.

Surveillance recommendations for carriers of *SMARCB1* or *SMARCA4* pathogenic variants are currently evolving, with proposed programs for unaffected carriers and long-term survivors of RT. However, the duration of long-term follow-up remains a topic of debate. Moreover, literature mentions nothing about the follow-up of parents of children affected by RTPS due to gonadal mosaicism. Further research and collaboration in this field are essential to provide better guidance and support to affected families.

## Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript..

## Acknowledgments

The authors thank the parents who shared valuable information and insight into this disease. We want to thank Cindy Melotte and Eftychia Dimitriadou for their technical assistance with SNP haplotyping.

REFERENCES

1. Geller JI, Roth JJ, Biegel JA. Biology and treatment of rhabdoid tumor. Crit Rev Oncog. 2015;20(3–4):199–216.
2. Del Baldo G, Carta R, Alessi I, Merli P, Agolini E, Rinelli M, et al. Rhabdoid tumor predisposition syndrome: From clinical suspicion to general management. Front Oncol. 2021 Feb 22;11.
3. Hart I. Fetal and neonatal rhabdoid tumor. Vol. 45, Journal of Pediatric Surgery. J Pediatr Surg; 2010. p. 619–26.
4. Nemes K, Clément N, Kachanov D, Bens S, Hasselblatt M, Timmermann B, et al. The extraordinary challenge of treating patients with congenital rhabdoid tumors—a collaborative European effort. Pediatr Blood Cancer. 2018 Jun 1;65(6).
5. Eaton KW, Tooke LS, Wainwright LM, Judkins AR, Biegel JA. Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors. Vol. 56, Pediatric Blood and Cancer. Pediatr Blood Cancer; 2011. p. 7–15.
6. Sredni ST, Tomita T. Rhabdoid tumor predisposition syndrome. Pediatric and Developmental Pathology. 2017 Jan 1;18(1):49–58.
7. Teplick A, Kowalski M, Biegel JA, Nichols KE. Educational paper: screening in cancer predisposition syndromes: guidelines for the general pediatrician. Eur J Pediatr. 2011 Mar;170(3):285–94.
8. Schaefer IM, Qian X. The roles of the SWI/SNF complex in cancer. Cancer Cytopathol [Internet]. 2023 Jul 1;131(7):410. Available from: /pmc/articles/PMC10330080/
9. Kim KH, Roberts CWM. Mechanisms by which SMARCB1 loss drives rhabdoid tumor growth. Cancer Genet. 2014 Sep 1;207(9):365–72.
10. Frühwald MC, Biegel JA, Bourdeaut F, Roberts CWM, Chi SN. Atypical teratoid/rhabdoid tumors-current concepts, advances in biology, and potential future therapies. Neuro Oncol. 2016 Jun 10;18(6):764–78.
11. Wilson BG, Roberts CWM. SWI/SNF nucleosome remodellers and cancer. Nat Rev Cancer. 2011 Jul;11(7):481–92.
12. Foulkes WD, Kamihara J, Evans DGR, Brugières L, Bourdeaut F, Molenaar JJ, et al. Cancer surveillance in Gorlin syndrome and rhabdoid tumor predisposition syndrome. Vol. 23, Clinical Cancer Research. Clin Cancer Res; 2017. p. e62–7.
13. Frühwald MC, Nemes K, Boztug H, Cornips MCA, Evans DG, Farah R, et al. Current recommendations for clinical surveillance and genetic testing in rhabdoid tumor predisposition: a report from the SIOPE Host Genome Working Group. Fam Cancer. 2021 Oct 1;20(4):305–16.
14. Bruggers CS, Bleyl SB, Pysher T, Barnette P, Afify Z, Walker M, et al. Clinicopathologic comparison of familial versus sporadic atypical teratoid/rhabdoid tumors (AT/RT) of the central nervous system. Pediatr Blood Cancer. 2011 Jul 1;56(7):1026–31.
15. Seeringer A, Bartelheim K, Kerl K, Hasselblatt M, Leuschner I, Rutkowski S, et al. Feasibility of intensive multimodal therapy in infants affected by rhabdoid tumors - Experience of the EU-RHAB registry. Klin Padiatr. 2014;226(3):143–8.
16. Pawel BR. SMARCB1-deficient Tumors of Childhood: A Practical Guide. Vol. 21, Pediatric and Developmental Pathology. Pediatr Dev Pathol; 2018. p. 6–28.
17. I-iii S. Umbrella protocol siop-rtsg 2016. 2016;(October).
18. Michael C. Frühwald. European Rhabdoid Registry Eu-Rhab. 2010;1–384.
19. Li M, Li C, Guan W. Evaluation of coverage variation of SNP chips for genome-wide association studies. Eur J Hum Genet. 2008 May;16(5):635–43.
20. Illumina ® Dna analysis. Available from: https://www.cancer.gov/ccg/research/structural-genomics/tcga/using-tcga-data/technology/illumina-hd-beadchip-data-sheet
21. Bourdeaut F, Lequin D, Brugières L, Reynaud S, Dufour C, Doz F, et al. Frequent hSNF5/INI1 germline mutations in patients with rhabdoid tumor. Clin Cancer Res. 2011 Jan 1;17(1):31–8.
22. Gigante L, Paganini I, Frontali M, Ciabattoni S, Sangiuolo FC, Papi L. Rhabdoid tumor predisposition syndrome caused by SMARCB1 constitutional deletion: prenatal detection of new case of recurrence in siblings due to gonadal mosaicism. Fam Cancer. 2016 Jan 1;15(1):123–6.
23. Lee M, Lui ACY, Chan JCK, Doong PHL, Kwong AKY, Mak CCY, et al. Revealing parental mosaicism: the hidden answer to the recurrence of apparent de novo variants. Hum Genomics [Internet]. 2023;17(1):91. Available from: https://doi.org/10.1186/s40246-023-00535-y
24. Zemet R, Van den Veyver IB, Stankiewicz P. Parental mosaicism for apparent de novo genetic variants: Scope, detection, and counseling challenges. Prenat Diagn. 2022 Jun 1;42(7):811–21.
25. Harris TJ, Donahue JE, Shur N, Tung GA. Case 168: Rhabdoid predisposition syndrome - Familial cancer syndromes in children. Radiology. 2011 Apr;259(1):298–302.
26. Bhatt MD, Al-Karmi S, Druker H, Gupta A, Lu M, Malkin D, et al. Second rhabdoid tumor 8 years after treatment of atypical teratoid/rhabdoid tumor in a child with germline SMARCB1 mutation. Pediatr Blood Cancer. 2019 Mar;66(3).
27. Fukushima H, Yamasaki K, Sakaida M, Tsujio N, Okuno T, Ishii N, et al. Rhabdoid tumor predisposition syndrome with renal tumor 10 years after brain tumor. Pathol Int. 2021 Feb 1;71(2):155–60.
28. Berchuck A, Witkowski L, Hasselblatt M, Foulkes WD. Prophylactic oophorectomy for hereditary small cell carcinoma of the ovary, hypercalcemic type. Gynecol Oncol Rep [Internet]. 2015;12:20–2. Available from: http://dx.doi.org/10.1016/j.gore.2015.02.002

# 1 OP 2 BABY'S KRIJGT VOOR DE LEEFTIJD VAN 6 MAANDEN TE MAKEN MET MINSTENS 1 FUNCTIONELE GASTRO-INTESTINALE STOORNIS.[1]

# DICHT BIJ JEZELF.


**Belangrijk:** Borstvoeding is de ideale voeding voor baby's. Informatie uitsluitend bestemd voor het (para)medisch korps.
Nutrilon® Omneo is een voeding voor medisch gebruik. Dieetvoeding bij krampen, kolieken, moeizame ontlasting, constipatie en milde regurgitatie.
Te gebruiken onder medisch toezicht.
Nutrilon® A.R. is een voeding voor medisch gebruik. Dieetvoeding bij reflux en regurgitatie. Te gebruiken onder medisch toezicht.
Referentie: 1. Iacono G, et al. Dig Liver Dis. 2005;37:432-8.

Nutrilon®

# *Salmonella paratyphi B* Sepsis with Secondary Hemophagocytic Lymphohistiocytosis in a Child

Leni Waeterschoot [a,b], Charles C. Obihara [a]

[a] Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands
[b] University Hospital Antwerp, Belgium

leniwaeterschoot@gmail.com ; c.obihara@etz.nl

## Keywords

*Salmonella paratyphi*, *Salmonella typhi*, Hemophagocytic Lymphohistiocytosis, HLH, secondary Hemophagocytic Lymphohistiocytosis.

## Abstract

Hemophagocytosis lymphohistiocytosis is a state of hyperinflammation with activated macrophages, cytokine storm and tissue destruction. It can be triggered by immune activation during infection. We report the case of an 8-year-old septic girl who presented with 8 days of fever, diarrhoea and splenomegaly. Laboratory abnormalities, blood and faeces cultures confirmed haemophagocytosis lymphohistiocytosis triggered by *Salmonella paratyphi B* infection, which has never been reported in children. We present a narrative review of the literature.

## Introduction

HLH is a syndrome with high morbidity and mortality caused by excessive immune activation. In patients with HLH, a trigger, such as an infection, causes a state of hyperinflammation by activation of macrophages. In addition, natural killer cells and cytotoxic T-lymphocytes fail to eliminate these activated macrophages. This results in a cytokine storm, haemophagocytosis and multi-organ involvement or failure. HLH is subdivided into primary HLH and secondary HLH.

Patients with primary HLH have a gene mutation and usually present with HLH the first few years of life and a have positive family history of HLH. Even less aggressive infectious agents like enteroviruses can trigger HLH. In secondary HLH patients have no genetic predisposition and only invasive microorganisms can provoke HLH by uncontrolled immune activation. The presence of a malignancy or primary immunodeficiency contributes to a predisposition to develop HLH (1, 2). Treatment of secondary HLH caused by an infection, as in our patient, consists of

**Figure 1**: Literature search.

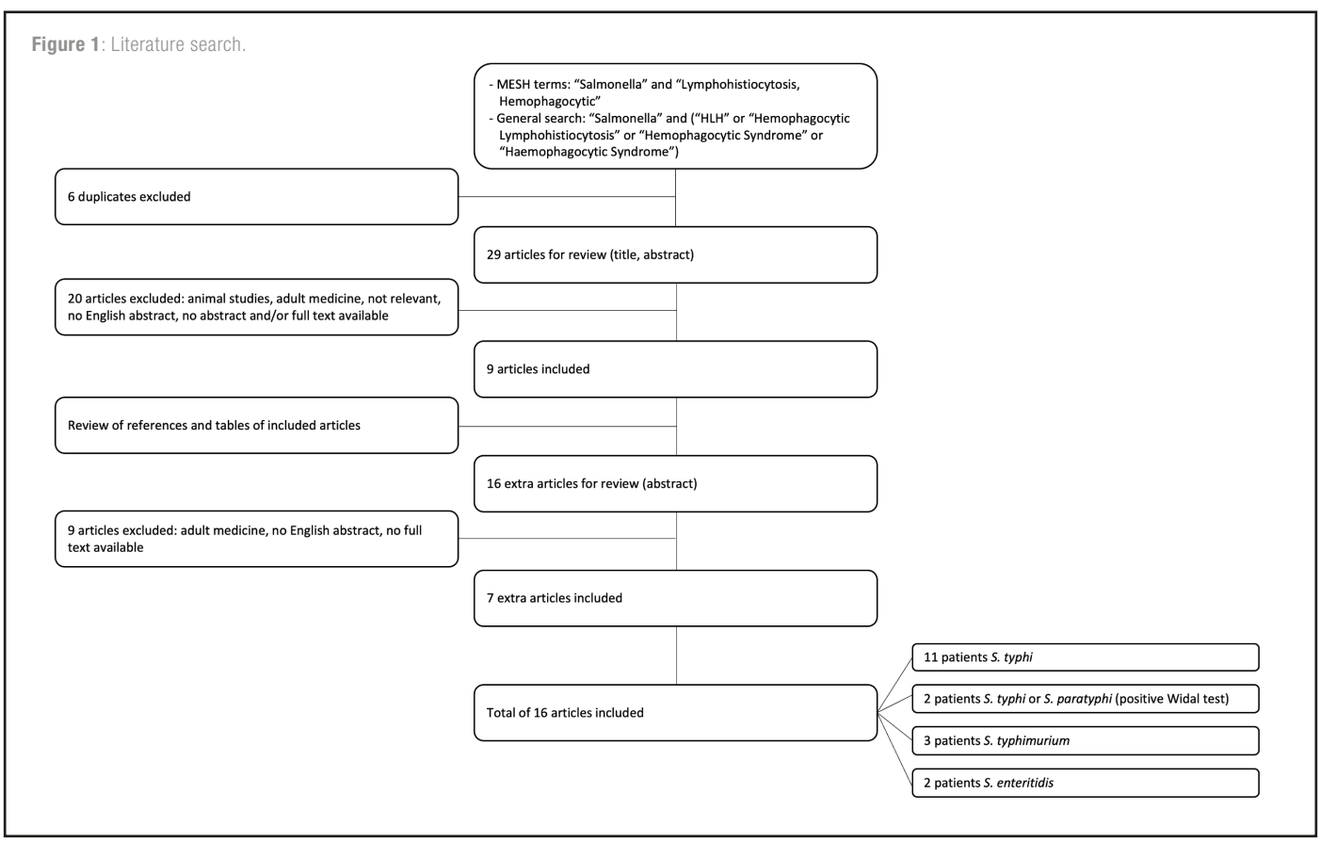


**Table 1**: Main blood laboratory parameters on presentation to the emergency department.

| Laboratory parameter | Laboratory value | Normal value[1] |
|---|---|---|
| **Haemoglobin** | 6,6 mmol/L (↓) | 7,2-9,6 mmol/L |
| **Leucocytes** | 2,9 10E9/L (↓) | 4-11 10E9/L |
| **Absolute lymphocytes** | 0,6 10E9/L (↓) | 1-5 10E9/L |
| **Thrombocytes** | 50 10E9/L (↓) | 150-400 10E9/L |
| **APTT** | 32,6 s | 24-37 s |
| **PT** | 12,8 s | 10-13,5 s |
| **D-dimers** | >128000 ng/mL (↑) | <500 ng/mL |
| **Fibrinogen** | 1,93 g/L (↓) | 2-4,5 g/L |
| **pH** | 7,47 (↑) | 7,32-7,43 |
| **pCO2** | 4,3 kPa (↓) | 5,5-6,8 kPa |
| **Bicarbonate** | 24 mmol/L | 23-29 mmol/L |
| **Base excess** | 0,4 mmol/L | -3 - 3 mmol/L |
| **Lactate** | 0,9 mmol/L | 0,5-2,2 mmol/L |
| **Glucose** | 6,4 mmol/L | 4-7,8 mmol/L |
| **Urea** | 4,3 mmol/L | 2,5-6 mmol/L |
| **Creatinine** | 58 µmol/L | 15-72 µmol/L |
| **Uric acid** | 0,25 mmol/L | 0,15-0,40 mmol/L |
| **Sodium** | 124 mmol/L (↓) | 135-145 mmol/L |
| **Potassium** | 2,5 mmol/L (↓) | 3,6-5 mmol/L |
| **Calcium** | 2 mmol/L (↓) | 2,2-2,7 mmol/L |
| **Gamma GT** | 14 U/L | <40 U/L |
| **ASAT** | 201 U/L (↑) | <31 U/L |
| **ALAT** | 40 U/L (↑) | <35 U/L |
| **LDH** | 1466 U/L (↑) | < 350 U/L (2-12 years) |
| **CK** | 932 U/L (↑) | <145 U/L |
| **Hs-Troponin T** | 11 ng/L | <12 ng/L |
| **NT-Pro-BNP** | 17,3 pmol/L (↑) | <9,8 pmol/L |
| **Triglycerides (non-fasting)** | 3,87 mmol/L (↑) | <2 mmol/L |
| **Ferritin** | 12986 µg/L (↑) | 8-110 µg/L |
| **Haptoglobin** | <0,1 g/L (↓) | 0,3-2 g/L |
| **CRP** | 157 mg/L (↑) | <10 mg/L |
| **Albumin** | 37 g/L | 35-50 g/L |
| **Soluble IL-2 Receptor** | >7500 U/mL (↑) | 158-623 U/mL |

[1] Normal values as reported by the local laboratory of the Elisabeth-Tweesteden Hospital Tilburg.

adequate treatment of the underlying infection in combination with corticosteroids (3). However, if the patient does not respond within 24-48 hours, a full HLH therapy including chemotherapy such as etoposide as proposed in the HLH 2004 guidelines, may be necessary (1, 4).

## Case report

An 8-year-old girl with no relevant medical history presented to the emergency department of the Elisabeth-Tweesteden Hospital (ETZ) in the Netherlands with a fever of 8 days' duration. Her parents reported that she had an average of three watery stools per day and she was suffering from extreme fatigue. A conjunctival injection of the left eye which they had initially observed, had resolved. There were no sick contacts at home or at school. She had received all the recommended immunizations. The last time she had travelled to the north of Iraq, her country of origin, had been 4 months ago. Her medical history was otherwise uneventful. On presentation, monitoring of her vital signs showed a free airway, respiratory rate of 28/min (normal value 15-25/min), oxygen saturation of 98% (normal value >95%), heart rate of 135 beats/min (normal value 70-120 beats/min), normal blood pressure of 105/59 mmHg (systolic blood pressure 50th percentile 90-110 mmHg) and body temperature of 36.9°C (normal value 36.5-37.5°C) (5).

On physical examination she appeared ill. She had a pale skin colour, minimal cervical lymphadenopathy, dry cracked lips, mild splenomegaly (1cm below the left costal margin) and a painful abdomen without guarding on palpation. The initial laboratory findings are shown in Table 1. There was marked pancytopenia, haemolysis, hyponatremia, hypokalaemia, elevated transaminases, elevated creatinine kinase, hypertriglyceridemia, hypofibrinogenaemia, elevated D-dimers, high inflammatory markers and elevated soluble interleukin-2 (IL-2) receptor. The chest x-ray was unremarkable. Abdominal ultrasound confirmed a mild splenomegaly of 13 cm (normal < 10,5 cm (6)) with some free intraperitoneal fluid collection and no hepatomegaly. After taking blood and faeces culture, we started empirical treatment with intravenous ceftriaxone and fluid challenge with 20 ml/kg normal saline 0.9% for impending circulatory shock. Sodium and potassium depletion was corrected. She was transferred to the regional paediatric intensive care unit (PICU) for further, diagnostic evaluation and management.

Additional serological and molecular testing during the PICU admission revealed negative infectious serology (negative immunoglobulin (Ig) G and IgM for parvovirus B19, cytomegalovirus and Ebstein-Barr virus, negative anti-streptolysin titre and anti-DNAse B and negative Leishmania DNA). A bone marrow examination was performed. It showed a moderately cell-rich bone marrow with mildly reduced erythropoiesis and lymphohistiocytic infiltration. There was no evidence of neoplasia or haemophagocytosis. Blood and faeces cultures were positive for *Salmonella paratyphi B*. Since the patient's fever persisted after 3 days of antibiotic treatment, other alternative diagnoses, such as haemophagocytic lymphohistiocytosis (HLH) were considered. Despite a bone marrow without signs of haemophagocytosis, the patient fulfilled at least 5 of the 8 clinical and laboratory diagnostic criteria as proposed by the HLH-2004 guidelines study: fever, splenomegaly, hypertriglyceridemia, high ferritin and a high soluble IL-2 receptor (1). Pancytopenia was also present, but the deficiencies were too mild to fulfil this criterion. Natural killer cell (NK-cell) activity was not tested.

Ceftriaxone therapy was continued intravenously for 10 days. To be on the safe side, because of the possibility of *S. paratyphi* drug resistance to ceftriaxone because of persistent fever after 48 hours, we pragmatically added oral azithromycin for 5 days, while waiting for the result of the antibiogram. We considered the patient's recent travel to Iraq and the possibility that she had been infected there. However, the susceptibility results showed sensitivity to ceftriaxone. In addition to ceftriaxone and azithromycin, we added intravenous dexamethasone at a dose of 0,15mg/kg for 5 days due to persistent fever after 48 hours. Due to another fever spike on the 5th day of intravenous dexamethasone treatment, we prolonged the treatment orally for 3 days at a dosage of 5 mg/m2. After this, the patient had no more fever. Despite the absence of bleeding, the patient presented with depleted serum fibrinogen (reported as too low by our laboratory) which required suppletion with 3 g intravenous fibrinogen (Haemocomplettan®) (7). Thereafter, there was a rapid clinical and laboratory improvement. All laboratory parameters normalised. She was discharged after 14 days of hospitalisation, including 7 days in the PICU. Immunological tests conducted during outpatient follow-up at 6 weeks after discharge showed a transient low CD-19 cell count of 197 x106/L (normal range: 300-700 x106/L). This normalised spontaneously after 5 months. There was no depletion of other lymphocytes, including NK-cells: 441 x106/L (normal range: 100-600 x106/L).

We concluded that this patient suffered from a secondary form of HLH triggered by the infectious agent, *S. paratyphi B*. The elevated liver enzymes and lipase were believed to be related to the multiorgan involvement caused by either the HLH or *Salmonella* sepsis, or both. However, it is not unthinkable to consider the side effects of ceftriaxone.

## Literature search

To our knowledge there are no similar reports of secondary HLH caused by *Salmonella paratyphi B* in children. We, therefore, conducted

**Table 2**: Literature review.

| First author | Year publication | Country | Patient details | Cultured *Salmonella species* | HLH criteria mentioned (HLH-2004 study) | Treatment | Comments |
|---|---|---|---|---|---|---|---|
| **Benz-Lemoine (8)** | 1984 | France | 7-year old, boy (with CGD) | *S. typhimurium* (blood culture) | Fever, splenomegaly, cytopenia(s), BME showing haemophagocytosis. | NA | Case report. |
| **Udden (9)** | 1986 | United States | 17-year old, boy | *S. typhi* (blood culture) | Fever, pancytopenia, BME showing haemophagocytosis. | NA | Case report. |
| **Fame (10)** | 1986 | United States | 13-year old, girl | *S. typhi* (stool and blood culture) | Fever, splenomegaly, pancytopenia, BME showing haemophagocytosis | Ampicillin IV switch to amoxicillin PO switch to trimethoprim-sulfamethoxazole IV then PO | Case report. |
| **Mallouh (11)** | 1987 | Saudi Arabia | 3 children | *S. typhi* | Fever, cytopenia(s), BME showing haemophagocytosis | NA | Case series. |
| **Stéphan (12)** | 2001 | France | 1 child | *S. enteritidis* | Fever, splenomegaly, hypofibrinogenaemia, hypertriglyceridaemia | NA | Retrospective study. |
| **Caksen (6)** | 2003 | Turkey | 6-year old, boy | Positive Widal test for *S. typhi* | Fever, splenomegaly, pancytopenia, BME showing haemophagocytosis | Chloramphenicol PO | Case report. |
| **Pandey (14)** | 2012 | India | 10-year old, boy | Positive Widal test | Fever, splenomegaly, pancytopenia, elevated ferritin, hypertriglyceridaemia, BME showing haemophagocytosis | Ceftriaxone IV | Case report. |
| **Pande (13)** | 2016 | India | 13-year old, girl | Positive Widal test, *Salmonella* (blood culture) | Fever, splenomegaly, pancytopenia, elevated ferritin, hypertriglyceridaemia, BME showing haemophagocytosis | Cefeperazone+sulbactam IV switch to piperacillin+tazobactam IV, prednisolone IV and PO | Case report. |
| **Abbas (15)** | 2018 | Pakistan | 4-year old, girl | *S. typhi* (blood culture) | Fever, pancytopenia, elevated ferritin, hypertriglyceridaemia, hypofibrinogenemia, BME showing haemophagocytosis | Ceftriaxone IV switch to tazobactam IV | Case report. |
| **Uribe-Londono (16)** | 2018 | Colombia | 8-year old, girl | *S. typhi* (bone marrow and blood culture) | Fever, splenomegaly, pancytopenia, elevated ferritin, hypertriglyceridaemia | Piperacillin-tazobactam IV with switch to ciprofloxacin, IVIG | Case report and literature review. |
| **Sánchez-Moreno (17)** | 2019 | Spain | 7-year old, boy | *S. typhi* (stool and blood culture) | Fever, splenomegaly, pancytopenia, elevated ferritin, hypofibrinogenemia | Ceftriaxone IV, methylprednisolone | Case report and literature review. |
| **Yasar (18)** | 2019 | Turkey | 14-year old, girl | *S. typhi* (blood culture) | Fever, pancytopenia, elevated ferritin, hypofibrinogenemia, BME showing haemophagocytosis | Ceftriaxone IV, dexamethasone, IVIG | Case report. |
| **Banday (19)** | 2020 | India | 12-year-old, boy | Positive Widal test, *S. enteritidis* (bone marrow and blood culture) | Fever, splenomegaly, cytopenia, elevated ferritin, hypofibrinogenemia, BME showing haemophagocytosis | Ceftriaxone IV with switch to meropenem IV, dexamethasone IV | Case report and literature review. |
| **Durmus (20)** | 2020 | Turkey | 9-year old, boy | *S. typhimurium* (blood culture) | Fever, splenomegaly, cytopenia, elevated ferritin, hypertriglyceridaemia, hypofibrinogenemia | Ceftriaxone IV, IVIG | Case report. |
| **Wei (21)** | 2020 | China | 3-year old, boy (with CGD) | *S. typhimurium* (bone marrow and blood culture) | Fever, splenomegaly, pancytopenia, elevated ferritin, elevated soluble CD25, hypofibrinogenemia, decreased NK cell activity, BME showing haemophagocytosis | Meropenem IV, methylprednisolone | Case report. |
| **Dange (22)** | 2021 | India | 5-year old, girl | Positive Widal test, *S. typhi* (cerebrospinal fluid and blood culture) | Fever, splenomegaly, pancytopenia, elevated ferritin, hypertriglyceridaemia, BME showing haemophagocytosis | Ceftriaxone IV, dexamethasone, etoposide | Case report. |
| **Waeterschoot (our report)** | 2022 | The Netherlands | 8-year old, girl | *S. paratyphi B* (stool and blood culture) | Fever, splenomegaly, elevated ferritin, hypertriglyceridaemia, hypofibrinogenemia, elevated soluble CD25 | Ceftriaxone IV, azithromycin PO, dexamethasone | Case report and literature review. |

a literature search in PubMed on 30th of March 2023, with the following search terms: "*Salmonella*" AND "Lymphohistiocytosis, Hemophagocytosis" as MeSH search terms or "*Salmonella*" AND "HLH" OR "Hemophagocytic Lymphohistiocytosis" OR "Hemophagocytic Syndrome" OR "Haemophagocytic Syndrome". The summary of the results of our search is shown in Figure 1.

Of the 29 original articles we identified, 20 were excluded for the following reasons: animal study, disease onset > 18 years of age, irrelevant to the research question, no English abstract available, no abstract and full text available. The remaining 9 articles were all case reports or case studies. Screening of these papers based on the same criteria led to the inclusion of 7 extra articles, resulting in a total of 16 included articles.

## Results

All the 16 included papers were case reports or case studies, with 1 to 3 patients reported (4, 8-22). They included a total of 18 paediatric patients. Only 3 papers included a review of the literature. The microbiological diagnoses of included patients were *Salmonella typhi* [11], *Salmonella typhimurium* [3], *Salmonella enteritidis* [2] and *S. typhi* or *S. paratyphi* [2] (based on positive Widal tests). These studies are summarised in Table 3.

## Discussion

To our knowledge, this is the first paediatric report of HLH in which *S. paratyphi B* was cultured in both blood and stool.

Considering the pathophysiology of enteric fever, the *S. (para)typhi* organism penetrates the intestinal epithelium after ingestion of contaminated food or water. Within the endothelial cell, proliferation and subsequent hypertrophy of Peyer's patches occurs through recruitment of mononuclear cells and lymphocytes. Further dissemination and replication in the reticuloendothelial system causes hepatosplenomegaly and generalised sepsis. Activation of phagocytes plays a crucial role in the body's defence against enteric fever. However, if this is not appropriately regulated there is a risk of developing HLH (1, 23, 24).

Although infections with *Salmonella* species have been implicated as triggers of HLH, only a few cases have been reported so far in the literature (see Table 3). Our literature search did not yield any report of paediatric patients with HLH triggered by *Salmonella paratyphi* infection. In 2013, Nath et al. reported the case of an 18-year-old male with clinical criteria for HLH and a positive *S. paratyphi* A blood culture (25). His bone marrow examination showed haemophagocytic changes. He was successfully treated with a 10-day course of intravenous ceftriaxone and dexamethasone. Our case differs from this case not only in age, but also in the *S. paratyphi* serotype and in the absence of haemophagocytic changes in the bone marrow. However, it should remembered that this morphological hallmark of HLH is quite often absent in the bone marrow or lymph nodes, especially in the early stages of HLH (26).

The literature search identified 5 patients (4, 13, 14, 19, 22) in whom the diagnosis was based on a positive Widal test. The Widal test is a serological test for the detection of agglutinating antibodies to the O and H antigens of *S. typhi* and *paratyphi*. However, the World Health Organization doesn't recommend this test for diagnosis since it is time-consuming and unreliable due to low sensitivity (false-negative results due to hypoproteinaemia or weak and delayed antibody response in non-endemic areas) and specificity (false-positive results in vaccinated or previously infected patients) (27).

The incidence of HLH is unknown although it is associated with high morbidity and mortality. It is more common in children than in adults. The highest incidence is seen in children less under the age of 3 months (28).

The Netherlands is a low endemic country for typhoid and paratyphoid fever, both accounting for 0.36 cases per 100.000 persons in 2017 (latest available statistics from the European Centre for Disease Prevention and Control, ECDC) (28, 29). This number has been stable over the period 2013-2017, with a seasonal distribution and predominantly being a travellers' disease. Most of the reported cases were from travellers from endemic regions such as India and Pakistan (28). It is intriguing that the girl described in our case did not travel abroad in the three months preceding her illness. Regarding the distribution of patients with a *S. typhi* or *S. paratyphi* infection, the ECDC reported the following percentages in 2017: 68% S. typhi, 20% *S. paratyphi* A, 10% *S. paratyphi B*, 0,6% S. paratyphi C and 2% S. paratyphi unspecified (28). *S. typhi* and *S. paratyphi* show some similarities in epidemiology, pathogenesis, mode of transmission and clinical signs. Paratyphoid fever often has a milder course and is less likely to lead to a chronic carrier status (29, 30). The incubation period is between 1-10 days. It has been observed that the onset of travel-related infection can occur up to months after the end of travel (31). In this case chronic stool carriership was not determined in the girl's household members.

Finally, it is important to note that the diagnosis of HLH in a patient with enteric fever can be challenging, as mild pancytopenia, persistent fever and splenomegaly may be related to both the enteric fever itself and HLH (4). Maybe the suspicion of HLH in this case would have been low in a high-endemic low-income country due to the scarcity of sophisticated diagnostic test methods such as soluble IL-2 receptor, NK cell activity and a bone marrow examination. Perhaps the diagnosis would have been severe enteric fever. This is different in our low-endemic high-income country, with less exposure to severe enteric fever, but more availability of advanced diagnostic methods to confirm the diagnosis of HLH (32).

## Conclusion

This case illustrates the importance of considering a *Salmonella* infection in the differential diagnosis of HLH in patients with severe infection of enteric origin, without a history of recent travel to an endemic area.

## Disclosures

The authors have no conflicts of interest or funding to disclose.

REFERENCES

1. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatric blood & cancer. 2007;48(2):124-31.
2. Griffin G, Shenoi S, Hughes GC. Hemophagocytic lymphohistiocytosis: An update on pathogenesis, diagnosis, and therapy. Best practice & research Clinical rheumatology. 2020;34(4):101515.
3. Weitzman S. Approach to hemophagocytic syndromes. Hematology American Society of Hematology Education Program. 2011;2011:178-83.
4. Caksen H, Akbayram S, Oner AF, Kösem M, Tuncer O, Ataş B, et al. A case of typhoid fever associated with hemophagocytic syndrome. The Journal of emergency medicine. 2003;25(3):321-2.
5. European_Resuscitation_Council. The Current ERC Guidelines. Niel, Belgium: European Resuscitation Council; 2021 [cited 202 October, 27]. Available from: https://cprguidelines.eu/guidelines-2021.
6. Rosenberg HK, Markowitz RI, Kolberg H, Park C, Hubbard A, Bellah RD. Normal splenic size in infants and children: sonographic measurements. AJR American journal of roentgenology. 1991;157(1):119-21.
7. Crighton GL, Huisman EJ. Pediatric Fibrinogen PART II-Overview of Indications for Fibrinogen Use in Critically Ill Children. Frontiers in pediatrics. 2021;9:647680.
8. Benz-Lemoine E, Bordigoni P, Schaack JC, Briquel E, Chiclet AM, Olive D. [Systemic reactive histiocytosis with hemophagocytosis and hemostasis disorders associated with septic granulomatosis]. Archives francaises de pediatrie. 1983;40(3):179-82.
9. Udden MM, Bañez E, Sears DA. Bone marrow histiocytic hyperplasia and hemophagocytosis with pancytopenia in typhoid fever. The American journal of the medical sciences. 1986;291(6):396-400.
10. Fame TM, Engelhard D, Riley HD, Jr. Hemophagocytosis accompanying typhoid fever. Pediatric infectious disease. 1986;5(3):367-9.
11. Mallouh AA, Sa'di AR. White blood cells and bone marrow in typhoid fever. The Pediatric infectious disease journal. 1987;6(6):527-9.
12. Stéphan JL, Koné-Paut I, Galambrun C, Mouy R, Bader-Meunier B, Prieur AM. Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients. Rheumatology (Oxford, England). 2001;40(11):1285-92.
13. Pande V, Agarkhedkar S, Tandon A, Agarwal A. Haemophagocytic Lymphohistiocytosis (HLH) in a case of Enteric Fever. . International Journal of Bioassays. 2016;5:4882-4.

14. Pandey M, Dhingra B, Sharma S, Chandra J, Pemde H, Singh V. Enteric Fever presenting as secondary hemophagocytic lymphohistiocytosis. Indian journal of pediatrics. 2012;79(12):1671-2.

15. Abbas A, Raza M, Majid A, Khalid Y, Bin Waqar SH. Infection-associated Hemophagocytic Lymphohistiocytosis: An Unusual Clinical Masquerader. Cureus. 2018;10(4):e2472.

16. Uribe-Londono J, Castano-Jaramillo LM, Penagos-Tascon L, Restrepo-Gouzy A, Escobar-Gonzalez AF. Hemophagocytic Lymphohistiocytosis Associated with Salmonella typhi Infection in a Child: A Case Report with Review of Literature. Case reports in pediatrics. 2018;2018:6236270.

17. Sánchez-Moreno P, Olbrich P, Falcón-Neyra L, Lucena JM, Aznar J, Neth O. Typhoid fever causing haemophagocytic lymphohistiocytosis in a non-endemic country - first case report and review of the current literature. Enfermedades infecciosas y microbiologia clinica (English ed). 2019;37(2):112-6.

18. Şahin Yaşar A, Karaman K, Geylan H, Çetin M, Güven B, Öner AF. Typhoid Fever Accompanied With Hematopoetic Lymphohistiocytosis and Rhabdomyolysis in a Refugee Child. Journal of pediatric hematology/oncology. 2019;41(4):e233-e4.

19. Banday AZ, Mehta R, Vignesh P, Kanaujia R, Durgadevi S, Angrup A, et al. Case Report: Ceftriaxone-Resistant Invasive Salmonella Enteritidis Infection with Secondary Hemophagocytic Lymphohistiocytosis: A Contrast with Enteric Fever. The American journal of tropical medicine and hygiene. 2020;103(6):2515-7.

20. Durmus Y. Salmonella ser. Typimurium Bacteremia Related Hemophagocytic Lymphohistiocytosis: A Case Report. Journal of Pediatric Infection. 2020;14:35-7.

21. Wei A, Ma H, Zhang L, Li Z, Zhang Q, Wang D, et al. Hemophagocytic lymphohistiocytosis resulting from a cytokine storm triggered by septicemia in a child with chronic granuloma disease: a case report and literature review. BMC pediatrics. 2020;20(1):100.

22. Dange NS, Sawant V, Dash L, Kondekar AS. A Rare Case of Salmonella meningitis and Hemophagocytic Lymphohistiocytosis. Journal of global infectious diseases. 2021;13(2):100-2.

23. Saha T, Arisoyin AE, Bollu B, Ashok T, Babu A, Issani A, et al. Enteric Fever: Diagnostic Challenges and the Importance of Early Intervention. Cureus. 2023;15(7):e41831.

24. Pham OH, McSorley SJ. Protective host immune responses to Salmonella infection. Future microbiology. 2015;10(1):101-10.

25. Nath U, Sinha N, De D. Hemophagocytic Lymphohistiocytosis Secondary to Salmonella paratyphi a Infection Presenting with Severe Pancytopenia and Multiorgan Dysfunction: The First Case Report. Journal of Bone Marrow Research. 2013;1(114).

26. Malinowska I, Machaczka M, Popko K, Siwicka A, Salamonowicz M, Nasiłowska-Adamska B. Hemophagocytic syndrome in children and adults. Archivum immunologiae et therapiae experimentalis. 2014;62(5):385-94.

27. Alhaj-Qasem DM, Al-Hatamleh MAI, Irekeola AA, Khalid MF, Mohamud R, Ismail A, et al. Laboratory Diagnosis of Paratyphoid Fever: Opportunity of Surface Plasmon Resonance. Diagnostics (Basel, Switzerland). 2020;10(7).

28. European_Centre_for_Disease_Prevention_and_Control. Typhoid and paratyphoid fevers. Annual epidemiological report for 2017 [Internet]. 2020 [cited 2023 October, 27]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2017_typhoid_and_paratyphoid_fevers.pdf.

29. Rijksinstituut_voor_Volksgezondheid_en_Milieu. Paratyphus Bilthoven, The Netherlands [cited 2023 October, 27]. Available from: https://lci.rivm.nl/richtlijnen/paratyfus#maatregelen.

30. Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. Lancet (London, England). 2005;366(9487):749-62.

31. Basnyat B, Qamar FN, Rupali P, Ahmed T, Parry CM. Enteric fever. BMJ (Clinical research ed). 2021;372:n437.

32. Cleves D, Lotero V, Medina D, Perez PM, Patiño JA, Torres-Canchala L, et al. Pediatric hemophagocytic lymphohistiocytosis: A rarely diagnosed entity in a developing country. BMC pediatrics. 2021;21(1):411.

Prix public **€ 86,52**

# Si vous ne recommandez pas la vaccination contre le MenB à vos patients,

# qui le fera ?

**81% des parents** considèrent leur médecin comme la source principale d'information concernant la vaccination de leurs enfants (n=800)[2]

**BEXSERO**
Vaccin méningococcique groupe B
(ADNr, composant, adsorbé)

**BEXSERO est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B.[1]**

**RÉSUMÉ ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT :** Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT :** Bexsero suspension injectable en seringue préremplie. Vaccin méningococcique groupe B (ADNr, composant, adsorbé) ; EU/1/12/812/001 ; EU/1/12/812/002, EU/1/12/812/003, EU/1/12/812/004. Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09. **COMPOSITION QUALITATIVE ET QUANTITATIVE :** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine recombinante NadA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine de fusion recombinante fHbp de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Vésicules de membrane externe (OMV) de Neisseria meningitidis groupe B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4[2] : 25 microgrammes • [1] produite dans des cellules d'E. coli par la technique de l'ADN recombinant - [2] adsorbée sur hydroxyde d'aluminium (0,5 mg $Al^{3+}$) - [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H). Pour la liste complète des excipients, voir rubrique 6.1 du RCP complet. **FORME PHARMACEUTIQUE :** Suspension injectable. Suspension liquide blanche opalescente. **DONNÉES CLINIQUES : Indications thérapeutiques :** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par Neisseria meningitidis de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration :** Posologie : **Tableau 1. Résumé de la posologie : Age lors de la première dose : Nourrissons de 2 à 5 mois[a]. Primovaccination :** Trois doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c] - Primovaccination : Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c]. **Age lors de la première dose : Nourrissons de 6 à 11 mois. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose au cours de la deuxième année de vie avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 12 à 23 mois. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 2 à 10 ans. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • **Age lors de la première dose : Adolescents (à partir de 11 ans) et adultes*. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • [a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. - [b] En cas de retard, la dose de rappel ne devrait pas être administrée audelà de l'âge de 24 mois. - [c] Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'autres doses de rappel n'ont pas encore été déterminés. - [d] Voir rubrique 5.1 du RCP complet. - * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration : Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, souscutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **Contreindications :** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **Effets indésirables :** Résumé du profil de sécurité : La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10 565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6 837 étaient des nourrissons et des enfants (de moins de 2 ans), 1 051 étaient des enfants (entre 2 et 10 ans) et 2 677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3 285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69 % à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et Haemophilus influenzae de type b), contre 44 % à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables : Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) - Fréquent : (≥ 1/100 à < 1/10) - Peu fréquent : (≥ 1/1 000 à < 1/100) - Rare : (≥ 1/10 000 à < 1/1 000) - Très rare : (< 1/10 000). Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles). Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans) :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Troubles du métabolisme et de la nutrition : Très fréquent : troubles alimentaires. Affections du système nerveux : Très fréquent : somnolence, pleurs inhabituels, céphalée. Peu fréquent : convulsions (y compris convulsions fébriles). Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections vasculaires : Peu fréquent : pâleur (rare après le rappel). Rare : syndrome de Kawasaki. Affections gastrointestinales : Très fréquent : diarrhée, vomissements (peu fréquents après le rappel). Affections de la peau et du tissu souscutané : Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel). Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans). Peu fréquent : eczéma. Rare : urticaire. Affections musculosquelettiques et systémiques : Très fréquent : arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité. Peu fréquent : fièvre (≥ 40 °C). Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois). **Adolescents (à partir de 11 ans) et adultes :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Affections du système nerveux : Très fréquent : céphalée. Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections gastrointestinales : Très fréquent : nausées. Affections de la peau et du tissu sous-cutané : Fréquence indéterminée : rash. Affections musculosquelettiques et systémiques : Très fréquent : myalgies, arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise. Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois). Déclaration des effets indésirables suspectés : La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique :** Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance - Boîte Postale 97 - 1000 Bruxelles - Madou - Site internet: www.notifieruneffetindesirable.be - e-mail: adr@afmps.be. **Luxembourg :** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ :** GSK Vaccines S.r.l.,Via Fiorentina 1, 53100 Sienne, Italie. **DATE D'APPROBATION DU TEXTE :** 26/04/2023 (v15). **MODE DE DELIVRANCE :** Sur prescription médicale.

**Références : 1.** SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

PM-BE-BEX-ADVR-230002 - Août 2023 | ER: GlaxoSmithKline Pharmaceuticals s.a./n.v. Site Apollo Avenue Pascal, 2-4-6 1300 Wavre Belgium

GSK

# NUTRILON GROEIT MET ZE MEE.

Nutrilon® Peuter Groeimelk

Peuters hebben een **6x hogere behoefte aan ijzer**[1,2]

En een **7x hogere behoefte aan vitamine D**[1,2]

## SAMEN VOOR JONGE IMMUUNSYSTEMEN IN VOLLE GROEI

Peuter groeimelk helpt om de voedingsbehoeften van het kind na 1 jaar te dekken, als aanvulling op een gezonde en gevarieerde voeding[3-6].
Ontdek het **unieke Nutrilon® peuter groeimelk** gamma:


**NUTRILON®**
Onze klassieke formule
Vanaf 1 jaar

**NUTRILON® PROFUTURA**
Onze meest geavanceerde formule
Vanaf 1 jaar

**De diëtisten van Nutricia Careline zijn er voor jou!**
Alle werkdagen van 8.30 uur tot 17.00 uur behalve op vrijdag tot 16.00 uur.
0800 16 685 +32 471 13 43 00 nutricia.be

**Vind meer informatie over onze Nutricia peuter groeimelk gamma op nutriciababy.be**

Informatie uitsluitend bestemd voor het (para)medisch korps. **1.** WHO Growth Standards;2006 **2.** Gebaseerd op CSS. Voedingsaanbevelingen voor België; per kg lichaamsgewicht voor een kind van 12 kg versus een volwassen man van 84 kg. **3.** Jong C, et al. TNO-rapport 2014;R11714. **4.** Akkermans MD, et al. AJCN. 2017;105(2):391-399. **5.** Akkermans MD, et al. JPGN. 2016;62(4):635-42. **6.** Goldbohm R, et al . Nutrients. 2016;8(7):428. • V.U.: N.V., Danone Belux – Werkhuizenkaai 160 – 1000 Brussel

# A Consensus Recommendation for Pediatric Intravenous Maintenance Fluid in Belgium

## On Behalf of the Be-PIV Group

Arne Boret[a], Milou Blits[b], Ann Raes[a], Sara Debulpaep[a], Elisabeth LIM Duval[c]

[a] Department of Pediatrics, Ghent University Hospital, Ghent, Belgium
[b] Department of Pediatrics, Antwerp University Hospital, Edegem, Belgium
[c] Department of Pediatric Critical Care Medicine, Antwerp University Hospital, Edegem , Belgium

els_duval@yahoo.com

## Keywords

Maintenance fluid ; Fluid therapy ; Intravenous infusion ; Child, hospitalized ; Algorithm.

## Abstract

Prescribing intravenous maintenance fluids is a daily practice for pediatricians worldwide. Failure to administer the correct fluid type or rate can impact morbidity and mortality. Despite this, different regimens are used based on old guidelines. This narrative review aims to formulate a guideline for the Belgian clinician. We searched databases for manuscripts on pediatric intravenous maintenance fluid therapy. Studies were evaluated on seven relevant topics, and our expert group discussed, formulated, and reviewed recommendations, resulting in a guideline for hospitalized children outside the neonatal period. We recommend the use of isotonic, preferably balanced, solutions with glucose 5 g/L and potassium 20 mEq/L with a restricted rate in most hospitalized children. Our guideline also provides recommendations for work-up and daily monitoring to avoid complications during maintenance therapy. Specific situations or comorbidities may warrant a tailored approach, as shown in the proposed algorithm.

## Introduction

Intravenous (IV) fluid therapy is one of the most common interventions in hospitalized children (1). Several reasons for prescribing IV fluid therapy can be distinguished: to resuscitate (and correct a relative or true fluid deficit), to replace (and correct abnormal losses, e.g., drains, burns, diarrhea, vomiting), or to maintain. Although there is no single definition for IV fluid maintenance, it is usually described as the water and electrolyte prescription designed to replace anticipated physiologic water and electrolyte losses over the ensuing 24-hour period (2). It aims to maintain electrolyte and free water homeostasis while also providing a source of energy (2-5).

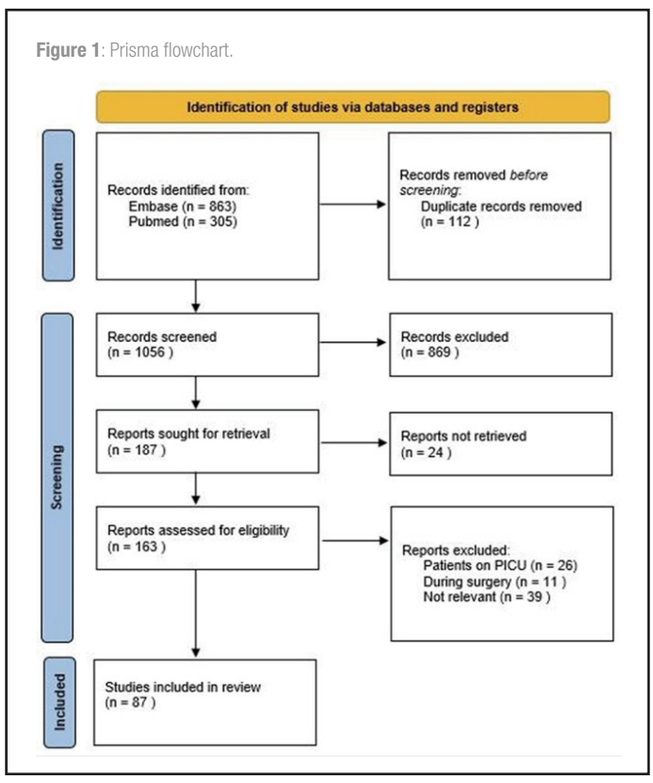
Fluids can thus be administered for different reasons, sometimes even simultaneously, and as such might have different contents and rates (2). Careful prescription, administration and monitoring of IV fluids are critical (6). Failure to administer IV fluids correctly can significantly impact morbidity and mortality (7). Prescribing them should be done with the same caution and accuracy as prescribing medications, considering the 4 D's: drug (which fluid?), dose (what rate?), duration (how long?), and de-escalation (monitoring) (8).

Our group has recently published a consensus recommendation on pediatric fluid resuscitation for the Belgian clinician (9). This narrative review will focus on IV maintenance therapy in hospitalized children. Based on this, we aim to formulate a guidance for Belgian clinicians applicable to children outside the neonatal period and under 15 years of age, in order to harmonize the quality of IV maintenance fluid administration in pediatrics according the current state of the art.

## Methods

There is no MESH term for 'maintenance fluid,' so we searched the databases PubMed and Embase for English articles with the terms: 'infusions, intravenous,' or 'fluid therapy' combined with 'child' and the free text term: 'maintenance.' We identified 1056 articles (Figure 1). These articles were screened for titles and abstracts: articles on IV fluid resuscitation, replacement, or other use were excluded. Other exclusion criteria included adults or neonates. The remaining 187 articles were retrieved and assessed. Articles concerning children with specific underlying diseases (e.g., diabetic ketoacidosis) or fluids used per-operatively were excluded. In the end, 87 articles were retained. In addition, the reference lists of landmark papers were also checked. In concordance with journal guidelines, the most important ones were withheld in the reference list.

**Figure 1**: Prisma flowchart.



Studies were evaluated on seven relevant topics: target population, fluid tonicity, balanced or non-balanced fluid, glucose, potassium and other components, rate and monitoring. A series of recommendations were derived and voted by our expert group through two rounds of voting using a modified Delphi process to reach consensus. For each question, the consensus within the expert group is expressed as a percentage. In most cases, the consensus was strong (>90%). Based on these recommendations, an algorithm was proposed.

## Results

**Recommendation 1.**
**Our IV maintenance guideline is applicable for children < 15 years (excluding neonates) in whom enteral fluid is not allowed or possible (consensus 86 %).**

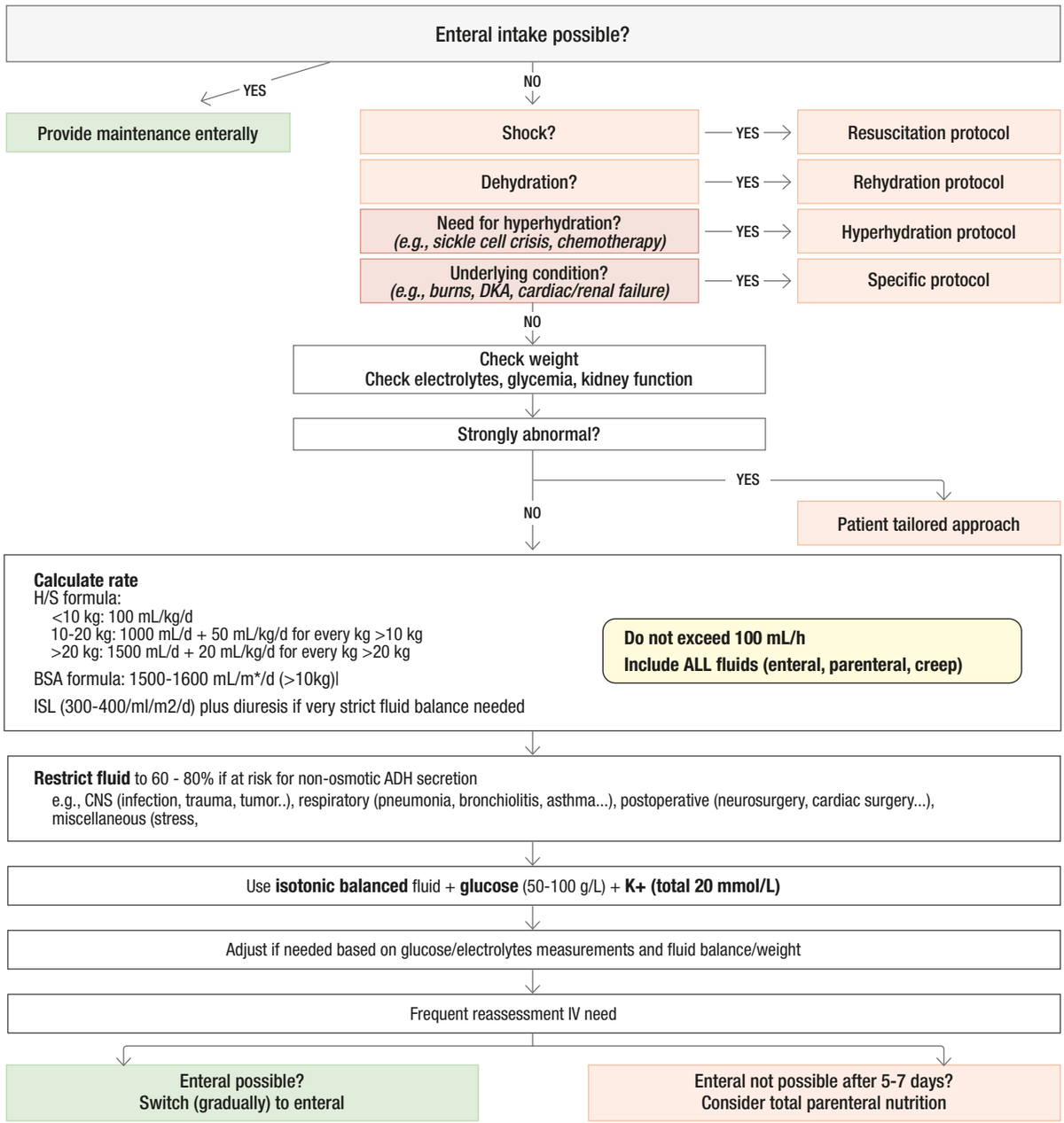
A practical approach regarding pediatric maintenance fluid is presented in Figure 2. This guideline concerns only maintenance fluid in children younger than 15 years of age, excluding neonates. It should be distinguished from fluid therapy in resuscitation, or during rehydration or replacement (e.g., burns, diabetes insipidus, diarrhea…). The expert group agreed that, where possible, maintenance fluid should always be provided orally or enterally, unless not possible or allowed. The need for (total or partial) IV maintenance fluid should be reconsidered daily.

Our proposed IV fluids cannot be given for a prolonged period of time. If the child is unable to start enteral intake within a week, parenteral nutrition should be considered (10).

In neonates, our proposed glucose content may be too low, with the risk of developing hypoglycemia, and the sodium content maybe too high (7). For the upper age limit, we base ourselves on the common definition of a child according to the pediatric care program.

This guideline is easily applicable in many patients with adequately functioning homeostatic renal, cardiocirculatory and metabolic systems. However, there is no "one size fits all" fluid. Most hospitalized children have underlying conditions or diseases, and their needs may vary accordingly (10-15). Some of the conditions that require careful consideration are added in the presented algorithm (Figure 2). The list is not exhaustive

**Figure 2**: Proposed algorithm for pediatric maintenance fluid in children < 15y, neonates excluded.



but provides a good overview (3, 10, 16). In these circumstances, the choice of IV fluid, its rate and its content should be tailored to the child's underlying illness and regularly reevaluated.

**Recommendation 2.**
**Maintenance fluid should be isotonic (consensus 100 %).**

Tonicity refers to the effect an IV fluid has on the osmolality of the extracellular fluid (ECF) (Table 1) (7). An isotonic solution has a concentration of dissolved particles equal to that of intracellular fluid (ICF). Osmotic pressure will be the same inside and outside the cells, so no fluid movement occurs. The tonicity of IV fluids is mainly determined by the concentration of sodium. However, different ranges of isotonicity are used throughout literature with sodium concentrations of 121 - 160 mmol/L (Cochrane), 131 - 154 mmol/L (National Institute for Health and Care Excellence or NICE) and 130 - 154 mmol/L (American Academy of Pediatrics or AAP) (1, 3, 7).

For decades, maintenance fluids in children were hypotonic, following recommendations by Holiday and Segar in 1957, who based maintenance requirements for water on caloric expenditure (5). This resulted in glucose-containing solutions with low sodium content. Because glucose is metabolized to carbon dioxide and water once it enters the cell, the net result is a hypotonic solution. Case reports and observational studies in the 1990s followed by reviews in the early 2000s, suggested a potential for hyponatremic encephalopathy and mortality with hypotonic fluids (17). Hypotonic fluids can generate dilutional hyponatremia, leading to an osmotic shift of free water from the ECF to the ICF. This is particularly worrisome in the brain, where edema could trigger hyponatremic encephalopathy, characterized by apathy, vomiting, agitation, headache, convulsions and coma. Children are at higher risk as they develop hyponatremic encephalopathy on higher plasma sodium levels than adults. Moreover, due to a higher brain/skull ratio and because children's brains contain more water, there is a higher risk of brain herniation (6, 18). Even mild hyponatremia was associated with adverse clinical outcomes in children (18).

The following years were characterized by ongoing debates between those in favor of isotonic solutions (arguing that fluids containing higher sodium reduce the risk of hyponatremia due to an inability to excrete free water) and those in favor of hypotonic solutions (who relate hyponatremia to excess volume administration and not to a dilutional effect of free water intake) (17). In the end, different randomized controlled trials (RCTs), systematic (Cochrane) reviews and meta-analyses provided increasing evidence that compared to hypotonic maintenance fluids, isotonic solutions do significantly reduce the risk of hyponatremia, particularly the first 24 hours, with some evidence that this effect persists at 48 hours (1-4, 7). Currently, supporting data are available in pediatric intensive care units (PICU) and non-intensive care settings: fluid type and not rate or volume, is the strongest significant predictor of hyponatremia (1, 3).

**Table 1 :** Tonicity.

| Type of fluid | Effect on extracellular fluid | Examples |
|---|---|---|
| **Hypotonic** | Decreases osmolality and ECF | Dextrose 5 - 10%<br>Glucion 5 - 10%<br>Glu 2.5% / NaCl 0.45%<br>Glu 3.3% / NaCl 0.3% |
| **Isotonic** | No effect | NaCl 0.9%<br>Plasmalyte<br>Hartmann's solution |
| **Hypertonic** | Increases osmolality and ECF | NaCl 3%<br>NaCl 5% |

ECF = extracellular fluid

The use of isotonic fluid could theoretically cause hypernatremia (4). However, different studies and a meta-analysis did not support this (1, 3). Inadequate fluid volume is thought to be more important to the development of hypernatremia than the actual amount of sodium (18).

Another theoretical concern with the use of isotonic fluids is the so-called sodium load (19). In adult patients, it is thought that an additional sodium burden, produced by the administration of isotonic fluids, could lead to a positive fluid balance and respiratory complications (20). The underlying mechanisms may be the inability of the kidneys to deal with a relatively high sodium load, which may promote fluid retention by inhibiting diuresis at renal collecting tubules (16). This effect is thought to be significant in cases of impaired diuresis or capillary leak (16). Reviews in pediatrics do not support this (16, 21, 22). However, a tailored approach with appropriate monitoring, bearing comorbidities in mind, should be advocated in very sick children (16).

When the risk of hypotonic fluids became apparent, new guidelines emerged with a shift from hypotonic to isotonic fluids (1, 4, 22). NICE recommends the use of isotonic crystalloids that contain sodium in the range of 131 - 154 mmol/L (7). The advice of both the AAP (promoting the use of isotonic solutions with appropriate potassium and dextrose) and the Canadian Pediatric Society (NaCl 0.9% with addition of glucose 5%) is similar (3, 23). A more recent article from the European society of Pediatric and Neonatal Intensive Care (ESPNIC) suggests that isotonic balanced solutions providing some glucose (4 - 10%) and limited amounts of potassium (+/- 4 mmol/L), would meet most children's requirements of IV maintenance fluid (2).

Despite these guidelines from highly respected institutes, a survey in 2021 still showed a wide variation in practice in prescribing IV maintenance fluids in hospitalized children, both in PICU and pediatric wards (22). Our own survey amongst Belgian pediatricians supports these findings: more than 50% of all pediatricians continue to use (different) hypotonic fluids as maintenance therapy with a wide variation (data to be published). Breaking through dogmas that have been followed for decades is always difficult. On top of that, most recommendations lack practicality and do not include all elements of IV maintenance fluids.

**Recommendation 3.**
**Maintenance fluid should be preferably balanced (consensus 100 %).**

A balanced solution has the entire content of all electrolytes equal to plasma, whilst at the same time maintaining electrical neutrality (the number of free cations equals the number of free anions). Most commercially available IV fluids add organic anions such as acetate or lactate (which are metabolized to bicarbonate) to balance the total amount of positive cations. NaCl 0.9% however, contains a supra-physiological concentration of chloride (Table 2). When using NaCl 0.9%, the rise in plasma chloride leads to increased excretion of bicarbonate and metabolic hyperchloremic acidosis ensues (16). This may be especially prominent in cases of increased bicarbonate losses (e.g., diarrhea) or when large volumes are used as in resuscitation (3, 16). Using balanced fluids lowers the risk of metabolic hyperchloremic acidosis (24). The latter showed to be related to worse outcomes in adults, including increased acute kidney injury (AKI) and mortality (25). Hyperchloremia alone was associated with morbidity and mortality in pediatric sepsis (26).

There is much data on the use of balanced fluids in resuscitation or perioperatively (9, 27). When looking at maintenance fluids, studies are scarce. In a meta-analysis of 5 studies with 283 patients, balanced solutions slightly but significantly reduced the length of stay (LOS) in critically and acute ill children (2). Another RCT also favored the use of balanced fluids postoperatively (28). In a retrospective cohort study, NaCl 0.9% as a maintenance fluid was a predictor of hyperchloremic acidosis, but this was not associated with an increased risk of AKI, feeding intolerance or PICU-acquired weakness. Of equal importance

**Table 2 :** Content of different isotonic solutions (all mmol/L).

| Substance | Plasma | NaCl 0.9% | Ringer's lactate | Hartmann's solution | Plasmalyte |
|---|---|---|---|---|---|
| **Sodium** | 135 - 145 | 154 | 130 | 131 | 140 |
| **Potassium** | 4.0 - 5.0 | 0 | 4.5 | 5 | 5 |
| **Calcium** | 2.2 - 2.6 | 0 | 2.7 | 4 | 0 |
| **Magnesium** | 1.0 - 2.0 | 0 | 0 | 0 | 1.5 |
| **Chloride** | 95 - 110 | 154 | 110 | 111 | 98 |
| **Acetate** | 0 | 0 | 0 | 0 | 27 |
| **Lactate** | 0.8 - 1.8 | 0 | 28 | 29 | 0 |
| **Gluconate** | 0 | 0 | 0 | 0 | 23 |
| **Bicarbonate** | 23 - 26 | 0 | 0 | 0 | 0 |

was the conclusion that substantial sources of chloride load appeared to come from fluids administered with medications and IV flushes (29). Other studies could not demonstrate beneficial effects of balanced fluids as maintenance (18).

A theoretical benefit of balanced solutions is their buffering effect: lactate and acetate are metabolized into bicarbonate, which alkalinizes plasma and could be beneficial in metabolic acidosis, a hallmark of shock. NaCl 0.9% on the other hand, could be beneficial to counter alkalosis occurring in significant vomiting (e.g., pyloric stenosis).

Studies in this area are not robust enough to be conclusive at this stage. Although the occurrence of hyperchloremic acidosis when using NaCl 0.9% seems common, more trials are needed to define its clinical importance (6, 10, 29). Yet balanced fluids have many physiologic advantages. Considering the limited extra cost and potential benefits, and in accordance with NICE, AAP and ESPNIC, the expert panel unanimously recommended using preferably balanced solutions (1-3).

There is a lack of evidence to recommend one balanced fluid over another, but Plasma-Lyte 148® seems to be a suitable choice for general use and even more in critically ill children because of its low chloride content (Table 2) (7, 10). Lactate buffer solutions should not be used in case of severe liver dysfunction to avoid lactic acidosis.

**Recommendation 4.**
**Maintenance fluid should contain an appropriate amount of glucose (50 g/L) (consensus 100 %).**

Glucose alters the osmolarity of IV fluids, but because it is rapidly metabolized after entering the bloodstream it does not affect the tonicity of solutions in vivo (3, 6). Glucose in maintenance fluid is necessary to prevent starvation ketoacidosis and hypoglycemia but cannot be excessive to avoid hyperglycemia. Guidelines remain vague about its concentration: sufficient but not excessive (2).

Again, most of the available data on the use of glucose-containing solutions in children is derived from a perioperative setting: a concentration of glucose of 1 to 2.5% is recommended as a compromise between hypoglycemia (and lipolysis) and hyperglycemia (due to stress-induced insulin resistance) (30). These concentrations may however not provide enough glucose if used outside the perioperative setting (2). In one trial almost 40% of children <6 years receiving glucose 2.5% postoperatively developed hypoglycemia and/or ketosis (18). The use of glucose 5% in these circumstances might be a safer approach and it does not seem to induce hyperglycemia (11).

The expert panel recommends that glucose (50 g/L) be added to pediatric maintenance IV fluids guided by bedside glycemia monitoring. However, local compounding may pose significant risks to the patient regarding the uncertainty in physicochemical stability, microbial contamination, prescription and preparation errors in electrolyte manipulation, and alteration of the tonicity and/or the balanced nature of the original fluid (31). A commercially available balanced isotonic fluid containing 5% glucise could be PlasmalyteG5, available in Belgium. The use of higher glucose concentrations (e.g. 100 g/L) could be considered for subgroups outside our target population (e.g., neonates) or when severe fluid restriction is needed.

**Recommendation 5.**
**Maintenance fluid should contain 20 mEq/L of potassium (consensus 83 %). There is insufficient evidence to recommend routinely adding other electrolytes, vitamins or trace elements (consensus 100 %).**

Evidence is lacking on the use of potassium in IV maintenance fluid; it is probably not necessary to add potassium if only a short period must be bridged (6). However, If the period is longer, the addition of potassium is important and should be appropriate: it helps regulate fluid balance, muscle contractions and nerve signals (3, 10). Usually, a daily intake of about 2 mEq/100 mL/day is advocated, based on the same article by Holiday and Segar, after confirmation of normal serum potassium and in patients without concern for hyperkalemia (e.g., severe kidney disease, rhabdomyolysis) (5, 10, 16). Note that the recommended daily potassium intake is based on 100 mL of fluid to be infused and not on kg of body weight, which is routinely forgotten (12).

If a total of 20 mEq/L is used, potassium intake will decrease from 3 mEq/kg/day in an infant of 3 kg, to 2 mEq/kg/day in a toddler of 10 kg, 1 mEq/kg/day in a child of 30 kg and 0.6 mEq/kg/day in an adolescent of 60 kg, acceptable amounts to temporarily meet daily need. Several RCTs contained 20 mmol/L of potassium, but there were no data on serum potassium levels (10). If a balanced solution is used, it is thought that no additional potassium is needed (10). However, most balanced solutions contain only around 5 mEq/L of potassium (Table 2).

Careful attention should be paid to the child with kidney failure. Fluids containing potassium, such as balanced crystalloids, have historically been avoided in these children due to the risk of hyperkalemia. However, their potassium content is usually lower than that of a hyperkalemic patient. Moreover, potassium shifts (due to unbalanced solutions) may have a greater effect on the serum potassium than the actual concentration of potassium in the infused solution. For most patients (with or without hyperkalemia) the effect of the potassium already present in balanced solutions is minimal.

There is insufficient evidence for the routine addition of magnesium, calcium, phosphorus, vitamins or other trace elements to maintenance fluid outside the neonatal period (2). Therefore, we don't recommend it except in children with observed deficiencies. Some balanced fluids contain calcium (e.g., Ringer's lactate or Hartmann's solution), which is incompatible with blood products or ceftriaxone (6). The addition of magnesium (as in Plasma-Lyte 148® with or without glucose) is presumed to have less significant incompatibilities (6, 10).

**Table 3 :** Different ways to calculate rate (excluding neonates).

| Weight (kg) | H/S | 4-2-1 | Oh |
|---|---|---|---|
| **<10** | 100 mL/kg/day | 4 mL/kg/h | 4 mL/kg/h |
| **10 – 20** | 1000 mL/d<br>+ 50 mL/kg/day for kg > 10 kg | 40 mL/h<br>+ 2 mL/kg/h for kg > 10 kg | 20 mL/h +<br>weight (kg) x 2 |
| **> 20** | 1500 mL/day<br>+ 20 mL/kg/day for kg > 20 kg | 60 mL/h<br>+ 1 mL/kg/h for kg > 20 kg | 40 mL/h<br>+ weight (kg) |
| Alternative approach for children > 10 kg based on body surface area: 1500 - 1600 mL/m2/day | | | |
| Alternative approach if strict fluid balance is required: ISL within the range of 300-400 mL/m²/day plus urinary output. | | | |

H/S = Holliday and Segar. ISL = insensible losses.

**Recommendation 6.**
**Rate should be based on the Holliday/Segar or BSA (if > 10 kg) formula, provided the following restrictions are applied: do not exceed 100 mL/h, restrict in children with non-osmotic ADH release, and include all fluids given (par)enterally (consensus 89%).**

Holiday and Segar (H/S) published their data on maintenance water requirements parenterally in 1957. They observed a linear relationship between water needs (urinary and insensible losses (ISL)) and energy metabolism. Since maintenance therapy replaces these losses, water requirements roughly equal caloric expenditure (1 mL of water equals 1 kcal). The relationship between weight and energy expenditure on the other hand was nonlinear. The caloric expenditure, and therefore fluid requirement, for the hospitalized child was arbitrarily estimated to be midway between the basal energy requirement and the energy requirement of normal active children (Figure 3). The nonlinearity led to the well-known formula of maintenance needs: 100 mL/kg/day for the first 10 kg, 50 mL/kg/day for the next 10 kg and 20 mL/kg/day for each kg over 20 kg (Table 3) (5). In anesthetics, the formula was simplified to an hourly requirement referred to as the "4-2-1 rule" (4 mL/kg/h for the first 10 kg, 2 mL/kg/h for the second 10 kg and 1 mL/kg/h for each subsequent kg). In 1980, Oh alternatively changed the formula into: 4 mL/kg/h for children between 3 - 10 kg, 20 mL/h + weight (kg) × 2 mL/h for children between 10 - 20 kg, 40 mL/h + weight (kg) for children over 20 kg (13). It was only later that Adelman and Solhaug calculated the rate using the body surface area (BSA), assuming that caloric expenditure is related to BSA (1500 - 1600 mL/m2/day). Their method however cannot be used for children under 10 kg.

The H/S formula remains the most widely used formula since its original publication many decades ago. Although safe and easy to use, some remarks should be considered.

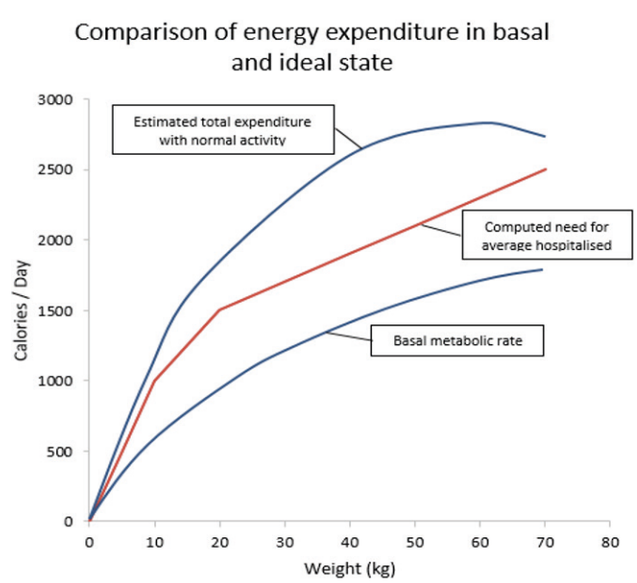
First, a maximum of 2400 mL/day should not be exceeded (7, 10). Second, there is often confusion about the difference between oral and IV fluid requirements for infants. The water requirement is identical for both routes of administration (100 mL/kg/day). However, the relatively low energy density of milk means that infants need larger volumes of milk to provide adequate nutrition, leading to volume of 150-170 mL/kg/day if all intake is enteral.

Third, all fluids administered to a child must be considered, including fluids as medication vehicles and flushes to keep lines open which often contribute to a significant volume load (29). These fluids have been termed fluid creep and should be subtracted from the total daily maintenance needed before prescribing rates (14).

Finally, the total maintenance fluid as calculated by the H/S formula was based on the usual water and electrolyte requirements of the average hospitalized child fifty years ago. Today, the average hospitalized child is different, with many having complex diseases, undergoing complex operative procedures, often with substantially shortened LOS. Often these children have increased levels of antidiuretic hormone (ADH), which reduces the ability to excrete free water (6, 10). Excess ADH secretion due to non-osmotic stimuli can result from postoperative stress, central or respiratory infection, persistent nausea, coma, head injury or positive pressure ventilation, to name but a few (6, 17, 18). These children require less fluid than prescribed by the abovementioned formula (2). If fluid is not restricted, hyponatremia will develop regardless of its tonicity (15). The safest approach is tailoring fluid need by assessing urine output and concentration, but this approach is difficult to achieve and not practical. Different restrictions of calculated fluid requirements by the H/S formula have been proposed: 50 - 66% in children with central or respiratory infections, 65 - 85% for children in PICU, and 50 - 60% in several central nervous conditions (e.g., cerebral edema, meningitis, encephalitis, or major head injury) (2, 6, 10). NICE recommends fluids restriction to 50 - 80% or fluid reduction calculated based on ISL within the range of 300-400 mL/m²/day plus urinary output (7).

Even in the absence of increased ADH secretion, other situations may warrant careful fluid prescription, such as when children are at risk for edema, as in heart, kidney or hepatic failure (2). Fluid requirements can also increase in children with high solute loads, such as glycosuria in diabetic ketoacidosis, or severe catabolism with high protein losses as in burns or crush injuries. To a lesser extent this may also be the case in children with recurrent episodes of high fever or prolonged tachypnea. In these

**Figure 3**: Energy expenditure in children with normal activity, basal and when hospitalized. Adapted from Holliday and Segar (5)..



children the BSA formula may be more appropriate, adding the increased amount of ISL (extra 100 mL/m2/day for each degree above 37.8°C).

Restricting IV maintenance fluid tends to lower the LOS in the PICU, and other studies have shown a lower occurrence of hyponatremia (2). However, robust data are difficult to obtain, when maintenance therapy has been applied erroneously (e.g., as a deficit therapy for which it was not designed) or the exact volume provided is not reported.

Taking all of this into consideration, the expert panel decided that either the H/S or BSA (if > 10 kg) can be used, but only if these restrictions are strictly followed:

- A rate of 100 mL/h should not be exceeded.
- Restrict the rate (50 - 80%) in children with conditions at risk for non-osmotic ADH release.
- All fluid, including fluid creep and enteral fluid, should be considered.

**Recommendation 7.**
**Regular monitoring is mandatory when giving IV maintenance fluid to children to prevent fluid overload and prolonged stay (consensus 92 %).**

If indicated, IV maintenance should be considered after a work-up including at least weight and an evaluation of the hydration status (both clinically and by blood tests including glycemia, electrolytes and kidney function tests) (3, 7). During IV maintenance therapy it is recommended to monitor the child (heart rate, blood pressure) and to check the fluid balance and weight regularly. Fluid balance charts are notoriously difficult to maintain accurately, clinical assessment is not always easy and objective, and even urine output can be difficult to follow, especially in a young child. Daily measurement of body weight is the most optimal fluid balance parameter but is not always feasible in a very sick child (7, 10). However, we recommend assessing body weight daily in children under two years of age and 2-3 times per week in older children. A change of 5% of body weight should alert the clinician to reconsider fluid intake (2). In acutely ill children, electrolyte concentrations should be checked at least daily (2, 7). In other children this should be done according to the risk level and proportion of IV maintenance fluid (e.g., daily if > 50% of maintenance fluid requirements are intravenous) (10). In case of electrolyte abnormalities, paired urine and plasma osmolarity and electrolyte profiles may be useful to guide fluid prescription (10). A combination of careful monitoring of clinical signs, strict recording of fluid intake and output and measurement of patient weight is likely to be more effective in estimating body fluid status than reliance on one single approach.

## Conclusion

Our group attempted to provide the Belgian clinician with recommendations regarding IV maintenance therapy in hospitalized children. Outcome proved to be inconsistent between studies and the target population was often heterogeneous. Recommendations are therefore based on consensus within the expert group, and most, if not all, consistent with international guidelines.

As in other guidelines, we also recommend isotonic, balanced solutions with varying glucose concentrations (from 1 to 10%) and an appropriate amount of potassium (20 mEq/L) ensuring safe IV fluid therapy in children. These solutions should be available in a range of packaging formats to reduce their environmental footprint (31). Although isotonic balanced solutions containing 5% glucose are available in Belgium, their insufficient potassium content makes them less feasible for IV maintenance.

Obviously, this is less important if only a few of hours of IV fluid are needed. Nevertheless, when maintenance fluids are prescribed, they must be given the same consideration as other medicines regarding indications and contraindications, content, monitoring and, particularly, volume. Giving the wrong solution, the wrong volume, to the wrong patient is clearly inappropriate fluid management. The best way to avoid dangerous electrolyte imbalances, such as hyponatremia, is to monitor fluid balance (weight) and plasma sodium concentration regularly.


## Acknowledgements

We thank the Be-PIV group (Belgian Pediatric Task force on IV fluids) for critical reading and approving the final draft of the manuscript. Be-PIV members: X. Beretta-Piccoli, Department of Intensive Care, Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium; M. Blits, T. Boiy, M. Van Oort, Department of Pediatrics, Antwerp University Hospital, Antwerp University Hospital, Antwerp, Belgium;

A. Boret, S. Debulpaep, A. De Guchtenaere, Department of Pediatrics, Ghent University Hospital, Ghent, Belgium; V. De Smet, Department of Pharmacy, Ghent University Hospital, Ghent, Belgium; T. Detaille, Department of Anesthesiology, Cliniques Universitaires St. Luc, Catholic University of Louvain Medical School, Brussels, Belgium; E. Duval, Department of Pediatric Critical Care Medicine, Antwerp University Hospital, Antwerp, Belgium: N. Godefroid, Pediatric nephrology, Cliniques Universitaires St. Luc, Catholic University of Louvain medical School, Brussels, Belgium; A. Raes, Department of Pediatric Nephrology and Rheumatology, Ghent University Hospital, Ghent University, Ghent Belgium; K. Van Hoeck, Department of Pediatric Nephrology, Antwerp University Hospital, Antwerp, Belgium; F. Vermeulen, Department of Pulmonology, University of Leuven, Leuven, Belgium.

None of the authors have any conflicts of interest to declare. This narrative review was written without industry input. In addition, no member of the Be-PIV group received honoraria for any role in this process. All members have declared no potential conflicts of interest.


REFERENCES


1. McNab S, Ware RS, Neville KA, Choong K, Coulthard MG, Duke T, et al. Isotonic versus hypotonic solutions for maintenance intravenous fluid administration in children. Cochrane Database Syst Rev. 2014(12):Cd009457.
2. Brossier DW, Tume LN, Briant AR, Jotterand Chaparro C, Moullet C, Rooze S, et al. ESPNIC clinical practice guidelines: intravenous maintenance fluid therapy in acute and critically ill children- a systematic review and meta-analysis. Intensive Care Med. 2022.
3. Feld LG, Neuspiel DR, Foster BA, Leu MG, Garber MD, Austin K, et al. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. Pediatrics. 2018;142(6).
4. Wang J, Xu E, Xiao Y. Isotonic versus hypotonic maintenance IV fluids in hospitalized children: a meta-analysis. Pediatrics. 2014;133(1):105-13.
5. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics. 1957;19(5):823-32.
6. McNab S. Intravenous maintenance fluid therapy in children. J Paediatr Child Health. 2016;52(2):137-40.
7. National Institute for Health and Care Excellence: Guidelines. Intravenous fluid therapy in children and young people in hospital. London: National Institute for Health and Care Excellence (NICE) Copyright © NICE 2020.; 2020.
8. Malbrain M, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal PJ, Joannes-Boyau O, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann Intensive Care. 2018;8(1):66.
9. Blits M, Schepens T, De Breuker B, Duval ELIM. Consensus recommendations for pediatric fluid resuscitation in Belgium : On behalf of the Be-PIV group. Belgian Journal of Paediatrics. 2023;24(3):197-203.
10. Leung LCK, So LY, Ng YK, Chan WKY, Chiu WK, Chow CM, et al. Initial intravenous fluid prescription in general paediatric in-patients aged >28 days and <18 years: consensus statements. Hong Kong Med J. 2021;27(4):276-86.
11. Martínez Carapeto I, López Castilla JD, Fresneda Gutiérrez R. A comparison of post-surgical plasma glucose levels in patients on fluids with different glucose concentrations. Anales de Pediatria. 2018;89(2):98-103.
12. Friedman AL, Ray PE. Maintenance fluid therapy: what it is and what it is not. Pediatr Nephrol. 2008;23(5):677-80.
13. Oh TH. Formulas for calculating fluid maintenance requirements. Anesthesiology. 1980;53(4):351.
14. Van Regenmortel N, Verbrugghe W, Roelant E, Van den Wyngaert T, Jorens PG. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. Intensive Care Med. 2018;44(4):409-17.
15. Choong K, Arora S, Cheng J, Farrokhyar F, Reddy D, Thabane L, et al. Hypotonic versus isotonic maintenance fluids after surgery for children: a randomized controlled trial. Pediatrics. 2011;128(5):857-66.

16. Sensing W, Wenker M, Whitney E. Maintenance fluid management in pediatrics: Current practice and quality improvement achievements. Curr Probl Pediatr Adolesc Health Care. 2021;51(5):100996.

17. Choong K, McNab S. IV fluid choices in children: have we found the solution? J Pediatr (Rio J). 2015;91(5):407-9.

18. Neville KA, Sandeman DJ, Rubinstein A, Henry GM, McGlynn M, Walker JL. Prevention of hyponatremia during maintenance intravenous fluid administration: a prospective randomized study of fluid type versus fluid rate. J Pediatr. 2010;156(2):313-9.e1-2.

19. Holliday MA, Ray PE, Friedman AL. Fluid therapy for children: facts, fashions and questions. Arch Dis Child. 2007;92(6):546-50.

20. Van Regenmortel N, Moers L, Langer T, Roelant E, De Weerdt T, Caironi P, et al. Fluid-induced harm in the hospital: look beyond volume and start considering sodium. From physiology towards recommendations for daily practice in hospitalized adults. Ann Intensive Care. 2021;11(1):79.

21. Hasim N, Bakar MAA, Islam MA. Efficacy and Safety of Isotonic and Hypotonic Intravenous Maintenance Fluids in Hospitalised Children: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Children (Basel). 2021;8(9).

22. Morice C, Alsohime F, Mayberry H, Tume LN, Brossier D, Valla FV. Intravenous maintenance fluid therapy practice in the pediatric acute and critical care settings: a European and Middle Eastern survey. Eur J Pediatr. 2022;181(8):3163-72.

23. Friedman JN. Risk of acute hyponatremia in hospitalized children and youth receiving maintenance intravenous fluids. Paediatr Child Health. 2013;18(2):102-7.

24. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci (Lond). 2003;104(1):17-24.

25. Semler MW, Kellum JA. Balanced Crystalloid Solutions. Am J Respir Crit Care Med. 2019;199(8):952-60.

26. Stenson EK, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, et al. Hyperchloremia Is Associated With Complicated Course and Mortality in Pediatric Patients With Septic Shock. Pediatr Crit Care Med. 2018;19(2):155-60.

27. McFarlane C, Lee A. A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. Anaesthesia. 1994;49(9):779-81.

28. Coulthard MG, Long DA, Ullman AJ, Ware RS. A randomised controlled trial of Hartmann's solution versus half normal saline in postoperative paediatric spinal instrumentation and craniotomy patients. Arch Dis Child. 2012;97(6):491-6.

29. Bulfon AF, Alomani HL, Anton N, Comrie BT, Rochwerg B, Stef SA, et al. Intravenous Fluid Prescription Practices in Critically Ill Children: A Shift in Focus from Natremia to Chloremia? J Pediatr Intensive Care. 2019;8(4):218-25.

30. Sümpelmann R, Becke K, Crean P, Jöhr M, Lönnqvist PA, Strauss JM, et al. European consensus statement for intraoperative fluid therapy in children. Eur J Anaesthesiol. 2011;28(9):637-9.

31. Brossier DW, Goyer I, Morice C, Alsohime F, Mayberry HF, Porcheret F, et al. How to follow the guidelines, when the appropriate fluid is missing? Eur J Pediatr. 2024;183(6):2797-803.


**Apaise efficacement les peaux à tendance atopique** et l'esprit des parents.

**Crème relipidante anti-grattage**


99% d'ingrédients d'origine naturelle

COSMÉTIQUE BIO CHARTE COSMEBIO

Sans parfum

Apaise instantanément

Anti-récidive

ECOCERT COSMOS ORGANIC

# Brain Abscess of Suspected Otogenic Origin in a Seven-Year-Old Child with Atypical Neurologic Signs

Antje Geypen [a], Els Moens [b]

[a] University of Antwerp, Faculty of Medicine and Health Sciences, Antwerp, Belgium
[b] ZAS Palfijn, Department of Pediatrics, Merksem, Belgium

antje.geypen@hotmail.com

## Keywords

Brain abscess ; Streptococcus pneumoniae ; child ; pediatric neurosurgery.

## Abstract

Brain abscesses are a rare life-threatening condition in children. Even though the mortality rate has become relatively low in recent years, incomplete recovery remains a major concern. Clinical sequelae are associated with delayed diagnosis and treatment, often due to variable or subtle symptoms. We present a child with a large brain abscess whose diagnosis was complicated by atypical neurological symptoms. The diagnostic process, treatment and outcome are discussed. Brain abscesses may present with variable neurological signs in children. It remains clear that a high index of suspicion is crucial for making a timely diagnosis.

## Introduction

Brain abscesses are a rare but potentially life-threatening condition in children. The incidence has decreased over the last decennia due to global improvements in health care and widespread use of antibiotics. The international incidence rate is 0.3–1.8 per 100,000 persons, and children account for 25% of cases (1, 2). The incidence is higher in developing countries (2, 3). Underlying predisposing conditions include congenital heart disease and immunosuppression (1, 2, 4, 5). Notwithstanding a decrease in mortality over the years, recent data still show mortality rates of 4-12% in children (2, 3, 5). In addition, only 50-70% of children make a full recovery. Factors associated with incomplete recovery and a higher mortality rate are delayed diagnosis, severe neurologic impairment at presentation or rapid neurological deterioration, and development of complications (1, 2, 5, 6). The predominant neurological sequel is epilepsy. Other possible sequelae include motor/visual/hearing deficits, hydrocephalus and language impairment (7, 8).

Brain abscesses are most commonly the result of pathogens spreading to the brain through contiguous sites (middle ear, mastoid or sinus infections) or through a skull discontinuity (head trauma or neurosurgery). Hematologic spread is less frequent and is typically associated with underlying congenital heart disease, pulmonary infection, or pulmonary arteriovenous fistula. Rarely, usually in neonates, brain abscesses are a complication of meningitis. No predisposing factor can be identified In 10-30% of brain abscesses.

The causative pathogens are similar to adult cases, with *Streptococcus* species (including *Streptococcus pneumoniae*) being the most frequent (36-70%), commonly associated with sinusitis, otitis media and endocarditis (*Streptococcus viridans*). *Staphylococcus* species are also common and are related to penetrating head trauma. Less frequent are gram-negative anaerobic bacilli, *Enterobacteriaceae* and fungi (2, 4, 5, 9-12).

In immunocompromised hosts, fungal abscesses (mainly *Aspergillus* and *Candida*), *Toxoplasma*, *Nocardia* species, *Listeria* and *Mycobacterium tuberculosis* can be identified. Identification of *S. viridans*, microaerophilic *Streptococci* and *Haemophilus* species is related to congenital heart defect (2, 4, 9, 10).

In children, the classic symptomatic triad (headaches, fever, and neurologic deficits) occurs in only 15-20% of cases, with headaches (60-70%) being the most common symptom, followed by fever (50-80%). Headaches, vomiting and altered level of consciousness can be associated with increased intracranial pressure. Depending on the location of the abscess, different focal neurologic signs have been described, including seizures, unilateral paresis or motor function deficits, cranial nerve palsies, dysphasia, dyspraxia, ataxia, visual field defects, eye movement abnormalities, spatial neglect, irritability, personality changes and frontal release signs.

The symptoms and the timing of onset are variable and depend on the abscess size and location (2, 4-6, 8, 9, 11). In absence of the diagnostic triad, symptoms and signs can be misunderstood, resulting in delayed diagnosis (1, 7).

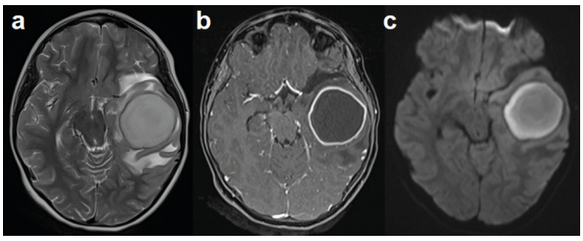
The golden standard for diagnosis is an MRI with and without contrast. If MRI is not available, contrast-enhanced CT is recommended (4, 13, 14). Treatment consists of antibiotic therapy, often combined with surgery. Of course, the underlying causes should be addressed. According to recent guidelines by Bodilsen et al. prompt neurosurgery is recommended whenever feasible. Others suggest antibiotic therapy alone in the case of multiple or small abscesses (<2.5 cm), when the etiology is known, and when patients are in good clinical condition and/or in situations where surgery is risky (12, 14, 15).

The surgical approach is a patient-specific decision. Aspiration seems suitable for deep-seated, small or multiple abscesses, or when general anesthesia is contraindicated. Drainage by craniotomy, craniectomy or excision is common for superficial or posterior fossa abscesses and post-traumatic or postoperative cases (15). Large abscesses (>2.5 cm), behaving as space-occupying processes sometimes require craniotomy and excision (12).

## Case report

A fully vaccinated 7-year-old girl, with a history of teeth grinding and chronic otalgia for 2 years, presented to our clinic with acute progressive left-sided otalgia, abdominal pain and retrosternal pain without fever. Clinical examination revealed left-sided myringitis bullosa for which analgesic treatment was prescribed. Two weeks later, she reconsulted with persistent symptoms accompanied by malaise, vomiting and left-sided headaches. Otitis media with effusion of the left ear was noted in association with myalgia and neck stiffness, although she was still afebrile. She was admitted for further investigations. A blood sample

**Figure 1**. Brain MRI performed at readmission of the patient. Axial T2-weighted image shows a large mass with a T2-hypointense capsule and T2-hyperintense (cystic) content in the left temporal lobe, with surrounding edema (a). The mass has a thin enhancing capsule on contrast-enhanced T1-weighted images, the central content is not enhancing (b). The cystic content has a high signal on diffusion-weighted images (c) with corresponding low signal on the ADC-map (image not shown), compatible with thick viscous fluid. These imaging findings are pathognomonic for cerebral abscess. Due to mass-effect there was subfalcine herniation to the right (images not shown) and a left-sided uncal hernation.




revealed elevated inflammatory markers: white blood cell (WBC) count 29.6x10E9/L [reference value: 4.5-13.5x10E9/L], C-reactive protein (CRP) 82.3 mg/L [reference value: <10 mg/L]. A lumbar puncture was unsuccessful due to the patient's lack of cooperation, but blood and urine cultures were collected before empirically starting intravenous (IV) ceftriaxone. The blood and urine cultures came back negative, and there was a rapid clinical and biochemical improvement with complete resolution of symptoms after 4 days. The patient remained afebrile during hospitalization and she was discharged with a presumptive diagnosis of viral meningitis after 4 days of IV antibiotic treatment.

After discharge, symptoms returned promptly and intermittently. Complaint free episodes were alternated with pain and vomiting. She remained afebrile. Over-the-counter analgesics and antiemetics provided no relief.

After 3 weeks the patient was readmitted because of weight loss (of 1 kg) and inconsistent signs of meningeal irritation (neck myalgia and tenderness on passive neck flexion). Neurological examination on admission showed equal pupils and reactive to light, normal deep tendon reflexes and normal cranial nerve examination, balance and coordination. Except for a slightly elevated CRP (19,6 mg/L), the blood examination was unremarkable. Intravenous fluids, analgesics and antiemetics provided little relief. Papillary edema was urgently ruled out and an otorhinolaryngological examination revealed no middle ear pathology.

At this time, personality changes were noted as well as impaired awareness and increased reaction time. Episodes of irritability and delayed responses emerged, often associated with headache and/or vomiting. However, these symptoms occurred intermittently with asymptomatic periods with normal behavior.

An electroencephalogram (EEG) showed focal slowing over the left hemisphere. Subsequently, an MRI revealed a brain abscess in the left temporal lobe (5,0 cm x 5,4 cm x 5,8 cm) with midline shift, for which the patient underwent urgent neurosurgical abscess drainage. IV ceftriaxone and metronidazole were then empirically started. Cultures were positive for *Streptococcus pneumoniae* type 21, after which ceftriaxone monotherapy was continued according to the sensitivity profile. Within one week, central imaging showed decrease in abscess size, and the neurological examination and EEG normalized. After 3 weeks, the patient was discharged with oral amoxicillin.

Brain MRI after 6 weeks (2,4 x 2,1 x 2,5 cm) and 14 weeks (1,1 cm anteroposterior diameter) showed further volume reduction. Based on imaging and clinical improvement, the antibiotic treatment was discontinued after a total treatment duration of 5 months. One month later, MRI showed cystic and fibrotic tissue transformation.

Considering the unremarkable medical history and the involvement of a *Streptococcus pneumoniae* serotype not currently included in available vaccines, suspicion of an underlying immunodeficiency was limited. However, immunological screening was performed, encompassing analyses of white blood cell subsets, immunoglobulin levels (including subclasses), complement cascade pathways, pneumococcal vaccine antibody response, and splenic function (evaluated by the absence of Howell-Jolly bodies). This work-up revealed a mannose-binding lectin deficiency, a minor immunodeficiency that occurs in a small part of the normal population. Abdominal and cardiac ultrasounds were normal.

## Discussion

Brain abscess is a rare but life-threatening condition in children, associated with significant mortality and morbidity. Early detection is crucial because delay in treatment is associated with incomplete recovery and mortality. However, diagnosis can be challenging, especially in absence of the diagnostic triad (headaches, fever, and neurologic deficits). A wide range of neurological symptoms have been described in combination with headaches and vomiting (1, 2, 4, 5, 7, 9).

Our case describes a large temporal lobe abscess in a child, suspected to be of otogenic origin based on the patients' history. Neurological symptoms consisted of impaired awareness with delayed response time and personality changes. However, these signs presented intermittently. In addition, personality changes are atypical for the abscess location, as behavioral disturbances and personality changes are associated with frontal lobe abscesses. In contrast, temporal lobe abscesses usually cause dysphasia or visual field defects (4, 9).

Furthermore, our patient never experienced fever during the disease course, which probably contributed to the delayed diagnosis. In the literature, fever appears to be absent in 20-50% of cases (5, 6, 8, 9).

Empiric antibiotics were started after surgical aspiration. The treatment duration was 5 months and consisted of IV antibiotics for 3 weeks, followed by oral antibiotics for 17 weeks.

Currently, research determining the treatment duration for pediatric brain abscess is lacking. Recent retrospective studies report prolonged antibiotic courses. For instance, a 2019 case series reported a median treatment duration of 92 days (8). However, the current literature recommends antibiotic treatment for 4-6 weeks in surgically treated abscesses and a 6-8 week course for conservative treatment.(3, 13, 15). Notably, Bodilsen et al. recommend treating aspirated abscesses similar to nonsurgically managed abscesses, recommending 6-8 weeks of treatment in both situations (14). Imaging studies should be performed at regular intervals to monitor treatment response (13, 14).

In conservatively treated patients, surgery should be reconsidered in the case of clinical detoration or when there is no clinical and radiological improvement within two weeks. In the case of aspiration, failure to see abscess size regression after four weeks is unusual (2, 15). There is no consensus on the required abscess size for discontinuation of antibiotics (15). In addition, residual contrast enhancement on brain imaging may persist for up to 6 months, making it inappropriate to prolong antibiotic treatment based on radiological findings alone (14).

Furthermore, there is currently insufficient evidence regarding the role of oral antibiotics in the treatment (14, 15). Arlotti et al. propose considering converting to oral treatment when causative pathogens and sensitivity profiles are known, and when the antibiotic agent demonstrates effective central nervous system penetration (15). More research is needed on this subject.

Our case illustrates an atypical presentation of pediatric brain abscess, possibly suggesting less demarcated symptoms related to abscess location. In addition, to our knowledge, an intermittent pattern of neurological symptoms has not yet been described.

Neurological signs such as focal neurological deficit, new-onset seizures or altered mental status along with fever, headaches or other signs of increased intracranial pressure, should prompt central imaging studies. A lumbar puncture is also indicated to rule out intracranial infection. However, if signs of increased intracranial pressure are present, brain imaging should always be performed first due to the potential risk of brain herniation.

In conclusion, a high level of suspicion is crucial for early detection of pediatric brain abscess, particularly in the case of history of acute otorhinolaryngological infections or a skull discontinuity.

## Acknowledgments

We thank dr. An-Sofie Schoonjans, dr. Koen Vanden Driessche and dr. Sven Dekeyzer for critical reading and for approving the final draft of the manuscript.

## Disclosure of potential conflicts of interest

The authors have no conflict of interest to declare.

REFERENCES

1. Xiang Q JC, Wen J, Deng B. Unusual presentation of brain abscess in a 23-month-old infant. Child's Nervous System. 2021 Jan;37(1):305-9.
2. Mameli C GT, Madia C, Doneda C, Penagini F, Zuccotti G. Brain abscess in pediatric age: a review. Child's Nervous System. 2019 Jul;35(7):1117-28.
3. Bonfield CM SJ, Dobson S. Pediatric intracranial abscesses. J Infect. 2015;71.
4. Sheehan JP, Jane, J. A., Jr., Ray, D. K., & Goodkin, H. P. (Brain abscess in children. Neurosurgical Focus FOC. 2008;24(6).
5. Sahbudak Bal Z EC, Bolat E, Avcu G, Kultursay N, Ozkinay F, Kurugol Z, Vardar F. Brain Abscess in Children: A Rare but Serious Infection. Clinical Pediatrics. 2018;57:574-9.
6. Rivera K TR, Furiato A, Martinez S. The Diagnostic Challenge of the Pediatric Brain Abscess. Cureus. 2021;13(6).
7. Duarte MJ KE, Barshak MB, Reinshagen K, Knoll RM, Abdullah KG, Welling DB, Jung DH. Otogenic brain abscesses: A systematic review. Laryngoscope Investig Otolaryngol. 2018 Apr 25;25(3):198-208.
8. van der Velden FJS BA, Pareja-Cebrian L, Ross N, Ball SL, Emonts M. . Paediatric focal intracranial suppurative infection: a UK single-centre retrospective cohort study. BMC Pediatr. 2019;19(1):130.
9. Saez-Llorens X. Brain abscess in children. Semin Pediatr Infect Dis. 2003;14(2):108-14.
10. Brouwer MC TA, McKhann GM 2nd, van de Beek D. Brain abscess. N Engl J Med. 2014;371(5):447-56.
11. Prasad R BJ, Singh K, Mishra OP, Singh A. Clinical Profile and Outcome of Brain Abscess in Children from a Tertiary Care Hospital in Eastern Uttar Pradesh. Ann Indian Acad Neurol. 2020 May-Jun;23(3):303-307.
12. Lajolo C FG, Limongelli L, Tempesta A, Zuppa A, Cordaro M, Vanella I, Giuliani M. Brain abscess of odontogenic origin in children: a systematic review of the literature with emphasis on therapeutic aspects and a new case presentation. Acta Otorhinolaryngol Ital. 2019;39(2):67-74.
13. Felsenstein S WB, Shingadia D, Coxon L, Riordan A, Demetriades AK, Chandler CL, Bassi S, Koutoumanou E, Stapleton S, Sharland M, Bryant PA. Clinical and microbiologic features guiding treatment recommendations for brain abscesses in children. Pediatr Infect Dis J. 2013 Feb;32(2):129-35.
14. Bodilsen J DAQ, Humphreys H, Iro MA, Klein M, Last K, Montesinos IL, Pagliano P, Sipahi OR, San-Juan R, Tattevin P, Thurnher M, de J Treviño-Rangel R, Brouwer MC. SCMID Study Group for Infections of the Brain (ESGIB). European society of Clinical Microbiology and Infectious Diseases guidelines on diagnosis and treatment of brain abscess in children and adults. E Clin Microbiol Infect. 2024;30(1):66-89.
15. Arlotti M GP, Pea F, Tomei G, Vullo V, De Rosa FG, Di Perri G, Nicastri E, Lauria FN, Carosi G, Moroni M, Ippolito G; GISIG (Gruppo Italiano di Studio sulle Infezioni Gravi) Working Group on Brain Abscesses. Consensus document on controversial issues for the treatment of infections of the central nervous system: bacterial brain abscesses. Int J Infect Dis. 2010;14.

# KLIMAATOPWARMING: EEN GOEDE HYDRATATIE IS CRUCIAAL OM DE NIEREN VAN PASGEBORENEN TE BESCHERMEN!

Verschillende factoren beïnvloeden de niergezondheid van pasgeborenen. Zo kunnen de gevolgen van de klimaatverandering, en in het bijzonder hittegolven, een invloed hebben op de ontwikkeling van de nieren tijdens de zwangerschap en, later in het leven, op de nierfunctie.[1]

## EEN GOEDE HYDRATATIE, NOODZAKELIJK VANAF DE ZWANGERSCHAP

Zwangere vrouwen zijn bijzonder kwetsbaar voor de gevolgen van de klimaatverandering, omdat ze meer problemen hebben met de thermoregulatie, gevoeliger zijn voor de gevolgen van uitdroging en vatbaarder zijn voor infecties. Blootstelling aan hitte en de klimatologische gevolgen daarvan (bijv. bosbranden, luchtvervuilingspieken enz.) worden in verband gebracht met een laag geboortegewicht en een verhoogd risico op vroeggeboorte en zwangerschapsvergiftiging. Deze factoren worden op hun beurt in verband gebracht met een afname van het aantal nefronen, nierfunctiestoornissen en een hogere bloeddruk bij de kinderen op latere leeftijd.[1]

## VAN VERANDERINGEN IN UTERO TOT LANGETERMIJNGEVOLGEN

Een laag geboortegewicht (< 2,5 kg), een laag gewicht voor de zwangerschapsduur (SGA, gewicht < 10$^{e}$ percentiel), vroeggeboorte (PTB, < 37 weken) en/of zwangerschapsvergiftiging zijn in verband gebracht met een hogere bloeddruk, een risico op proteïnurie en nierfunctiestoornissen achteraf.[1]

Studies hebben de gevoeligheid van de nefrogenese voor blootstelling tijdens de zwangerschap aangetoond: hoewel het aantal nefronen toeneemt met het geboortegewicht en de zwangerschapsduur, neemt dit aantal niet meer toe na de geboorte. Blootstelling tijdens de zwangerschap heeft dus een levenslange invloed op het nefronenreservoir van een individu.[1,2]

Er zijn ook meerdere moleculaire mediatoren betrokken bij de ontwikkeling van de nieren, met name veranderingen in de genexpressie, modulatie van de apoptose, versnelde senescentie en geslachtseffecten, die allemaal gevoelig kunnen zijn voor blootstelling aan hitte tijdens de zwangerschap. Andere factoren zoals zwangerschapsvergiftiging kunnen ook bijdragen aan individuele verschillen in het langetermijnrisico op het ontwikkelen van chronische nieraandoeningen gedurende het hele leven.[1]

## VEEL BABY'S LOPEN RISICO OP NIERPROBLEMEN

In 2020 werden wereldwijd bijna 20 miljoen baby's geboren met een laag geboortegewicht. Naar schatting is 10% van de geboorten te vroeg en is één op de vijf baby's klein in verhouding tot de zwangerschapsduur. De risico's die gepaard gaan met milieufactoren zoals het klimaat verdienen dus speciale aandacht op populatieniveau. Desondanks ontwikkelen niet alle te kleine of te vroeg geboren baby's noodzakelijkerwijs een nierziekte, en het is zeer waarschijnlijk dat andere factoren na de geboorte een rol spelen.[1]

## BELANG VAN LICHT GEMINERALISEERD WATER, OP HET JUISTE MOMENT

Borstvoeding wordt waar mogelijk aanbevolen voor alle baby's, zelfs bij warm weer. In dat geval is het niet nodig hen water te geven vóór de introductie van vaste voeding, rond de leeftijd van 6 maanden. Als het echter uitzonderlijk warm is of als de baby tekenen van uitdroging vertoont, kan een zeer kleine hoeveelheid water worden aangeboden.

Voor baby's die flesvoeding krijgen, kan water geïntroduceerd worden vóór de leeftijd van 6 maanden. Water moet geleidelijk en in kleine hoeveelheden worden gegeven. Bij zeer warm weer kan het nodig zijn om de hoeveelheid gegeven water aan te passen.[3]


Omdat de nierfunctie bij pasgeborenen nog onvoldoende uitgerijpt is, is het belangrijk om te kiezen voor zuiver water met een laag mineralengehalte, bij voorkeur uit flessen.[4,5]

De klimaatverandering kan een dubbel effect hebben, zowel op de ontwikkeling van de nieren van de foetus als op de accumulatie van nierschade na de geboorte. Bij hittegolven is het daarom essentieel ervoor te zorgen dat aanstaande moeders en baby's goed gehydrateerd zijn.[1]

SPA
NATURAL SINCE 1583

Spa steunt
BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE

Bronnen: 1. Alvarez-Elias A.C., Brenner B.M., Luyckx V.A., Climate change and its influence in nephron mass. Curr Opin Nephrol Hypertens. 2024 Jan 1;33(1):102-109. doi: 10.1097/MNH.0000000000000932. Epub 2023 Oct 6. PMID: 37800660; PMCID: PMC10715706. 2. Puelles, Victor, et al., Glomerular number and size variability and risk for kidney disease. Current Opinion in Nephrology and Hypertension 20(1):p 7-15, January 2011. | DOI: 10.1097/MNH.0b013e3283410a7d. 3. What are the recommendations for giving water during infancy? NHS, 2022. 4. Conseil Supérieur de la Santé. Qualité microbiologique de l'eau destinée à la préparation des biberons CHS 8123 2005. 5. Azoulay A. et al., Comparison of the mineral content of tap water and bottled waters. J. Gen. Intern. Med 2001.16 : 168-175.ed 2001.16 :168-175.

**Beter drinken. Beter leven.**

# Understanding and Management of Neurobehavioral Difficulties in Patients with Duchenne Muscular Dystrophy

PhD thesis presented on 24-06-2024 at KU Leuven, Leuven, Belgium

Sam Geuens [a]

Promoter: Liesbeth De Waele [a]
Co-promoters: Jurgen Lemiere [b], Nathalie Doorenweerd [c], Nathalie Goemans [a]

[a] Department of Child Neurology, University Hospitals Leuven, Belgium
[b] Department of Pediatric Haemato-Oncology, University Hospitals Leuven, Belgium
[c] C.J. Gorter Center for High Field MRI, Leiden University Medical Center, The Netherlands

sam.geuens@uzleuven.be

## Keywords

Duchenne Muscular Dystrophy ; brain ; corticosteroids ; behavior.

## Abstract

Patients with Duchenne muscular dystrophy (DMD) face an increased risk to develop neurobehavioral problems linked to brain dystrophin deficiency. This PhD thesis explores the impact of corticosteroid treatment and genotype on brain morphology and their correlations with neurobehavioral outcomes. Using MRI, significant differences in gray matter volumes, subcortical volumes, and brain morphology were found between DMD patients treated daily with corticosteroids and those treated intermittently. Additionally, differences were observed based on genotypes. A new term, Duchenne Muscular Dystrophy-Associated Neurobehavioral Difficulties (DuMAND), and the DuMAND Checklist were introduced for systematic screening of neurobehavioral difficulties in DMD. Finally, clinical experiences with psychopharmaceuticals to treat severe neurobehavioral difficulties in DMD patients were investigated.

## Introduction

Duchenne muscular dystrophy (DMD) is the most frequent muscular dystrophy (1). In addition to the severe and progressive muscular loss, patients with DMD face a heightened risk of developing neurobehavioral problems (2). These issues not only significantly impact the daily functioning of patients but also contribute to a substantial burden on both the affected individuals and their families (3). The etiology of these neurobehavioral problems has been associated with the absence of dystrophin expression in the brain, but till now effective treatments for these neurobehavioral problems remain elusive. To enhance clinical care for this burdensome aspect of DMD, new insights regarding the DMD brain, and the screening for and treatment of neurobehavioral difficulties, are urgently needed (4).

The overarching objective of this PhD project is to contribute to various domains of understanding and management of neurobehavioral challenges in patients with DMD.

## Different studies

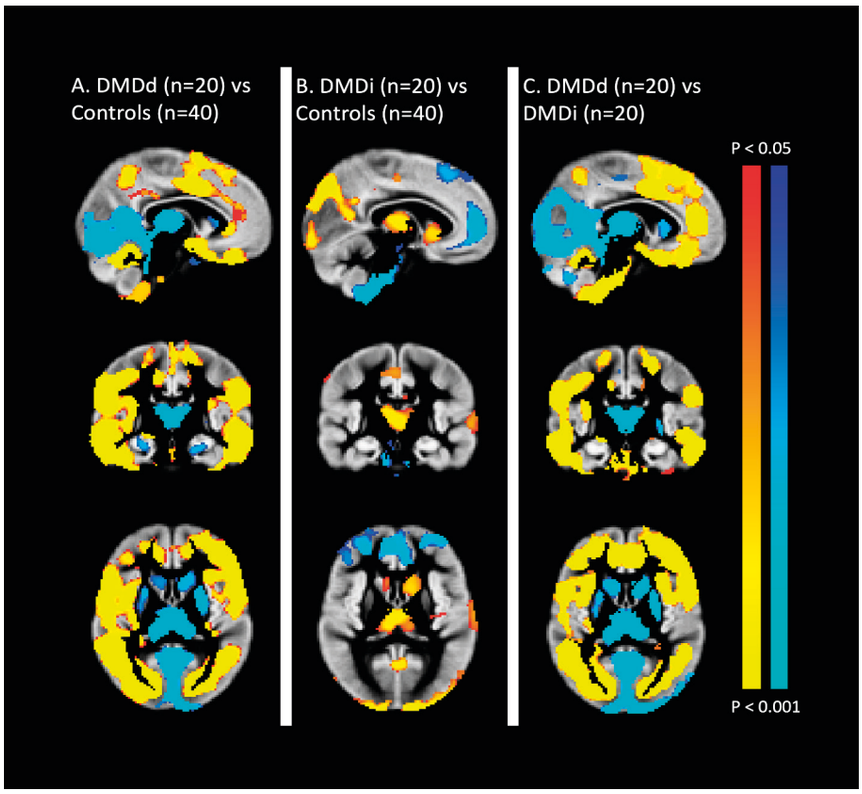
In the first study, we investigated the impact of different corticosteroid regimens on brain volumetrics in DMD using Magnetic Resonance Imaging (MRI). In a cross-sectional, two center study, T1-weighted MRI scans were obtained from three age-matched groups (9-20 years): DMD patients treated daily with deflazacort (DMDd, n=20, scan site: Leuven), DMD patients treated intermittently with prednisone (DMDi, n=20, scan site: Leiden), and healthy controls (n=40, both scan sites). FSL (the FMRIB Software Library) was used to perform voxel-based morphometry analyses and to calculate intracranial, total brain, gray matter, white matter, and cerebrospinal fluid volumes. A MANCOVA was employed to compare global volumetrics between groups, with site as covariate.

Voxel-based morphometry analyses revealed notable differences between patient groups and controls (Figure 1). Specifically, daily corticosteroid treatment in DMD patients exhibited more pronounced alterations in gray matter volumes compared to intermittent treatment. Global volume quantification further demonstrated significant differences in gray matter, white matter, and cerebrospinal fluid volumes in daily treated patients compared to controls, underscoring the need to consider corticosteroid treatment as a confounding variable in future brain imaging studies in DMD (5).

In the second study, we looked into specific regions of gray matter in the brain of DMD patients and explored whether variation in gray matter characteristics within the DMD population was influenced by corticosteroid treatment and genotype. The CAT12 toolbox in SPM was used for detailed MRI segmentations, assessing subcortical structures, cortical thickness, gyrification, and sulci depths. Comparisons were made between DMD (n = 40) vs. controls (n = 40), daily vs. intermittent corticosteroid treatment (n = 20 each), and Dp140+ vs. Dp140- gene mutations (n = 15 vs. 25). MANCOVA, CAT12 3D statistics and Pearson correlations were conducted. DMD patients showed significant differences in volumes of distinct subcortical volumes, left hemisphere cortical thickness, and gyrification in multiple brain areas compared with healthy controls. The daily treated DMD group exhibited differences in subcortical volumes and different patterns of cortical thickness, sulci depth, and gyrification compared to the intermittent treated DMD group. DMD Dp140+ patients displayed altered gyrification and sulci depth compared to DMD Dp140- patients. Finally, we found significant correlations between neurobehavioral outcomes and brain areas that showed significant differences in cortical morphology associated with corticosteroid treatment.

This study demonstrated that both genotype and corticosteroid treatment are associated with variations in subcortical volumes and cortical

**Figure 1**: Results of gray matter (GM) voxel-based morphometry (VBM)
*(A) Brain regions expressing lower (red-yellow) or higher (blue) GMV in the DMDd group compared with controls; (B) brain regions expressing lower (red-yellow) or higher (blue) GMV in the DMDi group compared with controls; (C) brain regions expressing lower (red-yellow) or higher (blue) GMV in DMDd group compared with the DMDi group. (p < 0.05, TFCE-corrected)*




morphology, albeit in different ways. Corticosteroid treatment appears to have a more profound association with differences in gray matter characteristics of brain regions that are associated with functional outcomes.

In study 3, we explored the strategies used by healthcare professionals to address neurobehavioral symptoms in DMD patients. Twenty-eight respondents from 16 different countries completed an online survey. Only 35% of the centers systematically screened for neurobehavioral difficulties in their DMD population. Predominant screening methods included history taking and clinical observation, mostly done by physicians relying on their own expertise and experience. Common neurobehavioral difficulties encompassed learning challenges, dependency from adults, anxiety, concentration difficulties, and social deficits. The participating centers frequently employed parental counseling and liaison with psychosocial healthcare professionals for psychosocial intervention. This study underscores the complex behavioral landscape in DMD, highlighting the need for validated screening, assessment and management strategies and collaborative efforts in implementing these. We advocate for international consensus recommendations for screening, assessment and management of neurobehavioral difficulties in DMD to enhance patient care and communication across healthcare settings (6).

In study 4 we introduced the term Duchenne Muscular Dystrophy-Associated Neurobehavioral Difficulties (DuMAND) and the DuMAND Checklist, which will facilitate comprehensive screening for neurobehavioral symptoms in DMD. DuMAND categories were derived through literature review, parent (48 mothers and 37 fathers), and expert (n = 28) input and feedback. The DuMAND Checklist subscales were developed iteratively, incorporating item selection, expert panel (n = 10) assessment for face validity, comprehensiveness, and a pilot validation study in a DMD sample (n = 20).

DuMAND encompasses five categories: cognition and learning, social responsiveness, emotion regulation, externalizing behavior, and eating and sleeping. Preliminary validation of the DuMAND Checklist indicates acceptable-to-excellent internal consistency and construct validity. By introducing the DuMAND concept, this study seeks to inspire a consensus approach for screening, assessing, and managing neurobehavioral issues in DMD. Incorporating screening, using the DuMAND Checklist, in addition to medical follow-up will facilitate early intervention, addressing a critical gap in identification of neurobehavioral disorders in DMD. Future research is needed to further evaluate psychometric properties of the DuMAND Checklist and investigate the natural course of DuMAND (7).

Finally, we reported on the clinical experience with psychopharmaceutical treatment in 52 DMD patients, assessing its efficacy in improving neurobehavioral symptoms. Electronic patient files were searched for patients with DMD that had been treated with psychopharmaceuticals between 2008 and 2022. Information about neurobehavioral symptoms, type of medication, side effects, and behavioral changes were collected. Two independent clinicians used the clinical global impression scale (CGI) to assess severity of the neurobehavioral problems before and the change in symptoms after treatment. Descriptive statistics were used. Our results include 52 males with DMD (mean age 11 years) treated with psychopharmaceuticals of which 55.8% had four or more comorbid neurobehavioral symptoms. The clinical condition was much improved on the CGI in 54.2% treated with methylphenidate, in 38.9% of the patients treated with fluoxetine, and in 22.2% treated with risperidone. Minimal effects and side effects were also reported.

Patients with DMD may experience severe neurobehavioral symptoms interfering with learning and/or development. Treatment with psychopharmaceuticals can improve these neurobehavioral symptoms, but further research is needed to gain better insights in psychopharmaceutical treatment in patients with DMD(8).

## Conclusion

This thesis aimed to address symptoms of Duchenne muscular dystrophy (DMD) beyond the physical components, which understandably receive priority in a disease with such devastating physical consequences. However, the disparity between physical and psychosocial research is intriguing, as it does not reflect the conversations we have with boys with DMD and their parents in clinical care. Naturally, everyone holds high hopes that new medical advances will lead to a cure, but there is also a sense of realism and acknowledgment that living with the disease will remain a significant challenge in the near future. Many struggle with the high burden of neurobehavioral difficulties, navigating the school system, accessibility, societal understanding, participation, isolation, social contacts, and self-fulfillment.

The physical symptoms of DMD may be devastating, but so is the psychosocial impact on daily life—not only for the patients but also for their families. This thesis aimed to shed light on these often-overlooked aspects, but a lot of work still needs to be done.

In conclusion, this thesis demonstrated the multifaceted factors contributing to variations in distinctive parts of gray matter in the DMD brain, emphasizing the importance of considering both genetic and treatment-related factors as confounding variables in future studies. Furthermore, our findings highlight the lack of a standardized approach to address neurobehavioral problems in DMD patients. To address this gap, we introduced the term DuMAND and developed the DuMAND Checklist, providing a tool for systematic screening of neurobehavioral difficulties in clinical practice. Lastly, our research demonstrates the potential of psychopharmacological treatment as a safe and effective approach to alleviating neurobehavioral difficulties in patients with DMD.

REFERENCES


1. Deenen JC, Horlings CG, Verschuuren JJ, Verbeek AL, van Engelen BG. The Epidemiology of Neuromuscular Disorders: A Comprehensive Overview of the Literature. J Neuromuscul Dis. 2015;2(1):73-85.
2. Darmahkasih AJ, Rybalsky I, Tian C, Shellenbarger KC, Horn PS, Lambert JT, et al. Neurodevelopmental, behavioral, and emotional symptoms common in Duchenne muscular dystrophy. Muscle Nerve. 2020;61(4):466-74.
3. Hendriksen JGM, Thangarajh M, Kan HE, Muntoni F, group Etws. 249th ENMC International Workshop: The role of brain dystrophin in muscular dystrophy: Implications for clinical care and translational research, Hoofddorp, The Netherlands, November 29th-December 1st 2019. Neuromuscul Disord. 2020;30(9):782-94.
4. Doorenweerd N. Combining genetics, neuropsychology and neuroimaging to improve understanding of brain involvement in Duchenne muscular dystrophy - a narrative review. Neuromuscul Disord. 2020;30(6):437-42.
5. Geuens S, Van Dessel J, Govaarts R, Ikelaar NA, Meijer OC, Kan HE, et al. Comparison of two corticosteroid regimens on brain volumetrics in patients with Duchenne muscular dystrophy. Ann Clin Transl Neurol. 2023.
6. Geuens S, Goemans N, Lemiere J, Doorenweerd N, De Waele L. Duchenne Muscular Dystrophy-Associated Neurobehavioral Difficulties: Insights from Clinical Practice. J Neuromuscul Dis. 2024.
7. Geuens S, Goemans N, Lemiere J, Doorenweerd N, De Waele L. Development and Pilot Validation of the DuMAND Checklist to Screen for Duchenne Muscular Dystrophy-Associated Neurobehavioral Difficulties (DuMAND). J Neuromuscul Dis. 2024;11(4):801-14.
8. Weerkamp PMM, Geuens S, Collin P, Goemans N, Vermeulen RJ, De Waele L, et al. Psychopharmaceutical treatment for neurobehavioral problems in Duchenne muscular dystrophy: a descriptive study using real-world data. Neuromuscul Disord. 2023;33(7):619-26.


Les **besoins en fer** des tout-petits sont **6 fois plus importants**[1,2]

Et **7 fois plus importants en vitamine D**[1,2]

## L'ALLIÉ DES PETITS SYSTÈMES IMMUNITAIRES EN CROISSANCE

Le lait de croissance aide à couvrir les besoins nutritionnels de l'enfant après 1 an, en complément d'une alimentation saine et variée[3-6].
Découvrez la gamme unique des laits de croissance Nutrilon®:


**NUTRILON®**
Notre formule classique
Dès 1 an

**NUTRILON® PROFUTURA**
Notre formule la plus avancée
Dès 1 an

**Les diététiciennes de la Nutricia Careline sont là pour vous !**
Tous les jours ouvrables de 8h30 à 17h sauf le vendredi jusqu'à 16h.
0800 16 685 +32 471 13 43 00 nutricia.be

**Retrouvez plus d'informations à propos de notre gamme de laits de croissance Nutricia pour tout-petits sur nutriciababy.be**

Informations exclusivement réservées au corps (para)médical. **1.** WHO Growth Standards;2006 **2.** Basé sur CSS. Recommandations nutritionnelles pour la Belgique ; par kg poids corporelle pour un enfant de 12 kg versus un homme adulte de 84 kg. **3.** Jong C, et al. TNO-rapport 2014;R11714. **4.** Akkermans MD, et al. AJCN. 2017;105(2):391-399. **5.** Akkermans MD, et al. JPGN. 2016;62(4):635-42. **6.** Goldbohm R, et al . Nutrients. 2016;8(7):428. • E.R.: Danone Belux S.A. – Quai des Usines 160 – 1000 Bruxelles

# Editorial Policy

Belgian Journal of Paediatrics
ISSN 2466-8907 (printed version) - ISSN 2566-1558 (digital version)

## Aims and scope

*The Belgian Journal of Paediatrics (Belg J Paediatr)* is the Official Journal of the Belgian Society of Paediatrics.

*The Belgian Journal of Paediatrics* publishes peer reviewed original research articles, review articles, short communications, case reports and images on all aspects of paediatrics. In addition, all official reports of the Belgian Academy of Paediatrics are published in the journal.

The Belgian Journal of Paediatrics aims to connect all Belgian paediatricians with stimulating, scientifically sound, peer-reviewed articles.

The Journal is published quarterly. The journal is available in a printed version and electronic version. The electronic version is accessible through the website of the Belgian Society of Paediatrics at https://bvk-sbp.be/bjp.php.

## Editors

**Editors-in-Chief:**
M. Raes, University Hospital Leuven and Jessa hospital, Hasselt, Belgium
C. Chantrain, CHC MontLégia, Liège, Belgium
**Associate editors:**
C. Barrea, University Hospital Liège, Liège, Belgium
O. Danhaive, Cliniques Universitaires Saint-Luc, Brussels, Belgium
I. Decuyper, ZAS Paola, Antwerp, Belgium
E. Duval, University Hospital Antwerp, Edegem, Belgium
V. Guy-Viterbo, Queen Fabiola Children's University Hospital, Brussels, Belgium
L. Hoste, University Hospital Ghent, Ghent, Belgium
L. Panneel, University Hospital Antwerp, Edegem, Belgium
I. Roggen, Queen Fabiola Children's University Hospital, Brussels, Belgium
Y. Vandenplas, University Hospital Brussels, Brussels, Belgium
K. Van De Maele, University Hospital Antwerp, Edegem, Belgium
K. van Hoeve, University Hospital Leuven, Leuven, Belgium
A. Vuckovic, Queen Fabiola Children's University Hospital, Brussels, Belgium
M. Wojciechowski, University Hospital Antwerp, Edegem, Belgium
**Editorial office:** N. Meignen, UZ Leuven, Herestraat 49, 3000 Leuven.
Mail: bjp@belgjpaediatrics.com.
**Website**: http://www.belgjpaediatrics.com/
**Publisher**: Vivactis, Gustave Demey Avenue 57, B-1160 Auderghem, Belgium.
**Owner**: Belgische Vereniging voor Kindergeneeskunde – Société Belge de Pédiatrie.
Editorial Policy (version 9, September 2024)

## Editorial principles

**Editorship**: All papers submitted to the *Belgian Journal of Paediatrics* are previewed by a member of the editorial team. Papers that are of sufficient novelty and impact for publication are forwarded for peer review. Other papers are returned without review after editorial decision. If one of the editors has a conflict of interest with a submitted manuscript or with the authors, he or she will abstain from the editorial board decision process.

**Invited Editors**: Invited Editors are appointed by the Editors to coordinate the compilation of a special chapter of the Journal dedicated to a particular subject. They choose the topics of the chapter; they contact the authors with expertise in the field and protect the expected deadlines for the reviews. In addition, they write an editorial letter for the special chapter.

**Manuscript submission**: Guidelines for preparing and submitting manuscripts are described in the section "Instructions for authors". No publication fee is charged, neither for the manuscript nor for illustrative figures whether or not in colour. The editors will ensure the confidentiality of the author's work.

**Authorship criteria**: Authors should meet the criteria for authorship according to the recommendations of International Committee of Medical Journal Editors (ICMJE) available at www.icmje.org. Only persons that have substantially contributed to all of the following are considered as authors: conception and design, acquisition, analysis and interpretation of data; drafting the article or revising it critically; final approval of the version published. The corresponding author should declare in the online submission that these criteria have been satisfied. Persons who have contributed to the study or manuscript but who do not fulfil the criteria for authorship have to be listed under a heading "acknowledgments". Financial and material support should also be acknowledged. Any change in authors after initial submission must be approved by all authors and must be explained to the Editor. The Editor may contact any of the authors and / or contributors to verify whether they agree to any change. The authors are fully responsible for the propositions and statements in their article. Although the Editors try to recognize and reject misconduct to the best of their ability, neither the Editorial Board of the Belgian Journal of Paediatrics, nor the Executive Board of the Belgian Paediatric Society are responsible for malpractice by authors.

**Misconduct**: Reviewers of the manuscripts and readers of the journal are encouraged to report malpractice. Whenever misconduct is effectively established, the Editors will notify the author's institution and inform the readers of the Journal.

**Copyright**: By accepting publication in the Belgian Journal of Paediatrics authors automatically transfer copyright to the journal.

**Ethical standards**: Human subjects research requires ethics committee approval. This should be documented in the 'methods' section of the paper. It is the author's responsibility to ensure that a patient's anonymity is carefully protected. Information that could possibly identify patients should not be included in the paper, unless the information is essential for scientific purposes and a written informed consent for publication was obtained from patients and/or both their parents or guardians. This should be added as a separate page(s) to the manuscript. Even when consent was given, identifying details should be omitted if not essential. Special attention should be given to patient's images, names, initials, hospital numbers. The registration number and the site of registry of clinical trials should be provided in the 'methods' section of the manuscript.

When reporting experiments on animals, authors should indicate whether the institutional rules and/or national legislation for the care and use of laboratory animals was respected.

**Negative studies**: The Belgian Journal of Paediatrics agrees with the International Committee of Medical Journal Editors statement regarding the obligation to publish negative studies.

**Duplicate or prior publication**: Only original manuscripts that have not been published before (except in the form of an abstract or as part of a published lecture or a thesis) can be accepted.

**Reproduction of material from other sources**: any written or illustrative material that has been or will be published elsewhere must be duly acknowledged and accompanied by the written consent of the copyright holder and credit the source(s) in the article.

**Publication embargo**: Every submission accepted for publication in the Belgian Journal of Paediatrics is under embargo until it is published. This means that until then it may not be disclosed to third parties. However, prior presentation of study data as an abstract or poster at a scientific meeting is acceptable, as well as publication of abstracts in print and online conference proceedings, but authors should not distribute copies of the original manuscript.

**Peer review**: All received papers will be peer reviewed after editorial approval by at least two external and independent reviewers solicited by the Editors. In order to avoid conflicts of interest, these reviewers cannot belong to the same institution as the authors. Following the review process, a decision will be made to accept as such or with minor or major revisions, or to reject. In case of controversy or strong disagreement regarding the merits of the work, an additional review may be solicited or one of the journal's editors might give an evaluation. The reviewers' names will be blinded to the authors. Manuscripts will be resubmitted to the reviewers after revision by the authors if the manuscript satisfactorily addresses the comments from the reviewers and editors. The editors are responsible for the final decision to accept or reject a manuscript. Authors will be notified about the decision and, if the manuscript is accepted, the timing of publication. Roles and responsibilities of peer reviewers are described in the section "Instructions for peer reviewers".

**Advertising**: Advertisers are not allowed to influence or modify the content of accepted articles before publication. Advertisement of products like alcohol, tobacco or products known to be harmful for children's health are not allowed in the journal. Editors have the final authority to accept advertisements in each published issue of the Journal. Each advertisement is clearly identified as such and is preferably not inserted in the body of the manuscript. The Belgian Society of Paediatrics oversees the advertising policy of the Journal. The Editors are not responsible for the advertising on linked sites of the electronic version of the journal.

**Complaints**: Complaints regarding Editorial decisions have to be addressed to the Editorial Office bjp@belgjpaediatrics.com . All complaints will be analysed by the Editorial Team and a detailed answer will be provided.

## Instructions for authors

### Journal Sections

The *Belgian Journal of Paediatrics* publishes the following types of manuscripts:

**Research Articles**: Research articles are papers reporting the results of original research (clinical study, clinical trial, meta-analysis). Articles are limited to 250 words for the Abstract, 500 words for the Introduction, 1500 words for the Discussion and overall 4500 words (excluding abstract and references), 30 references and eight figures or tables. We ask authors to aim for accuracy, clarity and brevity and not to repeat results in detail that are clearly shown in a table or figure. We encourage the use of the EQUATOR reporting guidelines (https://www.equator-network.org). For clinical trials and clinical studies, the number and place of approval by an ethical committee has to be mentioned in the 'methods' section, as well as the registration number and the site of registry for clinical trials.

**Review Articles**: Review articles are broadly based and should sum up the current state of the research on a particular topic in an authoritative way. Reviews should include an abstract of no more than 250 words and have a main text range between 1500-4000 words (excluding abstract and references), with up to 30 references, three figures and three tables.

- **Systematic Review:** A systematic review aims to answer a research question by a systematic literature search based on specific in and exclusion criteria and an evaluation of the methodological quality of the included articles. A systematic review may possibly be accompanied by a meta-analysis of the results. Authors are encouraged to use the PRISMA checklist (available from https://www.prisma-statement.org). A PRISMA style flow diagram has to be included (https://www.prisma-statement.org/prisma-2020-flow-diagram).
- **Scoping review**: A scoping review shares similarities with a systematic review as it also addresses a research question but with less strict inclusion criteria than a systematic review. Scoping reviews focus on nature, characteristics and number of studies with the purpose to identify knowledge gaps. Authors are encouraged to use the PRISMA checklist for scoping reviews available from https://www.prisma-statement.org/scoping.
- **Narrative Review**: A narrative review gives an update on the current understanding of the pathophysiology, diagnosis and treatment of a disease, in a descriptive format. Authors are expected to briefly describe how the literature search was conducted: e.g. which database(s), search terms, timeframe and any inclusion and exclusion criteria. A narrative review may be illustrated by one or more case descriptions.

**Case Reports**: Case reports are limited to an abstract of 100 words, main text of 1500 words (excluding abstract and references), three tables and/or figures, and 10 references. Authors are encouraged to follow the CARE Case Report Guidelines (https://www.care-statement.org).

**Photo quiz**: The aim of this section is to stimulate visual recognition of clinical images that paediatricians may encounter in their practice. Clinical images include photographs of visible clinical signs, medical imaging, procedures, histological or cytological preparations. Submissions to this section should consist of 2 separate parts. The title of the manuscript should not mention the diagnosis. Manuscripts should be submitted without abstract. Keywords may be descriptive but must not contain the diagnosis. Make sure to remove any information that could identify a patient.

A first part with maximum 2 high quality figures without legends and a brief clinical history of maximum 500 words, but no mention of diagnosis. The last sentence should be 'What is the diagnosis?'

Second part: maximum 800 words for diagnosis, description of figures and short discussion and maximum 5 references.

Written informed consent for publication of the images should be obtained from the patient (if possible) and both parents or guardians. This should be added to the manuscript as a separate page(s).

**Short Communications**: Manuscripts must be submitted online at http://belgjpaediatrics.com/index.php/bjp/submissions. Authors should agree to the statement that the paper has not been published previously, nor is it under consideration by another journal (or provide an explanation in the Comments to the Editor).

- **Brief communication**: Contains reports of original research. Can include any of the study types listed under Research Articles.
- **Made in Belgium**: Summary of a PhD thesis defended by a paediatrician affiliated with a Belgian institution or working in Belgium. The title of the PhD thesis must be followed by a subtitle "PhD thesis presented on [date¬] at [university or high school], [city], Belgium. The author is the PhD student. Promotors and co-promoters are listed under the author. For this article type, no abstract is requested.
- **Focus on symptoms**: A short schematic or algorithmic approach for symptoms that are frequently encountered by a clinician. For this article type, no abstract is requested.

**Insights**: Insight pieces are written pieces deemed insightful to the work and/or life of paediatricians and can be submitted by everyone. They should be limited to 1500 words and should be approved for publication by the editors. For this article type, no abstract is requested and may include one table or figure, if essential, and five or fewer references.

**Correspondence to the Editor**: Correspondence should be limited to 400 words and may include one table or figure, if essential, and five or fewer references. Correspondence relates to a specific aspect of a previously published papers of which the authors of that paper are invited to write a reply that is published together with the letter.

**Reviews of books**: Book reviews related to paediatrics can be submitted by authors who want to share their experience with the readers of BJP. Book reviews should not exceed 500 words and may include one table or figure, if essential, and five or fewer references. The editors take the decision whether or not to publish.

### Submission information

Manuscripts must be submitted online at http://belgjpaediatrics.com/index.php/bjp/submissions.

### Outline of the online submission process

The online submission platform consists of five modules: 'Start', 'Upload Submission', 'Enter Metadata', 'Confirmation', 'Next Steps'.

1.1. 'Start'

1.1. Make a choice of section and category of the manuscript.

1.2. Check all submission requirements.

1.3. Letter to the editor: provide a brief explanation of why the manuscript should be considered for publication in the *Belgian Journal of Paediatrics* and mention additional information that may be useful to the editor. Authors are strongly encouraged to provide the names and email addresses of 4 potential reviewers.

1.4. Check author under 'Submit As'.

1.5. Check 'Acknowledge the copyright statement'.

2. 'Upload submission'

2.1. Pay attention please: in this module only the manuscript body and supplementary files, such as figures, tables, authorizations, parental consent, letter to the editor or other supplements) can be uploaded. The title, abstract, authors' names and affiliations and keywords should be entered in the metadata module.

2.2. Manuscripts should be submitted as single-line spaced Word files in Arial font size 10.

2.3. Please read carefully and apply the editorial rules underneath before submitting your manuscript.

3. 'Enter Metadata'

3.1. Title, abstract, list of contributors and keywords

3.1.1. Title: the first word of the title, all nouns, verbs, adjectives, adverbs and pronouns should be capitalised.

3.1.2. Authors should be entered in the list of contributors. Author's affiliation, e-mail address, and other personal data can be edited. The order of authors and corresponding author (principal author) can be defined.

3.1.3. Authors should pay particular attention to keywords as keywords are used by search engines to retrieve articles. To enhance traceability and impact of their work authors are encouraged to MeSH terms (Medical Subject Headings) as keywords. MeSH provides tools to help authors: MeSH on demand, an automatic identification of terms from the abstract text (available from: https://meshb.nlm.nih.gov/MeSHonDemand) and MeSH browser to search terms from an existing list of keywords (available from: https://meshb.nlm.nih.gov/search).

4. Confirmation: go back to review and adjust any of the information you have entered before continuing. When you are ready, click "Finish Submission"

**Authors** should meet the criteria for authorship according to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" available at www.icmje.org. Each person listed as an author is expected to have participated in the manuscript to a significant extent. Persons who have contributed to the study or manuscript but who do not fulfil the criteria for authorship have to be listed under a heading "acknowledgments". Although the editors and reviewers make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher.

**Language**: Manuscripts must be submitted in English. The chosen English spelling, UK

or US spelling must be used consistently throughout the article. It is recommended that authors, who are not very familiar with English, are strongly encouraged to seek assistance in writing the article.

**Scientific writing**:

- Bacteria names should be italicized, e.g. Staphylococcus aureus. After writing the complete name of a microorganism upon first use, the genus name can be shortened to just the capital letter, e.g. S. aureus. When discussing unnamed species, the abbreviation 'sp.' is used to refer to a single unnamed species, and 'spp.' refers to more than one unnamed species. More information can be found at https://www.enago.com/academy/write-scientific-names-in-a-research-paper-bacteria/.
- Virus names (the organism that makes you sick) should not be italicized. Virus species names should be written in italics and should not be abbreviated. More information can be found at https://ictv.global/faq/names.
- Gene symbols should be italicized, e.g. CFTR gene. Full written gene names should not be italicized, e.g. cystic fibrosis transmembrane conductance regulator gene. Gene products should not be italicized, e.g. CFTR protein. More information can be found at https://insight.jci.org/kiosks/publish/genestyle.

**Information that may allow identification of patients**: information that could possibly identify patients should not be included in the paper, unless the information is essential for scientific purposes. A signed informed consent from patients and their parents or legal guardians authorizing publication should be added as a separate file to the manuscript.

**Abstracts**: Abstracts should not contain references. Preferably, abbreviations should not appear in abstracts. However, if important for readability two or three different abbreviations can be accepted. These abbreviations should be spelled out at their first occurrence in the abstract. Abstracts for Research articles must be limited to 250 words and must be structured to the following headings: Objective, Methods, Results, Interpretation / Conclusion. Abstracts for Case reports or Short Communications must be limited to 100 words and should not include subsections.

**Abbreviations**: Always spell out abbreviations at first mention and place the acronym or abbreviation in parentheses immediately after. All subsequent uses, including tables and figures, should use the abbreviation or acronym. Abbreviations should be limited to terms that are both long and frequently (more than three times) repeated in the text. Try to avoid using more than six abbreviations in a paper, otherwise the text appears to be written in code.

**Text**: Organise the manuscript according to the instructions in the article type section. Sections must appear in the following order: Introduction, Materials and Methods, Results, and Discussion, Conclusion, Acknowledgements if any, Conflicts of Interest, References, Figure legends. Acknowledgements should include individuals who have contributed to the work (provided materials, technical assistance, etc.), but do not fulfil the criteria for authorship; all such individuals should agree to being included in this way before the manuscript is submitted. The Acknowledgements should also include sources of financial support for the work.

**Data Analysis**: Description of data analysis should provide the specific methods used, their rationale, the underlying assumptions, whether data met those assumptions, and how any missing data were handled.

**Units of measurement and laboratory values**: Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI. If applicable, normal values should be given in parenthesis when the value is first stated.

**Drugs and other products**: non-proprietary names of drugs or other products should be used, unless a specific trade name is essential for discussion.

**Eponyms and acronyms**: Eponyms should be used in their non-possessive form (e.g. Down syndrome and not Down's syndrome). Acronyms should be avoided. If this is not possible, they should be fully explained when first used.

**Tables**: Tables should be printable in a single page in portrait orientation. They should be typed in the same font as the rest of the paper, as text tables (rather than as figures). Screen captured tables are not allowed. Tables should be numbered in order of appearance in the text. Tables and their legends should be submitted as separate files.

**Figures**: All figures must be submitted as separate files. Flow charts or other diagrams should be submitted as a Word file (preferably) or as a PDF. However, copies of files embedded in Word cannot be used. Images and photographs should be submitted as JPEGs with a resolution of 600 dpi or higher. Publication of images or photographs should be authorised by the patient, parent or guardian. Figures should be cited in order of appearance. Each figure must have a legend. Figure legends should appear after the References, as part of the main document of the paper.

Please do not include extra text (including keys and headings) in the artwork, spell out keys and headings in the figure legend instead. Photographs of recognizable persons should be accompanied by a signed release from the patient or legal guardian authorizing publication, as described above. Masking eyes to hide identity is not sufficient.

**Supplementary materia**l: The authors can add supplementary material that enhances the online version of published research. Supplementary material includes relevant material that is additional to the main article, and may include extra data such as large tables, additional figures or methodological appendices. However, supplementary material can only be published in the digital version of the journal and will be available via the journal's website (see: https://www.belgjpaediatrics.com/index.php/bjp ).

**Patient privacy, informed consent and ethical standards**: If the work involves the use of human subjects, the author should ensure that the work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Authors should include a statement in the manuscript that written informed consent was obtained from the parents or guardians of the children who served as subjects of the study and, when appropriate, assent from the patients themselves. For clinical trials and clinical studies, the number and place of approval by an ethical committee has to be mentioned in the 'methods' section, as well as the registration number and the site of registry for clinical trials. The privacy rights of human subjects must always be observed. Race / ethnicity, gender or religion should only be mentioned if relevant to the content or purpose of the article.

**Animal rights**: All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study.

**References**: Arrange references in order of first appearance in the text. The references must be formatted according to Vancouver style (Quick reference guide available from: https://guides.lib.monash.edu/ld.php?content_id=48260115.

Reference numbers in the text must be put at the end of the sentence, between brackets and inside the punctuation. Separate by a comma if more than one reference is cited, for example (1,5,8). For sequences of consecutive numbers, the first and last number of the sequence should be separated by a hyphen, for example (1-4). Only published papers or papers in press should be included in the reference list. Personal communications or unpublished data must be cited in parentheses in the text with the author's names, the source and year.

The reference list, numbered in the order of mention in the text, must appear at the end of the manuscript.

**Authors**. Title of the Article. Name of the Journal. Publication year;Volume number (Issue number) :pagination. According to the Uniform Requirements the first six authors are named, followed by et al. if there's more than six. Authors are referenced as their surname followed by initials. Separate authors' names by a comma if more than one author. Abbreviate journal titles in the style used in the NLM Catalog (available from: https://www.ncbi.nlm.nih.gov/nlmcatalog/journals/ ). If in a journal a volume page numbering goes uninterrupted, the number of the issue may be omitted.

Examples:

Less than 6 authors: Gonzalez-Aguero A, Vicente-Rodriguez G, Gomez-Cabello A, Ara I, Moreno LA, Casajus JA. A combined training intervention programme increases lean mass in youths with Down syndrome. Res Dev Disabil. 2011;32(6):2383-8.

More than 6 authors: Bervoets L, Van Noten C, Van Roosbroeck S, Hansen D, Van Hoorenbeeck K, Verheyen E, et al. Reliability and Validity of the Dutch Physical Activity Questionnaires for Children (PAQ-C) and Adolescents (PAQ-A). Arch Public Health. 2014;72(1):47.

For an article published online ahead of the print version: Bilal J, Riaz IB, Naqvi SAA, Bhattacharjee S, Obert MR, Sadiq M, at al. Janus Kinase Inhibitors and Risk of Venous Thromboembolism: A Systematic Review and Meta-analysis. Mayo Clin Proc. 2021 Apr 8:S0025-6196(21)00054-9. doi: 10.1016/j.mayocp.2020.12.035. Online ahead of print.

***For journal articles:***

Authors. Title of the Article. Name of the Journal. Publication year;Volume number[1] (Issue number) :pagination. According to the Uniform Requirements the first six authors are named, followed by et al. if there's more than six. Authors are referenced as their surname followed by initials. Separate authors' names by a comma if more than one author. Abbreviate journal titles in the style used in the NLM Catalog (available from: https://www.ncbi.nlm.nih.gov/nlmcatalog/journals/ ). If in a journal a volume page numbering goes uninterrupted, the number of the issue may be omitted.

***Examples***:

Less than 6 authors: Gonzalez-Aguero A, Vicente-Rodriguez G, Gomez-Cabello A, Ara I, Moreno LA, Casajus JA. A combined training intervention programme increases lean mass in youths with Down syndrome. Res Dev Disabil. 2011;32(6):2383-8.

*1. If available.*

More than 6 authors: Bervoets L, Van Noten C, Van Roosbroeck S, Hansen D, Van Hoorenbeeck K, Verheyen E, et al. Reliability and Validity of the Dutch Physical Activity Questionnaires for Children (PAQ-C) and Adolescents (PAQ-A). Arch Public Health. 2014;72(1):47.

For an article published online ahead of the print version: Bilal J, Riaz IB, Naqvi SAA, Bhattacharjee S, Obert MR, Sadiq M, at al. Janus Kinase Inhibitors and Risk of Venous Thromboembolism: A Systematic Review and Meta-analysis. Mayo Clin Proc. 2021 Apr 8:S0025-6196(21)00054-9. doi: 10.1016/j.mayocp.2020.12.035. Online ahead of print.

***For electronic journal articles:***

The word [Internet] in square brackets should be inserted after the abbreviated journal title.

The date cited [in square brackets] must be included after the date of publication.

The URL (web address) must be included at the end of the reference.

For electronic journal articles with a DOI, include the DOI (digital object identifier) at the end of the reference, after the URL

***Examples***:

Stockhausen L, Turale S. An explorative study of Australian nursing scholars and contemporary scholarship. J Nurs Scholarsh [Internet]. 2011 Mar [cited 2013 Feb 19];43(1):89-96. Available from: http://search.proquest.com/docview/858241255

Kanneganti P, Harris JD, Brophy RH, Carey JL, Lattermann C, Flanigan DC. The effect of smoking on ligament and cartilage surgery in the knee: a systematic review. Am J Sports Med [Internet]. 2012 Dec [cited 2013 Feb 19];40(12):2872-8. Available from: http://ajs.sagepub.com/content/40/12/2872 DOI: 10.1177/0363546512458223

***For a book:***

*Print book*: Authors. Title of book. Edition number (if not first). Place of Publication: Publisher; Year of publication. Pagination.

*Electronic book*: Authors. Title of web page [Internet]. Place of publication: Publisher (or sponsor of website); year published [cited YYYY Mon DD]. Number of pages. Available from: URL DOI: (if available).

***Examples***:

*For a book:* Carlson BM. Human embryology and developmental biology. 4th ed. St. Louis: Mosby; 2009. 541 p.

*For an electronic book:* Shreeve DF. Reactive attachment disorder: a case-based approach [Internet]. New York: Springer; 2012 [cited 2012 Nov 2]. 85 p. Available from: http://dx.doi.org/10.1007/978-1-4614-1647-0.

***For a chapter in a book:***

*In a print book: Authors*. Title of chapter. In: Editor AA, Editor BB, Editors. Title of book. Edition number (if not first). Place of publication: Publisher, year of publication. Start and end page (of chapter).

*In an electronic book*: Authors. Title of chapter. In: Editor AA, Editor BB, Editors. Title of book [Internet]. Place of publication: Publisher, year of publication. [cited YYYYMonDD]. Page or chapter number/. Available from: URL DOI (if available).

***Example:***

*In a print book:* Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

*In an electronic book:* Halpen-Felsher BL, Morrell HE. Preventing and reducing tobacco use. In: Berlan ED, Bravender T, editors. Adolescent medicine today: a guide to caring for the adolescent patient [Internet]. Singapore: World Scientific Publishing Co.; 2012 [cited 2012 Nov 3]. Chapter 18. Available from: http://www.worldscientific.com/ doi/pdf/10.1142/9789814324496_0018.

More examples of other published, particularly material from internet, and unpublished material can be found in the quick Vancouver reference guide (https://guides.lib.monash.edu/ld.php?content_id=48260115) or on the website of the U.S. National Library of Medicine: https://www.nlm.nih.gov/bsd/uniform_requirements.html.

Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/archive/20130415/tsd/serials/lji.html.

**Disclosure of potential conflicts of interest**: The corresponding author must disclose any conflicts of interest on behalf of all co-authors. Co-author enquiries should be recorded and retained by the corresponding author. The disclosure declaration must be written in a separate paragraph after the conclusion and before the references.

**After submission**

All manuscripts considered for publication undergo peer review. The editors assign at least two external and independent reviewers. The reviewers' names are blinded to the authors. Reviewers are requested to maintain the confidentiality of the review process: not sharing, discussing with third parties, or disclosing information from the reviewed paper.

When resubmitting a manuscript after review the authors should indicate clearly their responses to the reviewers' comments. A document in which the reviewers' comments are answered point by point should be provided with the revised manuscript and include a copy of the original manuscript with track changes displaying the changes made. All co-authors should approve the revised manuscript version. The corresponding author should confirm approval in the point-by-point answer document. All components of the manuscript (point-by-point response letter, clean revised manuscript, manuscript with track changes, figures, tables, etc.) must be resubmitted even if no changes have been made at revision. To submit a revision, go to https://belgjpaediatrics.com/index.php/bjp/login and log in as an Author. Your submission record can be found by clicking on "View" → "Revisions" → "Upload file".

**After acceptance**

Corresponding authors will receive electronic page proofs to check the copy-edited and typeset article before publication. Portable document format (PDF) files of the typeset pages and support documents will be sent to the corresponding author by e-mail. It is the author's responsibility to ensure that there are no errors in the proofs. Changes that have been made to conform to journal style will stand if they do not alter the authors' meaning. Only the most critical changes to the accuracy of the content will be made, no substantial changes can be made at this point. The publisher reserves the right to deny any changes that do not affect the accuracy of the content. Proofs must be checked carefully, and corrections returned within 1 week of reception. Any errors found after this time will result in an erratum and not an article correction.

*Publication embargo*: Publication embargo as described in the editorial policy section applies until effective publication of an accepted manuscript.

*Corrections*: Requests to publish corrections should be sent to the editorial office. Corrections are reviewed by the editors and published in the next journal issue as an erratum.

*Copyright*: By accepting publication in the Belgian Journal of Paediatrics authors automatically transfer copyright to the journal.

*Reprints*: Reprints are available from the website of the Belgian Journal of Paediatrics at https://www.belgjpaediatrics.com/index.php/bjp . The journal is indexed in Google Scholar, where articles are searchable ( https://scholar.google.com/ ).

## Instructions for peer reviewers

Review of a submitted manuscript by at least two external and independent reviewers who are solicited by the editors. The reviewers' names will be blinded to the authors. Authors' identities are not blinded to the reviewers.

Reviewers should only agree if they feel qualified to review a manuscript and are able to return the review within a reasonable time-frame of maximum three weeks. If they cannot review, it is helpful to make suggestions for alternative reviewers.

Reviewers must refuse to review a manuscript in case of any potentially conflicting or competing interest.

Reviewers are requested to maintain confidentiality about the manuscripts and the information they contain.

Reviewers must provide a fair, honest, and unbiased assessment of the strengths and weaknesses of the manuscript. Comments to the authors will be passed in full to authors. The reviewers can also provide additional confidential comments to the editors, which will not be passed to the authors.

If the reviewer has concerns about misconduct during the elaboration or submission of the manuscript, he must notify the editor. This also applies to the case where the reviewer notices important similarities between the manuscript and a published article.

## Instructions for invited editors

Each year, a number of issues address a special chapter dedicated to a particular topic. Two guest editors, a Dutch-speaking and a French-speaking, are responsible for the content of these chapters.

A number of six manuscripts per chapter is expected. If more than six articles are needed to elaborate the topic of the chapter correctly, the editors can decide to spread the chapter over two issues.

The tasks of the invited editors are:

- To make choices of topics
- To invite authors
- To supervise the manuscripts in terms of content
- To protect the expected deadline for publication
- To write an editorial introducing the chapter

Editorial review and solicitation of peer reviewers will be done by the editorial team of the BJP.

Pampers
premium protection™

# Double protection

Grâce à l'absorption immédiate, la peau est protégée et la poche Stop & Protect aide à éviter les fuites à l'arrière du lange.

## Protection de la peau

des millions de micro-aérations éloignent les selles molles de la peau



Nous faisons de la sécurité des bébés une priorité. Pour en savoir plus, allez sur notre site pampers.be

OEKO TEX®
STANDARD 100
17.HCH.22181
Hohenstein HTTI
www.oeko-tex.com

Standard 100 Certifié par OEKO-TEX sur les produits nocifs.

Dermatest
L'assurance d'une utilisation en toute sécurité pour le respect de la peau des bébés.

0%

Sans aucun des allergènes de parfum listés par l'UE (comme réglementé par la réglementation cosmétique de l'UE (CE) N° 1223/2009).

SKIN HEALTH ALLIANCE

Certifiés par la Skin Health Alliance. Nos langes Pampers Premium Protection prennent soin de la peau des bébés. Ils ont été approuvés dermatologiquement et sont certifiés par des experts dermatologues de la Skin Health Alliance.

Beyfortus®
(nirsevimab)

| Prijs Beyfortus® 1 juni 2024 | |
|---|---|
| Publiekprijs, incl. BTW | 777.44 € |
| Prijs terugbetaald (GZ) | 12.10 € |
| Prijs terugbetaald (PZ) | 8.00 € |

**NIEUW**

Beyfortus® is terugbetaald voor baby's ter preventie van RSV


# De kracht om de chaos van RSV te verminderen.

Beyfortus® is het **eerste** direct langwerkende antilichaam ontwikkeld **voor alle baby's.**

Beyfortus® **vermindert** het risico op RSV-infecties én de **ziekenhuisopnames** door RSV met een **goed tolerantie** -en **veiligheidsprofiel**.[1]

Één enkele injectie beschermt de baby **tijdens het volledige RSV-seizoen**.[1]

## Scan de QR code voor meer informatie over de immunisatie van baby's met Beyfortus®.

▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden. Zie rubriek 4.8 voor het rapporteren van bijwerkingen. NAAM VAN HET GENEESMIDDEL Beyfortus 50 mg oplossing voor injectie in een voorgevulde spuit. Beyfortus 100 mg oplossing voor injectie in een voorgevulde spuit. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Beyfortus 50 mg oplossing voor injectie in een voorgevulde spuit Elke voorgevulde spuit bevat 50 mg nirsevimab in 0,5 ml (100 mg/ml). Beyfortus 100 mg oplossing voor injectie in een voorgevulde spuit Elke voorgevulde spuit bevat 100 mg nirsevimab in 1 ml (100 mg/ml). Nirsevimab is een gehumaniseerd immunoglobuline G1 kappa (IgG1κ) monoklonaal antilichaam dat geproduceerd wordt uit ovariumcellen van de Chinese hamster (Chinese hamster ovary, CHO) met behulp van recombinant-DNA-technologie. FARMACEUTISCHE VORM Oplossing voor injectie (injectie).Heldere tot opalescente, kleurloze tot gele oplossing met een pH-waarde van 6,0. THERAPEUTISCHE INDICATIES Beyfortus is geïndiceerd voor de preventie van lagere-luchtwegaandoeningen veroorzaakt door het respiratoir syncytieel virus (RSV) bij pasgeborenen en zuigelingen tijdens hun eerste RSV-seizoen. Beyfortus dient te worden gebruikt in overeenstemming met officiële aanbevelingen. DOSERING EN WIJZE VAN TOEDIENING Dosering De aanbevolen dosering is een enkelvoudige dosis van 50 mg intramusculair toegediend voor zuigelingen met een lichaamsgewicht < 5 kg en een enkelvoudige dosis van 100 mg intramusculair toegediend voor zuigelingen met een lichaamsgewicht ≥ 5 kg. Beyfortus moet worden toegediend vóór het begin van het RSV seizoen, of vanaf de geboorte voor zuigelingen die tijdens het RSV seizoen zijn geboren. De dosering bij zuigelingen met een lichaamsgewicht van 1,0 kg tot < 1,6 kg is gebaseerd op extrapolatie. Hiervoor zijn geen klinische gegevens beschikbaar. Naar verwachting zal blootstelling bij zuigelingen van < 1 kg hogere blootstellingen opleveren dan bij zuigelingen die meer wegen. De voordelen en risico's van het gebruik van nirsevimab bij zuigelingen van <1 kg moeten zorgvuldig worden afgewogen. Er zijn beperkte gegevens beschikbaar over extreem premature zuigelingen (zwangerschapsduur < 29 weken) jonger dan 8 weken. Er zijn geen klinische gegevens beschikbaar over zuigelingen met een postmenstruele leeftijd (zwangerschapsduur bij geboorte plus chronologische leeftijd) van minder dan 32 weken (zie rubriek 5.1). Voor zuigelingen die een hartoperatie ondergaan met cardiopulmonale bypass, kan zodra de zuigeling stabiel is na de operatie een extra dosis toegediend worden om adequate nirsevimab-serumspiegels te garanderen. Als dit binnen 90 dagen na ontvangst van de eerste dosis Beyfortus plaatsvindt, dient de aanvullende dosis 50 mg of 100 mg te zijn, afhankelijk van het lichaamsgewicht. Als er meer dan 90 dagen zijn verstreken sinds de eerste dosis, kan de aanvullende dosis een enkelvoudige dosis van 50 mg zijn, ongeacht het lichaamsgewicht, om de rest van het RSV seizoen te dekken. Er zijn geen veiligheids- en werkzaamheidsgegevens beschikbaar over herhaalde dosering. De veiligheid en werkzaamheid van nirsevimab bij kinderen in de leeftijd van 2 tot 18 jaar zijn niet vastgesteld. Er zijn geen gegevens beschikbaar. Wijze van toediening Beyfortus is alleen voor intramusculaire injectie. Het wordt intramusculair toegediend, bij voorkeur in de anterolaterale zijde van de dij. De gluteale spieren mogen niet routinematig als injectieplaats worden gebruikt vanwege het risico op beschadiging van de ischiaszenuw. Instructies voor toediening Beyfortus is verkrijgbaar in een voorgevulde spuit van 50 mg en 100 mg. Controleer de etiketten op de doos en de voorgevulde spuit om er zeker van te zijn dat u de juiste dosis heeft (50 mg of 100 mg). Beyfortus 50 mg (50 mg/0,5 ml) voorgevulde spuit met een paarse zuigerstang. Beyfortus 100 mg (100 mg/1 ml) voorgevulde spuit met een lichtblauwe zuigerstang. Stap 1: Terwijl u de Luer-lock met één hand vasthoudt (vermijd het vasthouden van de zuigerstang of de cilinder), draait u het naaldkapje van de spuit los door deze met de andere hand tegen de klok in te draaien. Stap 2: Bevestig een Luer-lock-naald aan de voorgevulde spuit door de naald voorzichtig met de klok mee op de voorgevulde spuit te draaien totdat u lichte weerstand voelt. Stap 3: Houd de cilinder met één hand vast en trek met de andere hand voorzichtig de naaldbeschermer met een rechte beweging van de naald af. Houd de zuigerstang niet vast terwijl u de naaldbeschermer verwijdert, anders kan de rubberen stop bewegen. Raak de naald niet aan en laat deze niet met in contact komen met een oppervlak. Plaats de naaldbeschermer niet terug op de naald en haal de naald niet los van de spuit. Stap 4: Dien de volledige inhoud van de voorgevulde spuit toe als een intramusculaire injectie, bij voorkeur in de anterolaterale zijde van de dij. De gluteale spieren mogen niet routinematig als injectieplaats worden gebruikt vanwege het risico op beschadiging van de ischiaszenuw. CONTRA-INDICATIES Overgevoeligheid voor de werkzame stof of voor een van de in rubriek 6.1 vermelde hulpstoffen. BIJWERKINGEN Samenvatting van het veiligheidsprofiel De meest voorkomende bijwerking was rash (0,7%) die binnen 14 dagen na toediening optrad. Het merendeel van deze bijwerking was licht tot matig van intensiteit. Aanvullend werden pyrexie en injectieplaatsreacties binnen 7 dagen na toediening gemeld met een prevalentie van respectievelijk 0,5% en 0,3%. Injectieplaatsreacties waren niet ernstig. Lijst van bijwerkingen Hieronder staan de bijwerkingen die zijn gemeld bij 2.966 voldragen en premature zuigelingen (zwangerschapsduur, Gestational Age (GA) ≥ 29 weken) die nirsevimab kregen in klinische onderzoeken. De bijwerkingen die zijn gemeld in gecontroleerde klinische onderzoeken zijn ingedeeld volgens systeem/orgaanklasse (SOC) van MedDRA. Binnen elke SOC zijn voorkeurstermen gerangschikt op afnemende frequentie en vervolgens op afnemende ernst. De frequenties van optreden van bijwerkingen wordt gedefinieerd als: zeer vaak (≥ 1/10); vaak (≥ 1/100 tot < 1/10); soms (≥ 1/1.000 tot < 1/100); zelden (≥ 1/10.000 tot < 1/1.000); zeer zelden (< 1/10.000) en niet bekend (kan met de beschikbare gegevens niet worden bepaald). Huid- en onderhuidaandoeningen • Soms - Rasha a Rash is gedefinieerd door de volgende gegroepeerde voorkeurstermen: rash, maculo-papulaire rash, vlekkerige rash Algemene aandoeningen en toedieningsplaatsstoornissen • Soms – Injectieplaatsreactieb ; Pyrexie b Injectieplaatsreactie is gedefinieerd door de volgende gegroepeerde voorkeurstermen: injectieplaatsreactie, injectieplaatspijn, injectieplaatsverharding, injectieplaatsoedeem, zwelling van injectieplaats Zuigelingen met een verhoogd risico op ernstige RSV-ziekte De veiligheid is ook onderzocht in MEDLEY bij 918 zuigelingen met een verhoogd risico op ernstige RSV ziekte, onder wie 196 extreem premature zuigelingen (GA < 29 weken) en 306 zuigelingen met chronische longziekte van prematuriteit of hemodynamisch significante aangeboren hartziekte die hun eerste RSV seizoen ingingen, die nirsevimab (614) of palivizumab (304) kregen. Het veiligheidsprofiel was vergelijkbaar met het vergelijkende geneesmiddel palivizumab en consistent met het veiligheidsprofiel bij voldragen en premature zuigelingen GA ≥ 29 weken (D5290C00003 en MELODY). Immunogeniciteit Zoals met alle therapeutische eiwitten, is er potentieel voor immunogeniciteit. Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via: België: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – Afdeling Vigilantie – Postbus 97 – 1000 Brussel Madou – Website: www.eenbijwerkingmelden.be – e-mail: adr@fagg.be HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly, Frankrijk NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN EU/1/22/1689/001 - 50 mg, 1 voorgevulde spuit voor eenmalig gebruik EU/1/22/1689/002 - 50 mg, 1 voorgevulde spuit voor eenmalig gebruik met naalden EU/1/22/1689/003 - 50 mg, 5 voorgevulde spuiten voor eenmalig gebruik EU/1/22/1689/004 - 100 mg, 1 voorgevulde spuit voor eenmalig gebruik EU/1/22/1689/005 - 100 mg, 1 voorgevulde spuit voor eenmalig gebruik met naalden EU/1/22/1689/006 - 100 mg, 5 voorgevulde spuiten voor eenmalig gebruik DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING Datum van eerste verlening van de vergunning: 31 oktober 2022 DATUM VAN HERZIENING VAN DE TEKST Goedkeuringsdatum: 11/2023 Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau http://www.ema.europa.eu

**Referentie:**
**1.** Beyfortus SKP, nov 2023. Sanofi Belgium - MAT-BE-2400434-1.0-06/2024

sanofi