BjP
Belgian Journal of Paediatrics
PUBLICATION OF THE BELGIAN ACADEMY OF PAEDIATRICS

Belgian Academy of Paediatrics
FUSION OF BVK-SBP, GBPF & VVK

2025 | Volume 27 | number 4 | December

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

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NAAM VAN HET GENEESMIDDEL: Tiorfix zuigelingen en kinderen 4 mg/ml suspensie voor oraal gebruik. **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING:** Racecadotril 4 mg. Elke ml suspensie voor oraal gebruik bevat 4 mg racecadotril. De fles van 50 ml bevat 168 mg racecadotril, overeenkomend met 112 kg-doses. De fles van 180 ml bevat 660 mg racecadotril, overeenkomend met 440 kg-doses. Elke kg-dosis komt overeen met 1,5 mg/kg/dosis. Hulpstoffen met bekend effect: Elke kg-dosis suspensie voor oraal gebruik bevat 1,13 mg natriumbenzoaat, 0,84 mg natrium, 225 mg sucrose en 1,06 mg propyleenglycol. Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de Samenvatting van de productkenmerken (SKP). **FARMACEUTISCHE VORM:** Suspensie voor oraal gebruik. Witte tot gebroken witte suspensie. **THERAPEUTISCHE INDICATIES:** Tiorfix zuigelingen en kinderen 4 mg/ml is geïndiceerd als aanvulling op orale rehydratie en dieetmaatregelen bij de symptomatische behandeling van acute diarree bij zuigelingen en kinderen ouder dan 3 maanden en met een gewicht van 7 kg en meer, wanneer de orale rehydratie en dieetmaatregelen op zich niet volstaan om de klinische aandoening onder controle te krijgen en waar een oorzakelijke behandeling niet mogelijk is. Als een oorzakelijke behandeling mogelijk is, kan racecadotril toegediend worden als een aanvullende behandeling. **DOSERING EN WIJZE VAN TOEDIENING:** Tiorfix zuigelingen en kinderen 4 mg/ml wordt oraal toegediend samen met orale rehydratie (zie rubriek 4.4 van de SKP). **Dosering:** Pediatrische patiënten: *Enkel voor zuigelingen en kinderen ouder dan 3 maanden en met een gewicht van 7 kg tot 52 kg:* De gebruikelijke dosering is gebaseerd op het lichaamsgewicht van het kind. Deze bedraagt 1,5 mg/kg/dosis (wat overeenkomt met één kg-dosis). Op dag één: een eerste dosis onmiddellijk toedienen, vervolgens afhankelijk van het tijdstip van de eerste dosis, tot maximaal 3 doses verdeeld over de dag, waarbij de eerste dosis in deze drie doses wordt meegerekend. De doses worden bij voorkeur aan het begin van de drie hoofdmaaltijden toegediend. Op de volgende dagen: 3 doses verdeeld over de dag, bij voorkeur aan het begin van de drie hoofdmaaltijden. De maximale dosering per dag bedraagt 3 doses. Het geneesmiddel wordt oraal toegediend met een doseerspuit (met schaalverdeling in kg lichaamsgewicht) die een dosis van 1,5 mg racecadotril per schaalverdeling in kg geeft. Voor elke dosis: • Zuigelingen en kinderen tot 26 kg: vul de doseerspuit tot aan de maatstreep die het gewicht van het kind aangeeft. • Kinderen tussen 27 en 38 kg: vul de doseerspuit eenmaal tot aan de maatstreep van 13 kg en dien de suspensie toe aan het kind. Vul de doseerspuit een tweede keer tot een totaal is bereikt dat gelijk is aan het gewicht van het kind en dien de suspensie nogmaals toe aan het kind. • Kinderen tussen 39 en 52 kg: vul de doseerspuit eenmaal tot aan de maatstreep van 26 kg en dien de suspensie toe aan het kind. Vul de doseerspuit een tweede keer tot een totaal is bereikt dat gelijk is aan het gewicht van het kind en dien de suspensie nogmaals toe aan het kind. • Voor een gewicht van meer dan 52 kg dient u de meest geschikte farmaceutische vormen te gebruiken. Duur van de behandeling: De behandeling moet worden voortgezet tot er terug twee opeenvolgende vastere ontlastingen zijn, maar mag niet langer dan 7 dagen duren. Er zijn geen klinische onderzoeken bij kinderen jonger dan 3 maanden. **Wijze van toediening:** Oraal gebruik. 1: De fles vóór gebruik goed schudden om de suspensie te mengen. 2: Open de fles door de kinderveiligheidsdop te draaien en naar beneden te drukken. 3: Steek de spuit volledig in de opzuigopening. 4: Draai de fles ondersteboven om de spuit te vullen. Houd de spuit goed op zijn plaats en trek langzaam en gelijkmatig aan de zuiger tot de gewenste maatstreep in kg. 5: Zet de fles weer rechtop en verwijder de spuit. 6: Steek de spuit zonder kracht te gebruiken in de mond van het kind en dien de volledige hoeveelheid suspensie toe door de zuiger zachtjes en geleidelijk naar beneden te duwen. Haal na elk gebruik de doseerspuit voor orale toediening uit elkaar, spoel met water en droog af. Het gebruik van deze doseerspuit voor orale toediening is strikt voorbehouden voor de toediening van Tiorfix zuigelingen en kinderen 4 mg/ml. Bijzondere populaties: Er zijn geen onderzoeken uitgevoerd bij kinderen met lever- of nierfunctiestoornissen (zie rubriek 4.4 van de SKP). **CONTRA-INDICATIES:** Overgevoeligheid voor de werkzame stof of voor een van de in rubriek 6.1 van de SKP vermelde hulpstoffen. **BIJWERKINGEN:** Klinische studies met Tiorfix granulaat voor orale suspensie, een andere farmaceutische vorm voor zuigelingen en kinderen met acute diarree, verschaften veiligheidsgegevens over het gebruik bij 860 zuigelingen en kinderen behandeld met racecadotril en bij 411 behandeld met een placebo. De bijwerkingen die hieronder staan vermeld, werden vaker waargenomen met racecadotril dan met de placebo in klinische studies of werden gerapporteerd tijdens de marketing periode. Bijwerkingen worden gerapporteerd volgens MedDRA systeem/orgaanklassen. Binnen elke systeem/orgaanklasse worden de bijwerkingen gerangschikt volgens frequentie. Binnen elke frequentiegroep worden de bijwerkingen gerangschikt naar afnemende ernst. De frequentie van bijwerkingen is 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). Ernstige huidreacties (SCAR's), waaronder geneesmiddelexantheem met eosinofilie en systemische symptomen (DRESS), werden in verband met de behandeling met racecadotril gemeld (zie rubriek 4.4 van de SKP). Infecties en parasitaire aandoeningen: Soms: tonsillitis. Huid- en onderhuidaandoeningen (zie rubriek 4.4 van de SKP): Soms: rash, erytheem. Niet bekend: urticaria, angiooedeem (Quincke's oedeem), oedeem van de tong, het gezicht, de lippen of de oogleden, erythema multiforme, erythema nodosum, papuleuze rash, pruritus, prurigo, toxicodermatitis, geneesmiddelexantheem met eosinofilie en systemische symptomen (DRESS). Immuunsysteemaandoeningen: Niet bekend: anafylactische shock. **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 Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten, www.fagg.be. Afdeling Vigilantie: Website: www.eenbijwerkingmelden.be – e-mail: adr@fagg-afmps.be. **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN:** Bioprojet Pharma, 9 rue Rameau, 75002 Paris, Frankrijk. **NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN:** BE661445. **AFLEVERINGSWIJZE:** Geneesmiddel op medisch voorschrift. **DATUM VAN HERZIENING VAN DE TEKST:** 04/2024. Versie 06/2024

Publieksprijs	
4mg / ml	
50 ml	€ 16,49
180 ml	€ 22,06

1. Lehert P. et al., Digestive and Liver Disease 2011; 43. 707-713 - **2.** Baumer et al. Effects of acetorphan, an enkephalinase inhibitor, on experimental and acute diarrhoea, Gut, 1992, 33, 753-758 - **3.** Salazar-lindo et al., racecadotril in the treatment of acute watery diarrhea in children,N Engl J Med 2000;343:463-7 - **4.** Cezard et al., Efficacy and tolerability of racecadotril in acute diarrhea in children, 2001; Gastroenterology 2001 120:799-805 - **5.** EMEA, reflection paper: Formulations of choice for the paediatric population, May 2005 - **6.** SKP Tiorfix, current version

065-09-2025 BENL, September 2025

bioprojet BENELUX NV

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THE HEALTH OF THE EARTH AND HUMAN HEALTH ARE INEXTRICABLY LINKED.
(Pierre Rabhi)

The winter issue of the Belgian Journal of Paediatrics is devoted to climate change. Our two guest editors, Els Duval and Mark Wojciechowski, have brought together contributions from various authors detailing the impact of these changes on the health of children, families and present and future generations. We sincerely thank them and hope that you will appreciate the relevance of their work.

While the gravity of this issue is clear, the entire editorial committee has chosen to adopt a tone of mobilisation and hope. We are fortunate to be able to know and understand. We have a responsibility to inform, reflect, suggest, adapt, innovate and lead by example. As previously announced, this issue will be followed in the coming months by a special section entitled 'Seeds for the Future', in which we invite you to share the personal or professional initiatives you have taken to better respect and protect the Earth and the environment. These small gestures or initiatives may seem insignificant, but as the French essayist and ecologist Pierre Rabhi liked to remind us, it is important that everyone does their part. Yes, moving a stone can change the flow of the river. Please feel free to send us your texts via the online platform *(https://www.belgjpaediatrics.com/index.php/bjp/about/submissions)* in the short communication format.

This approach is also supported by our cartoonist Serge Ernst. With the talent and humour we have come to know over many years, he has created a festive cover!

This reminds us that the situation in our complex world, that the challenges we face, can be opportunities, that they are compatible with optimism and celebration, with the values we all want to live by at the end of 2025 or at the dawn of 2026. Life is not just about consuming and accumulating. Life is also about engagement for justice and solidarity, attention and dignity for everyone. Above all, it is a wonderful opportunity to forge bonds and connect with those around us, our colleagues, our families and our loved ones. Good health also means being able to nurture these bonds, to take the time to meet, listen and share with others.

This is our wish for each and every one of you: Happy New Year and good health!

Christophe Chantrain and Marc Raes

UW VRAGEN OF COMMENTAAR
VOS QUESTIONS OU COMMENTAIRES

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Guest Editors' Editorial

Climate change is no longer a future scenario, in Belgium, we are already living with its consequences. Hot summers that break record after record, floods, air pollution in our cities and along major roads, all of this influences the world in which our children grow up today. As paediatricians, we cannot ignore this. Our work has always been about more than treating illness; it is also about protecting the conditions that allow children to grow, and advocating for those who cannot speak for themselves.

Our air quality remains among the worst in Western Europe, with high levels of NO_2 and fine particulate matter. Every day most Belgian children breathe air that exceeds WHO guidelines, especially in urban areas like Antwerp or Brussels, and most parts of Flanders. We see the impact: asthma and increasing respiratory illnesses. Heatwaves, once exceptional, are now common. Children dehydrate faster, sleep worse, and struggle more with chronic illnesses. The 2021 floods in Wallonia were another wake-up call. Families lost homes, schools were disrupted for months, and many children still carry the emotional impact. All this on top of rising levels of climate-related anxiety among adolescents.

Climate change makes social inequalities in Belgium more visible. Children growing up in poorly insulated houses, densely built areas or close to busy roads are more exposed to heat and air pollution. Families with fewer financial resources often have less access to green spaces, good nutrition, or timely healthcare. On top of that, displacement and migration, whether sudden after extreme events or more gradual due to drought, can further undermine children's safety, education and overall health.

On the global stage, we saw at the recent COP that progress remains slow. There was acknowledgement to move away from fossil fuels, but without strong commitments or timelines. For the children whose futures depend on action, this is simply not enough.

This special issue of the Belgian Journal of Paediatrics brings together articles that highlight these diverse impacts: air pollution and respiratory health, the dangers of extreme heat, the expansion of vector-borne infections into regions like ours, the mental health consequences of climate stress, the effects on neurodevelopment, the role of climate change in global migration patterns, and the implications for children's rights. Together, they form a clear message: climate change is already transforming paediatrics in Belgium.

We are also pleased to welcome an article by Frank Raes, who describes in "five easy pieces" how past and future impacts are intertwined with social, economic and environmental challenges that require urgent, coordinated action.

Yet this is not a story of hopelessness. The real opportunity lies in what we do here, in our communities, our hospitals, our consultations, and our policies. Belgian children cannot choose the air they breathe or the climate they inherit, but we can choose the systems we build around them. We can ask the government for national heat action plans, and meanwhile offer parents clear guidance on how to cool rooms safely, and recognise signs of heat stress. In our professional organisations, we can be the voice of children in climate policy. This includes advocating for clean air measures, greener school environments, climate-resilient childcare facilities, and social policies that protect vulnerable families. In our hospitals, we can push for more sustainable choices. Healthcare has a large environmental footprint: energy, waste, single-use plastics, transport. Reducing unnecessary tests, improving energy efficiency, choosing durable materials, these are not abstract actions; they are entirely aligned with our duty to "do no harm."

Climate change is without doubt a child-health issue. But it is also a moment to rethink how we build healthier, fairer environments for the next generation. Belgian children depend on us to speak up, to act, and to take their future seriously. Because their future is written by the choices we make today.

Els Duval and Mark Wojciechowski

Climate Change: Five Easy Pieces about the Past and the Coming 30 Years

Frank Raes

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Keywords
Climate change ; fossil fuels ; carbon dioxide ; ethics ; policy making

Climate change is upon us!

When we entered climate change research, 30 years ago, we were told that if we would not put a break on the use of fossil fuels -coal, oil and natural gas- and reduce their emissions of greenhouse gasses, we would warm up our Planet and create a serious problem for our grandchildren. Solving this was a matter of developing new energy technologies and implementing them through subsidies and innovative taxation mechanisms. However, the world did not nearly do enough of all this. In the meantime, most of us have grandchildren and climate change is upon us.

According to the latest report of the Intergovernmental Panel on Climate Change (IPCC) in 2023, it is a fact that humans have warmed up the Planet by 1,1 °C compared to pre-industrial times[1] (1). In 2024, the Planet reached 1,55 °C, be it only for that single year[2] (2). The report further states that the observed increase in local extreme weather events such as hot and cold spells, droughts and heavy precipitation, are a result of this global warming of "only" 1,1 °C. Every 0,1 degree more will further increase the frequency and intensity of these local events and it is only a matter of chance whether the next weather disaster will hit our backyard or that of our neighbour. A kind of Russian roulette, indeed, but one in which the number of bullets in the cylinder increases with time.

Compared to 30 years ago, the climate problem is now more complex to solve. We have to continue and try to phase out the use of fossil fuels to avoid the worst of climate change impacts, but we now also have to deal with the negative impacts that we could not avoid. We also learned that such impacts are mainly felt in poor and therefore vulnerable communities, both in developing and developed countries, communities that hardly use fossil fuels and hardly contribute to the problem. The impacts of today's fossil fuel use and its emissions of greenhouse gases will also be felt during the lifetime of those who aren't born yet and, obviously, didn't contribute to the problem either[3]. Climate change is fundamentally an ethical problem and if it is not solved it will only exacerbate existing inequalities. Who are we in the rich part of the world that we can destroy livelihoods in its poor part? Who are we adults that we can "*steal the dreams*" of the children about their future (3)? Who are we Homo Sapiens that we can destroy animal and plant species, glaciers, forests, entire landscapes?

We better treat it as an emergency, but we don't …

In 2018 the IPCC published a special report in which it states that: "*… instabilities [in the climate system, leading to multi-meter* sea level rise] could be triggered at around 1,5 °C to 2 °C of global warming" (1). The report further showed that, in a business as usual scenario, global warming could reach 1,5 degrees as early as 2030. After having read this report, Greta Thunberg, who had been concerned about climate change for years, got angry. Having the impression that nobody was seriously reducing the emissions of greenhouse gasses, and nobody asked to prepare for climate change impacts, she pointed out that the world is in a climate emergency: "around 2030 *[…] we will set off an irreversible chain reaction beyond human control [= tipping points] that will most likely lead to the end of our civilisation as we know it"* (3).

In 2021 the IPCC consensus was more prudent and stated that *"establishing links between specific levels of global warming with tipping points and irreversible behaviour is challenging … "*, but it continued saying: *"… [tipping points] however cannot be excluded, and their likelihood of occurrence generally increases at greater warming levels."* This all means that 1,5 °C of warming is not a hard wall where we risk crashing into. It is rather a signpost indicating that we are entering uncharted terrain in which the world's climate could tip into something much less benign for Life as we know it. That is something "too risky to bet against " (4). In this spirit of precaution and in a strange move that put climate policy-making ahead of climate science, low laying island States that are obviously vulnerable to raising sea levels, pushed the United Nations (UN) and finally succeeded to have an objective of 1,5 °C in the 2015 Paris Agreement. In practice, not going beyond 1,5 °C of global warming requires that the global net emissions of greenhouse gases should be zeroed by 2050.

Ten years on, the policies agreed so far by individual countries that signed up to the Paris Agreement are still not sufficient to comply with this (5). For instance: the global emissions of energy-related CO_2 continued raising and, after a small dip during the COVID period, reached again a record high in 2023[4] (6). This all means that the world is presently on course for a warming of 2,6 – 3,1 °C over the course of this century (5).

FIGURE 1: Most profitable companies according to Fortune 500 (9). Before COVID (2919) during COVID (2021) and after COVID (2024). Shown are the annual profit in billions of dollars.

most profitable companies in 2019	profit (billions $)	most profitable companies in 2021	profit (billions $)	most profitable companies in 2024	profit (billions $)
Saudi Aramco	110,9	Apple	57,4	Saudi Aramco	121,0
Apple	59,5	Saudi Aramco	49,2	Apple	97,0
Indust Com Bank of China	45,0	SoftBank Group	47,0	Berkshire Hathaway	96,2
Samsung	39,8	Indust Com Bank of China	45,7	Google (Alphabet)	73,8
China Construction Bank	38,4	Microsoft	44,2	Microsoft	72,4
JPMorgan Chase	32,4	Berkshire Hathaway	42,5	Indust Com Bank of China	51,4
Google	30,7	Google	40,2	JPMorgan Chase	49,6
Agriculture Bank of China	30,6	China Construction Bank	39,2	China Construction Bank	47,0
Bank of America	28,1	Agricultural Bank of China	31,2	FACEBOOK (Meta)	39,1
Bank of China	27,7	FACEBOOK	29,1	Agricultural Bank of China	38,0
Royal Dutch Shell	23,3	JPMorgan Chase	29,1	Exxon Mobile	36,0
Gazprom	23,2	Bank of China	27,9	Johnson & Johnson	35,2
Wells Fargo	22,3	Tencent Holdings	23,1	Toyota Motor	34,2
FACEBOOK	22,1	Alibaba Group Holding	22,2	Bank of China	27,9
Intel	21,1	Samsung	22,1	Amazon	30,4
Exxon Mobile	20,8	Amazon	21,3	Nvidia	29,8
AT&T	19,3	Toyota Motor	21,1	UBS Group	27,8
Citigroup	18,1	Intel	20,8	Taiwan Semiconductors	27,4
Toyota Motor	16,9	Pin An Insurance	20,7	Bank of America	27,0
China Development Bank	16,7	Bank of America	17,0	Petrobras	24,9

Why is it so difficult to solve?

Despite more than 30 years of IPCC reports and UN negotiations and resulting agreements, pacts, roadmaps, etc. the burning of coal and oil continued and its emissions of greenhouse gases increased year after year. Why? The problem is wicked, the reasons are many and intertwined.

One difficulty is undoubtedly bringing all 195 countries in the world around the table and come to an agreement about how to solve a problem that is created by only a few of those countries, but has impacts for all of them. However, the following is certainly also an important part of it, if not the most important one: in most of the past 30 years, a close-knit group of global investors and entrepreneurs, supported by neo-liberal policies that gave them free rein, increasingly put company and even personal profit ahead of the wellbeing of others and that of the Planet. Hence, investments were simply made where the returns were highest, i.e. in the most profitable companies. In the years before COVID, these companies were banks (one makes money with money …), high tech companies followed by oil and gas companies as well as car companies (Fig. 1).

In the COVID years 2020 and 2021, oil companies were much less profitable. In 2021, according to Fortune, BP, Royal Dutch Shell and Exxon Mobile even made annual losses of around 20 billion $ each (7). These losses were undoubtedly due to less demand for transport during the pandemic. As mentioned before, the economy recovered and some energy companies are now making even more profit than before COVID (Fig 1). However, in their forecasts for the next decades, European oil companies do consider lower demand because of greater public awareness and political discourse about climate change, as demonstrated by e.g. the 2015 Paris Agreement (8). Hence, there is a risk for investors and they might start turning away from fossil fuel companies and invest elsewhere. That "elsewhere" could well be renewable energies, for which demand is clearly on the rise and production cost has fallen significantly during the past decade. Putting all this together, many observers of the energy sector claim that a process might have been set in motion that could effectively phase out fossil fuels.

The crucial questions are: if this transition can be completed within the next 30 years, and if it can be done without leaving the neo-liberal logic in which the individual is blindly put above the collective. The answer, at least to the second question, must be negative, as demonstrated today by the USA where neo-liberal and "my country first" policies reign supreme and coincide with cancelling existing climate policies and suppressing even climate science (9).

Change, crises and social tipping points

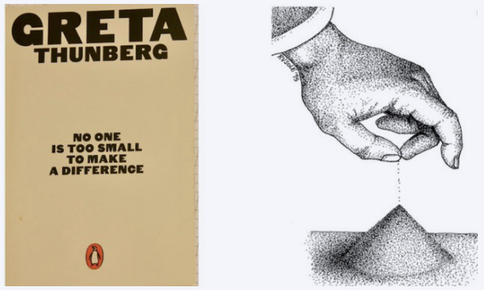
Despite the increase in global emissions, the emissions in the EU dropped by 33% between 1990 and 2022 (10). They decreased for three reasons: 1- moving heavy polluting industries outside the EU, 2- successful implementation of dedicated climate and environmental policies and 3- the occurrence of several unpredictable events (crises/opportunities). Each of the latter events (the fall of the Berlin Wall, the financial crisis 2008-2010, COVID 2020-2021, the War in Ukraine) lead to structural changes in the European economy and society (that were guided by policy making!) with a significant decrease in emissions as a result. About half of the 33% decrease mentioned before can be linked to these four crises.

Unpredictable events will also occur in the next 30 years, simply because society is a complex system, and a complex system *under stress (!)* can suddenly tip into another state. Such tipping points are now very much discussed in the climate system and are a main reason of concern. But history shows that also in society small events can lead to large and irreversible changes: revolutions they are often called. Crossing tipping points should not always be painful. Greta Thunberg, for instance, has clearly created a revolution. She has been that grain of sand that created an avalanche in the mountain of public awareness (Fig. 2). It came as something totally unpredicted, but it could only happen because that mountain of awareness had been built by scientists and activists in the decades before, piece by piece, steeper and steeper and under ever more stress.

In the coming decades there will be further crossings of social tipping points: new (or old) ideas can go viral (such as, e.g., "value

1. A Panel set up by the United Nations in 1990, to report every 5 years about the state of knowledge regarding climate change, its impacts and the solutions to the problem. All reports can be downloaded at www.ipcc.ch. The sixth report, consisting of different volumes, was published in the time period 2021-2023. The seventh report is scheduled for completion in 2027.
2. The 1,1 °C temperature increase mentioned in the IPCC report, refers to the difference between the average temperature over the past 30 years (1991-2021) and the average temperature over a 30 years' time period in pre-industrial times. The objectives of 1,5 °C or 2°C mentioned in the Paris Agreement also refer to 30 years averages. Hence the 1,55 °C temperature increase in 2024, which refers only to the average over that single year, does not yet mean that the 1,5 °C objective of the Paris Accord has been breached.
3. This is all a simple consequence of the fact that, once a molecule of CO_2 is emitted in the atmosphere, it stays there for about 100 years and has ample time to travel around the world.
4. According the International Energy Agency, the COVID pandemic has caused a reduction in global energy-related CO2 emissions of 5,8% in 2020 compared to 2019. But since 2021 these emissions have increased again and have reached record heights in 2022 and again in 2023.

FIGURE 2: Cover of Greta Thunberg's book: No one is too small to make a difference, that caused a landslide in public awareness about climate change 2019.



is more important than price" or "economy is part of ecology, not vice versa"), the financial world might indeed shift investments overnight, and there will certainly be technological breakthroughs. There will also be disastrous catastrophic events, including climate change related ones that can no longer be avoided. When they occur, we need to see also the opportunities to improve, so that the pain is not in vain.

Changing culture

Climate change is an ethical problem, which asks us to answer fundamental Political (with major P!) questions, about how we live on this Planet: among ourselves and with the rest of nature. We are in many to believe that solving the climate crises will require not only scientific knowledge, technological innovations or responsible financial investments, but also a much broader cultural change. Culture is the amalgam of stories and theories, shared by a group of people, that explains and justifies how they live on this Planet. Modern consumeristic culture is by now shared globally, and is based on a narrative that makes us believe that our way of living has nothing to do with climate or nature, that our Technosphere is totally separated from the Biosphere or any other sphere of the Earth System. That is obviously not true, and climate change is the most powerful proof of that. If we really care for all people and everything else that is on our Planet, we clearly have to rethink the relationships between humans and that everything else. We need a globally shared narrative in which respect for everyone and everything is central. For creating such a narrative and bring it down to Earth and real, we will not only need scientists, engineers and entrepreneurs, but all sort of story tellers and educators, Politicians, philosophers, … and last but not least: artists[5,6] (11). Art will not save the world but the world cannot do without art. We are stardust, yes, but we are also "… such stuff as dreams are made of"[7].

These seem like naïve words, especially in current times in which autarchic governments attack the scientific endeavour, attack hardly needed global institutions, and use economic blackmailing and outright violence to impose a totally different narrative (9). These are times that one would easily give up the fight against the causes of climate change and deal instead with the consequences of it, as long and as good as one can, knowing that there is a limit to that.

Still, giving up and doing nothing is not a choice, and if you think of it, it is only in the doing, in the action, that one can maintain a grain of optimism for a better world: pessimism in theory, optimism in practice (12).

This paper is an updated version of the paper "Cambiamento Climatico cinque pezzi facili sui 30 anni passati e su quelli futuri" published in Mediterraneo Dossier #68, p. 14, 2022, Fondazione Girolomoni.

5. In this short video Yuval Noah Harari explains with lucidity that to build an atomic bomb, you do not only need to know the physics (E=mc2), you also need a powerful story to make people believe that it is worthwhile to actually build it. It is exactly the same with solving the climate crisis (https://www.facebook.com/reel/1128761595336572)
6. Artists can be "truth-tellers and mirror holders, emotional translators, visionaries and hope weavers, cultural memory-keepers, challengers of powers, bridge builders, nature's ambassadors and community catalysts", i.e, everything that can be used for changing society and its culture.
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* En ligne avec les nouvelles recommandations ESPGHAN 2024. ESPGHAN position paper on the diagnosis, management, and prevention of cow's milk allergy. JPGN. 2024;78(2):386-413.

Avis important pour tous les (para) médicaux: l'Organisation Mondiale de la Santé (OMS) recommande d'informer les femmes enceintes et les mamans de nourrissons sur les avantages et la supériorité de l'allaitement maternel, et plus particulièrement sur le fait qu'il fournit la meilleure alimentation et la meilleure protection contre les maladies infantiles. Les mères devraient recevoir des conseils sur la préparation, et le maintien de la lactation, avec un accent particulier sur l'importance d'une alimentation équilibrée pendant la grossesse et après l'accouchement. L'introduction inutile du biberon, ou d'autres aliments et boissons, doit être découragée car cela aura un effet négatif sur l'allaitement au sein. De même, les mères doivent être averties de la difficulté de revenir sur une décision de ne pas allaiter. Avant de conseiller une mère d'utiliser un lait infantile, elle doit être informée sur les conséquences sociales et financières de sa décision: par exemple, un bébé exclusivement nourri au biberon nécessite plus de 450 g de poudre par semaine. Dès lors, les circonstances et le coût pour la famille doivent être pris en considération. Les mamans doivent savoir que l'allaitement au sein n'est pas seulement le meilleur aliment pour leur bébé mais aussi le plus économique. Si la décision d'utiliser une préparation pour nourrissons est prise, il est important de donner aux parents des instructions correctes sur les méthodes de préparation, en soulignant que l'eau non bouillie, des bouteilles non stérilisées ou dilution incorrecte peuvent rendre le bébé malade. **Avec les compliments de Nestlé.** Ce document est exclusivement réservé à l'information des professionnels de la santé. E.R.: Karlien Desmedt BEO, Nestlé Belgilux SA/NV, Rue de Birminghamstraat 221 - 1070 Bruxelles/Brussel, BCE/KBO 0402.231.383. PID3789 Septembre 2025

Climate Change, Child Health and Children's Rights: From Inequality to Inequity

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Keywords
Climate change; climate crisis; social gradients; child health ; climate policy ; pollution ; climate-related diseases; children's rights; inequality; inequity.

Abstract
Climate change is now recognized as the most significant global threat to child health and a major driver of inequity. The UNICEF Children's Climate Risk Index estimates that around one billion children are currently exposed to extremely high levels of climate and environmental risk, including heatwaves, air pollution, flooding, water scarcity, and vector-borne diseases. Children are biologically, developmentally, and socially more vulnerable than adults, and they will live longer into a warming world, accumulating a greater lifetime burden of exposure. At the same time, the countries where children are most at risk contribute only a small fraction of global greenhouse gas emissions, while high-emitting countries experience comparatively lower vulnerability. This mismatch between responsibility and impact exemplifies climate-related inequity and intergenerational injustice.

The 2025 Lancet Countdown confirms that children are increasingly exposed to extreme heat, air pollution, food insecurity, and climate-sensitive infectious diseases, with impacts that disproportionately affect the most vulnerable populations. These are not merely inequalities but structural inequities—avoidable and unjust differences arising from policy choices, governance gaps, and insufficient protection of children's rights. This narrative review synthesizes evidence on: [1] the dynamics of the climate crisis and its intersection with environmental pollution; [2] health effects across the paediatric life course; [3] mechanisms underlying children's unique vulnerability; and [4] the ways in which climate change undermines the rights set out in the UN Convention on the Rights of the Child, transforming inequalities into structural inequities. Finally, it outlines implications for paediatric practice, health systems, and climate governance, arguing that climate action must be explicitly child-centred and equity-oriented.

Introduction

Recent years were the warmest ever recorded, with global mean temperature approaching or exceeding 1.5 °C above pre-industrial levels. The 2024 report of the Lancet Countdown reported that in 2023, populations around the world experienced the highest levels of heat exposure ever recorded (1). Across all regions, the number of days with significant heat stress reached unprecedented levels, with elderly and children among the most affected and least protected groups. The 2025 report of the Lancet Countdown confirms that children are increasingly exposed to extreme heat, air pollution, food insecurity, and climate-sensitive infectious diseases, with impacts that disproportionately affect the most vulnerable populations (2). These are not merely inequalities but structural inequities, avoidable and unjust differences arising from policy choices, governance gaps, and insufficient protection of children's rights.

Europe is warming at roughly twice the global average, and extreme events - heatwaves, droughts, wildfires, storms, and floods - are increasing in frequency, intensity and duration. These changes, documented by the World Meteorological Organization, the Intergovernmental Panel on Climate Change (IPCC) and other agencies, demonstrate that anthropogenic climate change has entered a dangerous acceleration phase that affects ecosystems, economies and population health worldwide (3, 4).

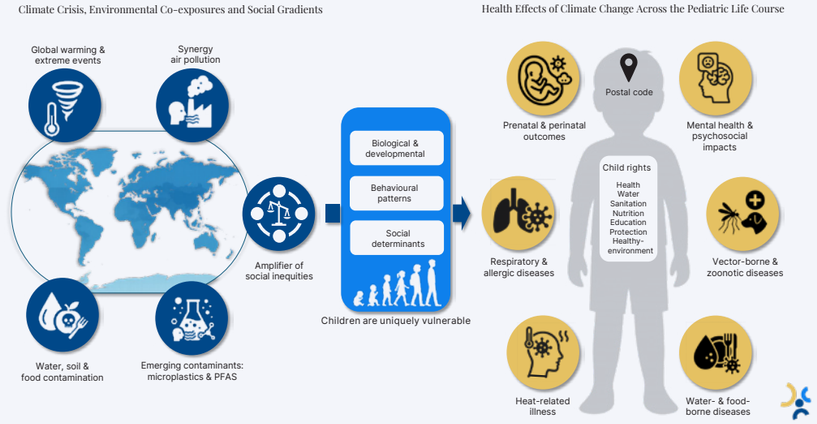
Among all demographic groups, children are disproportionately affected. Their developmental immaturity, higher exposure per body weight, physiological susceptibility and dependence on adults for protection lead to greater vulnerability (5-8). Moreover, children have the longest expected lifetime, so climate-related insults occurring during pregnancy, infancy and childhood can have irreversible and lifelong consequences.

Key findings from the 2025 Lancet Countdown Report on Health and Climate Change indicate that 12 out of 20 climate-related health indicators have reached an alarming level. Heat-related deaths have increased by 23% since the 1990s, reaching 546000 annually, and infants and the elderly being particularly vulnerable.

Droughts exacerbated food insecurity for 124 million people in 2023. Economic impacts reached $1.09 trillion in lost productivity due to heat exposure. Governments allocated $956 billion to fossil fuel subsidies, more than three times the climate finance pledged. Conversely, climate action yielded benefits, preventing 100000 premature deaths annually from cleaner air and creating 16 million jobs in renewable energy by 2022. The report underscores the need for urgent, health-centric climate initiatives.

UNICEF has framed the climate crisis as *a child-rights crisis* (9). The Children's Climate Risk Index (CCRI) combines indicators of hazard exposure (heat, cyclones, riverine and coastal flooding, water scarcity, vector-borne disease risk, air pollution) with indicators of child vulnerability (poverty, access to water and sanitation, health care, nutrition, education and social protection). The index shows that nearly half of the world's children live in "extremely high-risk" countries, most of which have contributed minimally to global emissions. This transforms climate change from a generic environmental problem into a central issue of children's rights, inequality and inequity with a life-long effect.

FIGURE 1: Climate Change, Child Health and Children's Rights: From Inequality to Inequity.



Climate Crisis, Environmental Co-exposures and Social Gradients

Dynamics of global warming and extreme events

Current warming is driven primarily by greenhouse gas emissions from fossil-fuel combustion, intensive agriculture, industrial processes and deforestation (3, 4). The resulting climate instability manifests in more frequent heatwaves, prolonged droughts, heavy precipitation and floods, rising sea level and increased wildfire activity. These phenomena occur in combination with urban heat island effects and land-use changes, further increasing local exposure, particularly in densely populated low-income areas (10, 11).

Synergy with air pollution

Climate change and air pollution are tightly interlinked. High temperatures accelerate photochemical reactions that generate secondary pollutants such as ozone and peroxyacyl nitrates. Periods of heat and atmospheric stagnation trap particulate matter and nitrogen oxides near the ground, increasing population exposure (12, 13). Pollutants can bind to aeroallergens, potentiate inflammatory responses and lengthen pollen seasons, thereby worsening asthma and allergic disease in children (14, 15).

Water, soil and food contamination

Extreme rainfall and flooding can mobilize heavy metals, pesticides, per- and polyfluoroalkyl substances (PFAS), hydrocarbons and microbial pathogens from industrial and agricultural sites into drinking-water systems; droughts concentrate contaminants in shrinking water sources (16, 17). Soil accumulation of pesticides, persistent organic pollutants and microplastics further contaminates the food chain. Climate-related stress on agriculture—heat, drought and altered humidity—reduces yields and increases mycotoxin formation and pesticide use, undermining both food quantity and quality (18).

Emerging contaminants: microplastics and PFAS

Micro- and nanoplastics are now ubiquitous in air, water and soil. Experimental and early epidemiological data suggest they can cross biological barriers, alter gut microbiota and carry endocrine-disrupting or toxic substances, with potential effects on immune and metabolic development (19). PFAS, highly persistent "forever chemicals," have been associated with immune suppression, endocrine disruption, dyslipidaemia and adverse pregnancy outcomes. Climatic events that disturb soils and water systems may enhance the dispersion and human uptake of these contaminants.

Climate as an amplifier of social inequities

Climate-related hazards do not act on a level social playing field. Children in poverty, informal housing, crowded urban heat islands, polluted industrial corridors or climate-sensitive rural livelihoods face overlapping exposures to heat, pollution, unsafe water, malnutrition and inadequate health care (5, 20). Migrants, displaced families, children with disability and those in conflict-affected or poorly governed contexts are particularly at risk. The American Academy of Pediatrics and other professional bodies emphasize that climate change magnifies existing inequities and constitutes a form of intergenerational injustice.

Health Effects of Climate Change Across the Paediatric Life Course

Prenatal and perinatal outcomes

Maternal exposure to ambient and household air pollution is associated with low birthweight, intrauterine growth restriction, preterm birth, impaired lung development, and neurodevelopmental disorders including ADHD and autism spectrum disorder (8). Indoor biomass combustion and second-hand smoke substantially increase the risk of pneumonia and respiratory mortality in children under five. Heat stress during pregnancy is linked to preterm birth, stillbirth, and congenital anomalies, mediated by placental inflammation, oxidative stress, and epigenetic changes.

Respiratory and allergic disease

Children's higher ventilation rates and narrower airways increase susceptibility to pollutants. Exposure to particulate matter ($PM_{2.5}$), ozone, and nitrogen oxides during gestation and early childhood elevates risks of asthma onset, wheezing, reduced lung function, and respiratory infections (11-13). Climate-driven increases in wildfire smoke, ozone episodes, and pollen loads contribute to acute asthma exacerbations. Elevated CO_2 enhances pollen production, and pollutant-coated pollen grains increase allergenicity, leading to severe allergic rhinitis, asthma, and atopic dermatitis (14).

Heat-related illness

Children are physiologically vulnerable to heat stress due to immature thermoregulation. Heatwaves are associated with dehydration, electrolyte imbalance, heat exhaustion, heat stroke, renal stress, and increased hospital admissions. Heat exposure also impairs sleep and cognitive performance and worsens behavioural and attention problems.

Water- and food-borne disease

Floods and heavy rainfall contaminate water supplies, increasing rates of gastrointestinal illness, skin and eye infections, cholera, and leptospirosis (16). Drought and high temperatures reduce hygiene practices, facilitating transmission. Food insecurity and nutritional stress contribute to undernutrition, which interacts with infection to drive morbidity and mortality. Malnutrition during the first 1000 days has lifelong impacts on growth, cognition, and metabolic disease risk.

Vector-borne and zoonotic diseases

Shifts in vector distribution and seasonality have expanded transmission of dengue, chikungunya, West Nile virus, and Lyme disease into new regions (21). Children are at increased risk of infection and severe disease due to greater outdoor exposure and thinner skin.

Mental health and psychosocial impacts

Climate-related disasters, displacement, and community disruption are associated with post-traumatic stress disorder, anxiety, depression, sleep disturbance, and behavioural problems. Even without direct disaster exposure, children may experience eco-anxiety, grief, and feelings of helplessness, particularly those with pre-existing vulnerabilities (22).

Why Children Are Uniquely Vulnerable

Biological and developmental factors

Children inhale more air, drink more water and consume more food relative to their body weight than adults, leading to higher internal doses of pollutants and toxicants. Immature detoxification and excretory systems slow elimination, while rapidly developing organs—especially the brain, lungs and immune system—are more easily disrupted (6, 7).

Critical developmental windows during gestation, infancy and early childhood determine the long-term architecture of the nervous, respiratory, endocrine and immune systems. Exposures during these windows can induce epigenetic modifications, alter organ structure and function, and change disease susceptibility across the lifespan (15).

Behavioural patterns

Children's exploratory behaviour increases exposure: they play close to the ground, engage in hand-to-mouth activities, and spend substantial time outdoors, often in polluted or overheated environments. Adolescents may engage in strenuous physical activity outdoors, increasing inhaled doses of pollutants during exercise (5, 14).

Social determinants and structural vulnerability

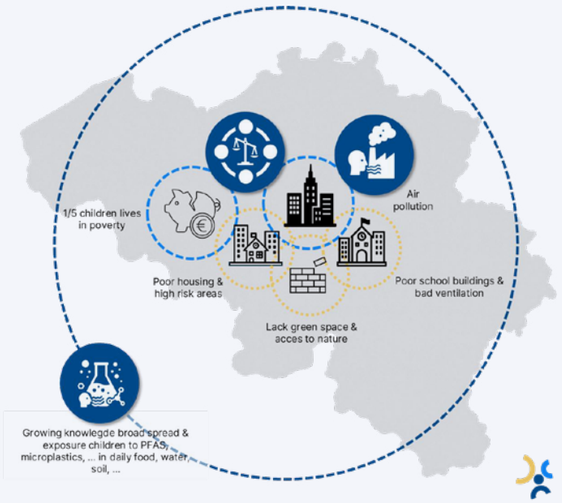
Children are completely dependent on adults and social systems for protection. Household income, caregiver education, housing quality, access to health care, urban planning, and the presence or absence of green spaces all shape exposure and resilience. Climate change interacts with these determinants, concentrating risks in those who are already disadvantaged.

In many low- and middle-income countries, health, WASH (water, sanitation and hygiene), food and social-protection systems are fragile. Floods, droughts and storms damage infrastructure, interrupt services and deplete already limited resources (16, 17, 23). Educational systems are also affected, with school closures, heat-related learning impairment and reduced attendance during climate shocks, which in turn perpetuate social inequities.

From Inequality to Inequity: A Child-Rights Perspective

Climate change is one of the biggest threats to children worldwide, and its impact particularly affects the most vulnerable families (9, 24). Children are not small adults: their bodies and minds are still developing, which makes them extra sensitive to air pollution, extreme heat and lack of water. The consequences are multifaceted and serious. Infectious diseases spread faster, crop failures lead to malnutrition and rising food prices, and extreme weather events cause trauma and mental health problems. In addition, millions of children lose access to education every year due to climate-related disasters, putting further pressure on their prospects.

FIGURE 2: Climate inequity and Belgium.



Unequal geographies of risk

UNICEF's CCRI shows that 850 million children are exposed to four or more hazards simultaneously, and that 33 countries—mainly in Sub-Saharan Africa, South Asia and small island states—are classified as "extremely high risk (25).These same countries collectively account for only a small fraction of global emissions, whereas the ten highest-emitting countries produce most of the total. This "exported risk" encapsulates the transformation of geographic inequality into moral and political inequity.

Child rights under the Convention on the Rights of the Child

The UN Convention on the Rights of the Child (CRC) codifies children's rights to life, survival and development; the highest attainable standard of health; adequate nutrition; safe water and sanitation; education; protection from harm; and a standard of living adequate for development (26). Climate change threatens each of these domains:

- Right to health: increased burden of respiratory disease, heat-related illness, infectious diseases, injuries and mental-health disorders (14, 21, 22, 27, 28).
- Right to water and sanitation: droughts and floods compromise safe water and sanitation infrastructure, increasing diarrheal disease and other infections (29, 30).
- Right to nutrition: climate-related food insecurity and micronutrient loss threaten growth and development (18).
- Right to education: damage to schools, displacement and heat-related learning difficulties disrupt education.
- Right to protection: climate-related migration and instability increase risks of exploitation, violence and trafficking (2).
- Right to a healthy environment: although not explicitly named in the CRC, a safe, clean and sustainable environment is increasingly recognized as a prerequisite for all other rights (25).

When predictable, preventable harms systematically fall on children—especially those in low-emission, low-resource settings—climate change becomes a structural violation of child rights and an archetype of intergenerational inequity (24, 31).

Climate crisis and child inequity

Climate change is one of the biggest threats to children worldwide, and its impact particularly affects the most vulnerable families. Children are not small adults: their bodies and minds are still developing, which makes them extra sensitive to air pollution, extreme heat and lack of water. The consequences are multifaceted and serious. Infectious diseases spread faster, crop failures lead to malnutrition and rising food prices, and extreme weather events cause trauma and mental health problems. In addition, millions of children lose access to education every year due to climate-related disasters, putting further pressure on their prospects.

What makes this crisis particularly poignant is the inequality that goes with it. UNICEF points out that one billion children worldwide live in an extremely high risk situation (25). They are often located in countries with weak health care, limited access to clean water and poor infrastructure. The irony is that it is precisely these countries that have contributed the least to greenhouse gas emissions. The distribution of international climate finance also reflects this inequality: only a fraction, about 2.4 percent, is focused on child-specific projects. This makes it clear that the interests of children are structurally neglected.

Concrete examples illustrate this reality. In Zambia, drought has plunged millions of families into food insecurity, leaving children malnourished and jeopardizing their development. In Bangladesh, severe air pollution causes respiratory problems and increases the mortality rate from lung diseases in children. In Cambodia, floods have closed schools and increased the risk of water-related diseases. These situations show that climate change is not only an ecological crisis, but also a children's rights crisis.

Focussing on Western Europe, and Belgium in particular, climate inequity is also a growing problem here (32). Extreme heat waves are becoming more frequent and intense and air pollution remains a persistent problem: in cities such as Brussels and Antwerp, children breathe air rich in particulate matter every day, impacting their health.

Implications for Paediatric Practice and Health Systems

Paediatricians, especially in primary care, are key actors in recognizing, documenting and mitigating climate-related risks (19, 33).

- Environmental history-taking should be integrated into routine visits, including questions on indoor air quality, smoking, heating and cooking sources, water supply, housing quality, heat exposure, proximity to major roads or industry, and use of plastics and chemicals.
- Climate-sensitive counselling can provide families with practical strategies for exposure reduction and climate resilience: ventilation and smoke-free homes, hydration and cooling during heatwaves, safe outdoor activity based on air-quality indices, plant-rich diets, and preparation for extreme weather events (18, 21, 27).
- Communication should emphasise co-benefits: cleaner air reduces asthma attacks; active transport improves cardiovascular health; sustainable diets support growth; green spaces enhance mental health and provide heat protection (2, 27, 34).
- Professional leadership includes advocating for clean-air policies, green urban planning, safe school environments, decarbonization of the health sector and inclusion of climate and planetary health in medical curricula.

Health systems themselves contribute significantly to greenhouse-gas emissions (35). Decarbonizing health care—through energy efficiency, low-carbon procurement, sustainable waste management and telehealth where appropriate—offers an additional avenue to protect child health while aligning practice with advocacy.

Practical and quickly applicable tips for paediatricians and teams

As a paediatrician, major climate actions may be beyond your own control. Nevertheless, you can still play a significant role in climate change mitigation and in raising awareness locally and in daily work.

The examples below focus on three themes: (A) clinical care and medication use, (B) daily operations, waste & waste management, and (C) team/organization & education. The advice is practical, evidence-based where possible and immediately implementable.

A: Clinical care & drug consumption

- Medication stewardship and rational prescribing
  Conduct short periodic audits of prescribing patterns (antibiotics, inhalers, medications). Reduce overtreatment where clinically safe (antibiotic stewardship). This reduces resistance and the ecological footprint of production and waste.
- Think about the choice of inhaler for asthma
  Where clinically justified and following shared patient/family decision-making, propellant-free inhalers (DPIs) or lower-GWP options can greatly reduce the carbon footprint of inhalation treatments. Use the existing decision-making tools (NICE/NHS guides) and make sure that patient safety and inhalation skills remain a priority. Return used inhalers for proper disposal (no household waste) (36).
- Avoid wasting medicines
  Give only the dose/amount that is needed; promote the reuse of unopened stock within guidelines; implement secure return and destruction routes via the pharmacy.

- Vaccination and prevention
  Optimize vaccination programs and preventive care: this prevents diseases, hospital admissions and thus indirect CO_2 emissions from care pathways.

B: Waste, consumption & pollution (quickly applicable)

- Reduce single-use where safe
  - Evaluate clinical procedures where reusable instruments (autoclavable) can be applied safely and cost-effectively. Start with a small pilot project (e.g. in outpatient clinic).
  - Network and look beyond your own hospital walls. Good (inter)national examples exist, such as in the Netherlands, where parents no longer have to wear surgical suits and hats when briefly accompanying their child in the operating theatre. In ordinary clothing, the contact is more natural and more comfortable for children; it is also better for the environment because protective surgical clothing is made of plastic and is single-use (37).
- Dispose of medicine and chemical waste correctly
  Ensure there are clear protocols and visible instructions for safe take-back of remaining medicines and used inhalers; train reception and waste management staff.
- Smart waste separation system
  Place clearly separated waste streams (infectious, pharmaceutical, recycling, residue) with simple instructional labels at workstations. Monitor monthly reduction.
- Reduce energy and water use
  Small measures: LED lighting, optimizing thermostat settings, timers on appliances, water-saving taps in waiting rooms. These actions are cheap and cost-effective with quick return on investment.

C: Team, education and policy

- Create a 'green team'
  Appoint a small team (2–4 people) that identifies monthly quick wins, starts small and makes successes measurable.
- Education of patients and families
  Integrate short messages into consultations: why return old inhalers, safe medication use and simple energy/resource-saving tips for use at home.
- Telemedicine where appropriate
  Use teleconsultations for routine check-ups when physical assessment is not necessary — reduces travel and therefore emissions. Make sure vulnerable families are not excluded.
- Reporting monitoring
  Measure and report simple indicators: number of unnecessary prescriptions, inhalers returned, and waste reduction. Short, data-driven cycles support ongoing improvement.
- Advocacy and collaboration
  Collaborate with local pharmacies, hospital sustainability/landscaping programs, and public health to support systemic improvements (e.g., green logistics, sustainable procurement).

Paediatricians are in a crucial position: they treat the direct and acute consequences in individual children and can achieve local CO_2 reductions and health gains through practice, patient education and collaboration. Through rational use of medicines, careful waste management, conscious choices in inhalation therapy and organisational improvements, paediatric care can both reduce the climate impact and improve the quality of care. The rationale is clear and the actions concrete and achievable — start small, measure progress and scale up similar successes. Important international reviews and reports (WHO, IPCC, UNICEF, Lancet Countdown, NHS/NICE practice guidelines) support both the urgency and practical interventions described above.

Conclusions

Climate change is both a paediatric health emergency and a *child-rights and equity crisis*. Children are more exposed, more vulnerable and affected for a longer portion of their lives than adults. The heaviest burdens fall on those who have contributed least to the problem—children in low-emission, structurally disadvantaged settings—transforming climatic inequalities into profound, preventable inequities.

Finally, this review outlines implications for paediatric practice, health systems, and climate governance, arguing that climate action must be explicitly child-centred and equity-oriented.

Indeed, differences in the impacts of climate change on children's health are not simply inequalities due to chance or geography; they are largely inequities—avoidable, preventable, and the result of policy decisions, economic models, and institutional arrangements that distribute risks and protections unequally.

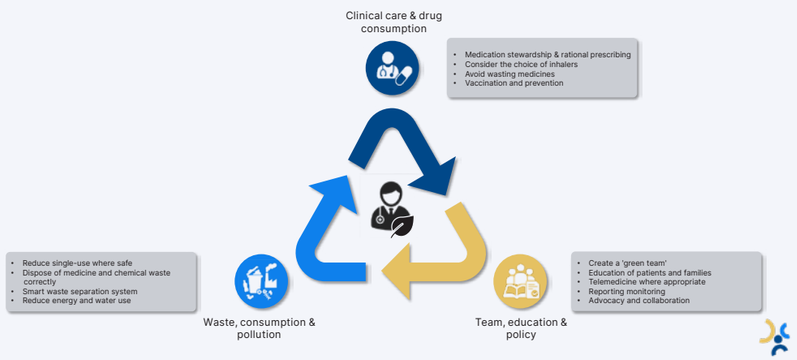
The child-rights-based approach allows us to move from an epidemiological to a normative perspective: if a risk is created or not mitigated by human choices, it becomes a violation of children's rights.

Therefore, children are not only more vulnerable; they are more exposed and less protected due to systems that fail to guarantee their fundamental rights (health, a clean environment, social protection, education, participation).

Climate change is transforming pre-existing inequalities into structured forms of injustice.

This is not only due to its effects on health, but also to a systemic failure to guarantee the rights and protections that all documents and reports from major international agencies recognize as children's due.

FIGURE 3: What can you do in your daily practice?



A child-centred, equity-driven approach to climate policy, health-system planning and paediatric practice is therefore essential. Integrating child-rights impact assessments into climate governance, prioritizing child health in adaptation finance and empowering paediatricians as advocates are critical steps. Protecting children from the harms of climate change is not only an environmental necessity; it is a legal and ethical obligation under the CRC and a prerequisite for sustainable development and intergenerational justice.

Acknowledgement

The authors thank Jeroen Verlinden (Growingtomorrowssolutions) for the inspirational infographics and layout support provided for this publication.

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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.

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PM-BE-BEX-ADVR-240003 - Maart 2024 | VU: GlaxoSmithKline Pharmaceuticals s.a./n.v. Avenue Fleming 20 - 1300 Waver Belgium

Protecting Children's Health through Hospital Decarbonisation

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Keywords
Climate change; decarbonisation; paediatric; net zero; NZHI; air pollution.

Introduction

Despite the hope raised by the 2015 Paris Agreement, the world is now dangerously close to breaching its 1.5 °C warming limit, with record-breaking temperatures in 2023 and 2024 already fuelling deadly climatic extremes (1). Children are particularly vulnerable due to physiological, social, and demographic factors. Their higher respiratory rates, immature thermoregulation, and developing organ systems make them more sensitive to environmental hazards, while their dependence on caregivers reduces their adaptive capacity. They also face the longest lifetime exposure to climate risks. Projections suggest that a child born in 2020 will experience nearly three times more climate-related extreme events than their grandparents (1). For paediatricians, climate change is not an abstract future concern but a present and escalating health crisis.

Health impacts of climate change on children

Systematic reviews show that pregnancy and early life are among the most sensitive windows of vulnerability besides old age. Heat is a major prenatal risk factor. A meta-analysis by Reichelt et al. reports that heatwaves increase preterm birth by ~16% and stillbirth by ~46%, with each additional degree Fahrenheit (~0.56 °C) raising risks by ~5%. Low birthweight rises by ~9% during hotter periods, with babies on average 26 grammes lighter (2). Another pooled analysis by Weeda et al. found that exposure to temperature extremes was associated with an average 60% increase in preterm birth risk, although heterogeneity was high and some studies reported null findings (3).

The heightened risks do not stop at birth. From infancy onward, children are already disproportionately affected by climate-related disease. Heatwaves increase paediatric emergency visits, particularly among infants who are physiologically less able to regulate body temperature (2,3). Heat also raises all-cause mortality, with under-fives among the most heat-sensitive age groups (3). Asthma, the most common chronic paediatric disease, is consistently aggravated by exposure to air pollution, pollen, and the intensified heat that accumulates in densely built urban areas (the so-called 'urban heat islands') (3). Each 10 µg/m³ increase in fine particulate matter ≤2.5 micrometres in diameter ($PM_{2.5}$) from traffic/urban sources is associated with a 2–3% rise in paediatric asthma admissions (2). During bush fires, an increase in PM 2,5 of at least 30% is often measured. Climate change also prolongs pollen seasons and increases allergenicity through higher CO_2 concentrations, drought, and heat, compounding the burden of allergic rhinitis and asthma (2).

Infectious diseases are shifting under warmer and wetter conditions. Europe has documented rising incidence of vector-borne infections such as West Nile virus, while globally dengue, chikungunya, and Zika are spreading to new regions (2). Extreme events such as floods and droughts increase waterborne disease and diarrheal burden, especially where sanitation systems are weak (3). Beyond physical illness, chronic exposure to polluted air has been linked to impaired neurodevelopment, reduced academic performance, and higher risk of behavioural disorders, including ADHD (3).

These risks are not equally distributed. Children in lower socioeconomic settings are disproportionately exposed to polluted environments and have fewer resources to adapt, reinforcing existing inequities (4). The crisis is also profoundly intergenerational: today's children are projected to face two to three times more climate-related extremes than their grandparents (5).

Air pollution and greenhouse gases: two problems, one solution

Air pollution is an essential pathway linking climate change and child health. Across the EU, air pollution contributes to 239.000 premature deaths annually. In Belgium, poor air quality is responsible for around 9.000 premature deaths each year (6). Because fossil fuel combustion is the dominant source of both greenhouse gases and air pollutants, strategies to achieve net zero emissions strongly overlap with strategies to reduce air pollution. Transitioning to a net zero society would eliminate a substantial share of outdoor air pollution, yielding immediate health benefits (7). For children, this means fewer asthma attacks, improved lung development, and healthier neurocognitive outcomes. The

concept of a "double dividend" is therefore powerful: every step taken to mitigate climate change also improves child health today.

The footprint of healthcare itself

Healthcare, while protecting health, also contributes to the crisis. Belgium's health sector emitted 9.901 kilotons CO_2 equivalent (CO_2e) in 2022, around 5% of national consumption-based emissions. Hospitals are the most emission-intensive providers, responsible for 55% of health sector emissions. The hospital's footprint is overwhelmingly Scope 3-dominant: 11% Scope 1, 3% Scope 2, and 86% Scope 3 (figure 1). The scope 1, 2, 3 approach relates to the Green House Gas Protocol standards: scope 1 consists of on-site combustion of greenhouse gases (such as anaesthetic gases, natural gas, …), scope 2 of the electricity produced off-site but used in the hospital, and scope 3 includes all the carbon generated in the supply chain including production of medical goods, pharmaceuticals, food, transport, and waste treatment. Within Scope 3, purchased goods account for 63%, driven by pharmaceuticals (31%), medical equipment (14%), and food and catering (8%). For paediatrics, certain categories are directly relevant: metered-dose inhalers contribute approximately 44 kilotons CO_2e nationally (0.4% of total), a small share overall but meaningful within respiratory care decisions (8).

Hospital-level data illustrate this picture. The Flemish hospital group *Maria Middelares* VZW with 707 accredited beds measured 35.288,3 tons CO_2e in 2024 across all scopes. More than 90% of emissions were Scope 3, with medical goods and pharmaceuticals together responsible for over half. Transport contributed 14%, food 10%, energy 9% (with green electricity already in place), construction 4%, waste 2%, and water less than 1% (own data (9)).

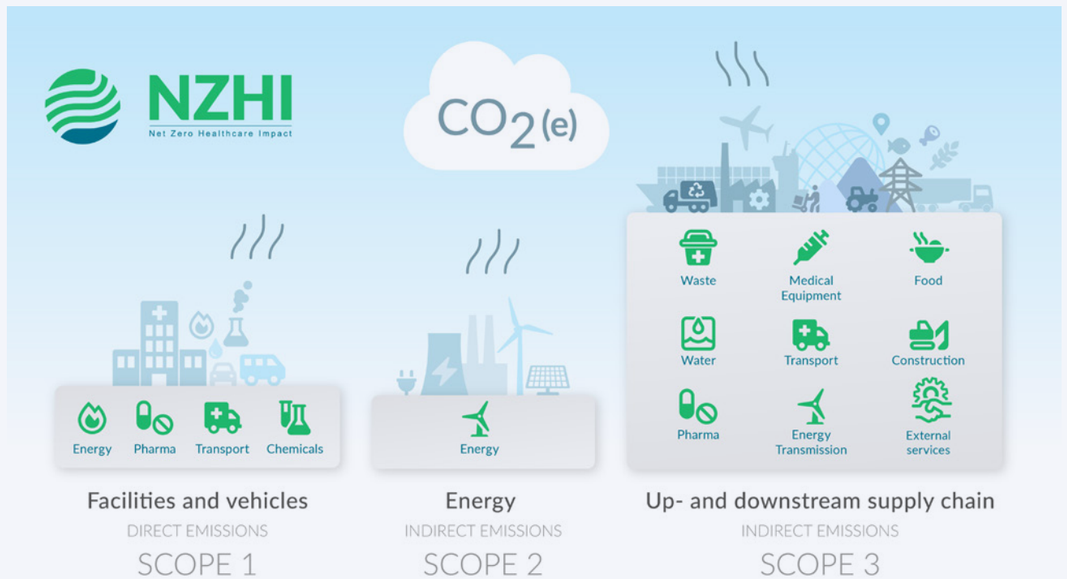
When nothing changes, the Belgian health-sector emissions will rise by over 60% by 2050, to around 16.000 kilotons CO_2e. A modelled package of 16 interventions business-as-usual, reducing emissions to 4.300 kilotons CO_2e in 2050, about 44% of today's level. Supplier decarbonisation standards are the single largest lever, responsible for ~43% of modelled reductions. Other high-yield actions include optimising and substituting pharmaceuticals (e.g. switching to clinically appropriate low-carbon inhalers), extending equipment lifetimes, shifting from single-use to multi-use instruments and garments, and reducing food waste. Futureproofing of existing hospital buildings and attention for sustainability in newly constructed hospitals is essential. This includes electrification, insulation, renewable power production and purchasing (10).

What this means for Belgian hospitals and paediatricians

Belgium's National Environmental Health Action Plan (NEHAP) explicitly identifies climate change as a key determinant of health (8). Decarbonisation aligns directly with paediatric health protection. Reducing high-GWP (global warming potential) inhalational anaesthetics and optimising inhaler choices cuts emissions without compromising care. Cleaner energy and sustainable procurement reduce the co-burden of air pollution, while resilient food systems support nutrition. NEHAP calls for monitoring environmental exposures, reducing vulnerabilities, and integrating climate-health risks into prevention strategies (10).

Hospitals hold powerful levers: formulary stewardship for high-impact medicines, sustainable anaesthetic gas choice and capture, prioritisation of reusable over disposable items where safe, sustainable supplier criteria, plant-based menus, mobility policies promoting active travel and telehealth, and full energy decarbonisation. Individual clinicians, especially paediatricians, can lead by example, avoiding unnecessary pressured metered-dose inhalers, supporting rational prescribing, and advocating for sustainable practice within their institutions.

FIGURE 1: Healthcare sector emissions by scope according to the Green House Gas protocol and the NZHI framework (9).



Net Zero Healthcare Impact (NZHI) is a Belgian start-up founded by emergency physician dr. De Tavernier, dedicated to driving the healthcare sector towards net zero carbon emissions and sustainability. The company has developed an evidence-based methodology to measure hospital emissions across all scopes, including the often-overlooked supply chain (Figure 1). By quantifying the footprint 10 core domains (pharmaceuticals, medical goods, waste, chemicals, transport, food, energy, mobility, water, construction, and external services), NZHI provides hospitals with precise data to identify high-impact areas and reduction opportunities. This approach allows hospitals to integrate climate performance into procurement, clinical decisions, and strategic planning, while ensuring that patient care remains uncompromised. NZHI also supports hospitals in meeting emerging European sustainability reporting requirements, providing benchmarks and pathways for compliance. By combining data analysis with practical solutions, NZHI empowers hospitals and clinicians to take ownership of their environmental impact, ensuring that the protection of human health is fully aligned with the protection of planetary health. These sustainability efforts are in practice often significant cost savings by reducing the use of single use goods, reducing energy costs and improving overall efficiency and performance of a hospital by stimulating a lean and resilient approach within the 10 domains. The NHS recently identified sustainability as the number one way to save healthcare related costs today (11).

Conclusion

Climate change undermines child health through multiple pathways. At the same time, hospitals remain a significant source of emissions, yet many opportunities to reduce their footprint are achievable and compatible with high-quality care. For paediatricians, this reality brings both responsibility and opportunity. As trusted advocates for children, they are uniquely positioned to make the health impacts of climate change visible to families, institutions, and policymakers. Recognising climate action as child health protection reframes sustainability as central to paediatrics. By embedding sustainable choices into daily medical practice, paediatricians can help protect children from today's illnesses and tomorrow's risks. By sharing their practices and advocating for sustainability within their hospitals, they can lead by example and encourage colleagues across disciplines. In doing so, paediatricians help safeguard future generations.

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World on Fire

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Keywords
Climate change ; heat ; child ; dehydration ; climate policy ; pollution

Abstract
Climate change is accelerating, with rising global temperatures leading to more frequent and severe heatwaves. This manuscript aims to outline current knowledge on the impact of heat, both direct and indirect, on child health, from the prenatal period to adolescence. Children represent a particularly vulnerable group due to their physiology, developmental stage, and dependence on adults.
Direct health effects include dehydration, heat exhaustion and life-threatening heatstroke, while indirect consequences range from increased asthma exacerbations and infectious diseases to reduced learning capacity and heightened exposure to air pollution. Pregnant women exposed to extreme heat are at higher risk of adverse outcomes such as preterm birth, low birth weight, and congenital anomalies. In addition to physical illnesses, climate change can have long-term implications for neurodevelopment and the development of chronic diseases.
Paediatricians play a key role in prevention, adaptation and advocacy, both at the clinical and policy levels. Establishing heat emergency protocols, integrating environmental health education in paediatric training, and supporting mitigation strategies are essential to safeguard future generations. Addressing the paediatric dimension of climate change is not only our medical duty but also a societal imperative. In this review we aim to oversee the consequences of heat on the paediatric population in Belgium.

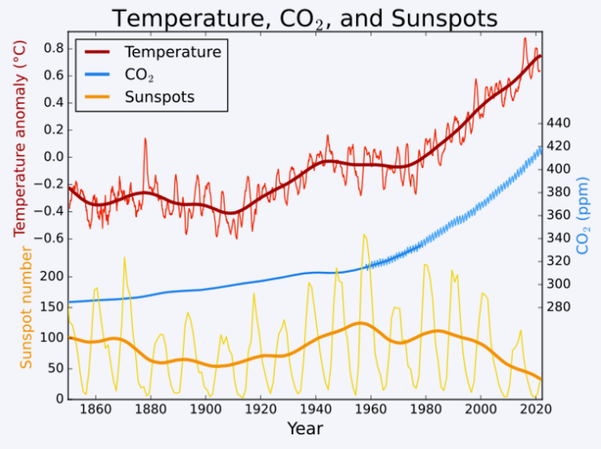
Introduction

Climate change represents a significant global health challenge in the 21st century. Rising temperatures, more frequent extreme weather events, and disruptions to ecological systems increasingly threaten human well-being. Within this context, children are an often overlooked but particularly vulnerable group (1). Due to their physiology, developmental stage and dependence on caregivers, children face disproportionate risks from heat-related illnesses.

The paediatric dimension of heat-related diseases extends beyond acute effects such as dehydration and heatstroke. Prenatal exposure to heatwaves has been linked to adverse pregnancy outcomes, while postnatal impacts range from exacerbation of respiratory diseases to long-term neurodevelopmental harm. In addition, climate change alters patterns of air pollution, allergen exposure, and vector-borne diseases, all of which have significant implications for child health.

This overview integrates epidemiology, physiology, and clinical management to support clinicians in understanding and addressing the impact of extreme heat on child health.

FIGURE 1: Global temperature, atmospheric CO_2, and sunspot activity since 1850. (*source: Leland McInnes at the English-language Wikipedia, CC BY-SA 3.0 <http://creativecommons.org/licenses/by-sa/3.0/>, via Wikimedia Commons).*



Weather, climate, and global warming

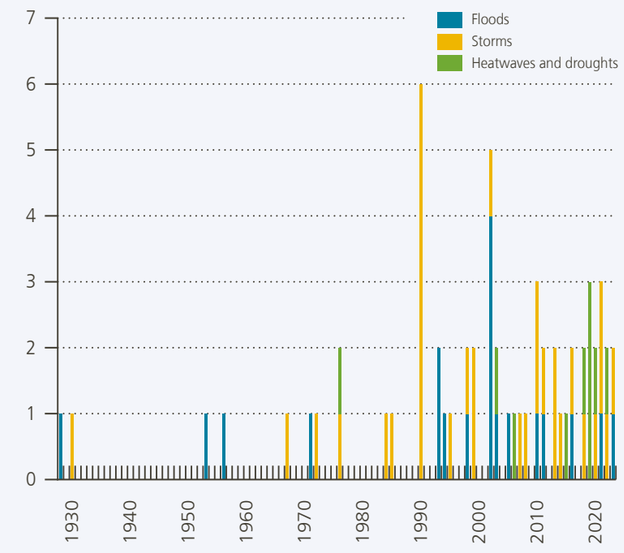
Weather describes the current conditions, such as temperature, precipitation or wind, in a specific location at a given moment. In contrast, climate refers to the average of weather conditions of a region, typically calculated over a period of 30 years or more. Belgium has a temperate maritime climate characterized by mild winters, cool humid summers, and relatively frequent rainfall. *Climate change* refers to long-term shifts in temperature and weather patterns. This distinguishes it from short-term weather fluctuations such as the El Niño-Southern Oscillation cycle which occurs every 2 to 7 years (2). Climate change, however, persists over decades.

Earth receives energy from the sun; this energy follows an 11-year solar cycle. During this cycle, solar flares and storms from the sun's surface can change, affecting the amount of energy reaching our planet. This solar variability has played a role in past climate changes. For example, a decrease in solar activity combined with increased volcanic eruptions contributed to the onset of the 16th century Little Ice Age (3). Figure 1 shows the increase in the average global temperature with a marked acceleration since the late 20th century, where the amount of sun-energy has either remained constant or decreased over the same period. The sun's impact is only one piece of the puzzle. The late 20th century was the start of the industrial revolution. Since that time, nitric oxide or NO (used in fertilizers) increased 18%, CO_2 from fossil fuel combustion 39% and methane 148%. These greenhouse gases (GHG) trap heat in the atmosphere leading to global warming. GHG emissions changed the planet by increasing global temperature, altering rainfall, causing sea levels to rise, acidifying oceans, increasing the frequency, strength, and duration of extreme weather events (1). Importantly, these effects are unevenly distributed: while some regions face catastrophic flooding or drought, others experience extended heatwaves or shifts in disease vectors. Also, some regions are more vulnerable to these events than others.

In Flanders an upward and accelerating trend is visible since the early 20th century (Figure 2). Where the mean average temperature worldwide has increased by 1.2-1.5°C compared to the pre-industrial period, the mean average temperature in Belgium has already increased by 2.9°C. This leads to more natural disasters, not only heatwaves and droughts but also storms and floods (Figure 3). Climate models predict that by the end of this century, children born today could experience summer temperatures several degrees higher (up to 8.5°C) than those faced by their (grand) parents: as a consequence, the 2020 birth cohort will experience 11 extreme heatwaves, increasing to 18 and 26 when global mean temperature increase reaches 2.5°C and 3.5°C, respectively (4).

FIGURE 2: Observed Annual Average Mean Surface Air Temperature of Vlaams Gewest, Belgium for 1901-2023. *(source: Climate Change Knowledge Portal, CCKP, World Bank. Permission obtained form AskClimate).*

FIGURE 3: Frequency of recorded natural disasters in Belgium (1928 to 2023, by type) *(source: The physical effects of climate change on food inflation, NBB Economic Review, 2024, Hoofdstuk 10 — PDF: https://www.nbb.be/doc/ts/publications/economicreview/2024/ecorevi2024_h10.pdf nbb.be, EM-DAT, RMI, NBB.)*



Heat and its effects on health

Heat and mortality

Temperature and mortality have a U-shaped relationship: deaths increase both at very low and very high temperatures, with a minimal mortality threshold (MMT) (Figure 4). This MMT is location-specific: populations in northern climates have a lower MMT (e.g., Vancouver, Canada, 17°C), compared to those in warmer regions (e.g., Austin, Texas, 27°C) (5). Heatwaves represent one of the deadliest manifestations of climate change; they especially increase mortality among the elderly, people with cardio-respiratory conditions, and children < 5 years. In the seventies, Belgium faced a heatwave every 5 years; now heatwaves happen at least yearly (4) (Figure 3). Unlike natural disasters such as floods or hurricanes, their impacts are less visible: the 2003 European heatwave, for example, caused more than 70,000 excess deaths directly related to heat, including nearly 400 children.

Heat and pregnancy

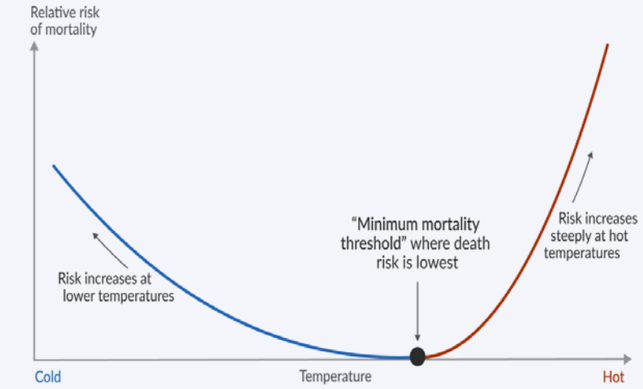
A range of physiological and behavioural adaptations must occur during pregnancy, including an alteration of thermoregulation. During gestation, heat production is increased due to metabolic heat from the developing placenta and foetus. The foetus is entirely dependent on maternal heat dissipation and temperature stability, which needs to be maintained within a narrow margin. Maternal heat dissipation mechanisms in pregnancy include reducing body temperature, cutaneous vasodilation, increased sweat production, increased plasma volume, and heightened thermal heat capacity due to increased body mass (6,7). These changes increase sensitivity to heat stress, especially during prolonged (nightly) exposure. Additionally, maternal overheating may compromise uteroplacental blood flow, reducing oxygen and nutrient delivery to the foetus. All these increase the risk of complications such as pre-eclampsia, gestational diabetes, and placental insufficiency (7).

An increasing number of studies show that heat can lead to adverse pregnancy outcomes, including stillbirth, low birth weight, and preterm birth (6,7). The risk is especially pronounced during the 3rd trimester, when maternal dehydration and heat stress may trigger uterine contractions or placental dysfunction. Research also suggests that exposure to high temperatures during the 1st trimester increases the risk of congenital heart defects and neural tube defects, such as spina bifida or anencephaly (8,9). While the precise mechanisms remain unclear, possible pathways include maternal hyperthermia disrupting protein synthesis, oxidative stress, or impaired folate metabolism.

Heat can also interfere with the pre-conception phase, causing menstrual irregularities and lower fertility rates. Or affect the success of IVF treatments, as heat can impact embryo viability (9).

Health impacts from heat in pregnancy are largely preventable through interventions to facilitate cooling (improved housing or workplaces, fluid availability, and limiting outdoor activity during heat waves) (6,8). In Belgium, implementing sustainable cooling centres in community buildings or schools during heat waves can provide respite for pregnant women, ensuring they are accessible to vulnerable populations. Additionally, increasing urban green spaces and introducing programs to subsidize sustainable air conditioners (featuring high energy efficiency, eco-friendly refrigerants, and smart or renewable-energy-based technologies) for lower-income households would further mitigate heat exposure risks. Public health campaigns tailored to reach expectant mothers could also emphasize the importance of staying hydrated and recognizing early signs of heat stress.

FIGURE 4: The relative risk of mortality (Y-axis) plotted against the mean temperature (X-axis) showing the minimum mortality threshold. *(source: Our World in Data. How many people die from extreme temperatures, and how this could change in the future: Part one. Oxford: Our World in Data. Available from: https://ourworldindata.org/part-one-how-many-people-die-from-extreme-temperatures-and-how-could-this-change-in-the-future. Permission obtained from Hannah Ritchie.)*



Heat and children

Children's bodies are less efficient at coping with thermal stress compared to adults:

- Their higher metabolic rate generates more heat, particularly during physical activity
- Their greater body surface area relative to their weight increases heat absorption from the environment
- Their sweat glands are less developed, reducing the effectiveness of evaporative cooling, the body's primary cooling mechanism
- Children typically have less prior exposure to hot weather and are less physiologically acclimatized to high temperatures than adults. Consequently, their adaptation to extreme heat is slower and less effective.
- Infants and young children are even more prone to dehydration because of their higher total body water content.

What makes them also vulnerable is their dependence on others to protect them from extreme heat, providing shade and water during prolonged exposure: infants, very young children and children who have disabilities are at greater risk because of their limited ability to communicate thirst or symptoms of heat stress (10).

Direct impacts of heat on children

Direct health effects of heatwaves include dehydration, heatstroke, heat exhaustion, electrolyte imbalances, kidney-related diseases, and respiratory and infectious diseases.

1. *Acute dehydration.* Water is a fundamental ingredient for life on earth as we know it. Nevertheless, it is estimated that 1 in 4 people do not have access to clean drinking water. Climate change, severe droughts, population growth, increasing demands, and poor management resulted in severe freshwater shortages in many regions (12, 13).

Dehydration reduces total body water (TBW), affecting both intra- and extracellular fluids. Infants, having higher TBW percentages, lose more body weight compared to older children at the same dehydration level (14). Furthermore, children need 2.5 times more water intake per body weight compared to adults. It is therefore no surprise that dehydration is a major cause of paediatric illness, leading to approximately 750,000 deaths annually, accounting for nearly 16% of global child fatalities. During healthy periods and sickness maintaining fluid balance in these children is influenced by many factors, but also significantly by exposure to a hot environment.

2. *Other effects of (chronic) dehydration*. There are several other effects linked to dehydration. Heat waves as we know, bring an elevated risk of acute dehydration, which, if occurring more frequently, can cause cognitive dysfunction and acute or chronic kidney injuries (13). Moreover, increased evaporation during breathing in a warming climate was recently linked to increased airway inflammation and exacerbations of lung disease (14).

Chronically dehydrated humans on the other hand, are less able to excrete toxins, leading to a higher serum concentration of salts and glucose. Those substances are linked with an increased risk for diabetes and metabolic syndrome, a combination of high blood sugar and cholesterol, hypertension and abdominal obesity. The physiology behind this phenomenon is well known in animals: when they develop dehydration, fructose production from carbohydrates is increased. Fructose stimulates the production of vasopressin, which helps store water in the body, but also stimulates the production of fat. Camels don't store water in their humps; they store fat. When the fat is burned, it produces water. Fat production is the body's reaction to dehydration. While these mechanisms are established in animals, in humans, the fructose–vasopressin pathway is proposed as a likely contributor to obesity risk, though longitudinal data is still required for confirmation. Chronically hypo-hydrated children, who clinically seem well-hydrated but maintain normal water levels primarily through vasopressin stimulation and

FIGURE 5: Heat exhaustion and heat stroke: know the signs. *(Source: Centers for Disease Control and Prevention, National Weather Service. Heat exhaustion vs. heat stroke. The Scientific Parent)*

other water conservation mechanisms, are at increased risk for obesity (13).

3. *Heat exhaustion and heat stroke*. Heat exhaustion and heat stroke are critical heat-related conditions requiring prompt action. Heat exhaustion, a milder yet significant form, manifests with symptoms like fatigue, dizziness, nausea, and muscle cramps. If untreated, it can escalate to heatstroke, a medical emergency marked by core body temperature exceeding 40°C, hot, dry skin, and neurological dysfunctions such as confusion, lethargy, or coma (Figure 5). In this stage, the body can no longer sweat to regulate temperature. This is a life-threatening emergency, quickly leading to rhabdomyolysis, acute kidney failure, electrolyte disturbances, and coagulopathies or severe neurological damage. Prompt recognition and rapid cooling are crucial as clinical outcomes depend on the duration of hyperthermia. Effective heatstroke management starts with removing the patient from the heat source and performing ABCDE stabilization. Aggressive cooling should be initiated immediately, preferably through evaporative methods (spraying and fanning) or cold-water immersion. In children under five, lukewarm immersion is advised to avoid hypothermia, while in older children ice packs can be added to the axillae, groin, and neck. Antipyretics are ineffective, as hyperthermia results from failed thermoregulation rather than infection. Cooling must be stopped once the temperature falls to 38.5 °C. Fluid resuscitation with isotonic, balanced crystalloids supports circulation and thermoregulation, and benzodiazepines may be given to suppress shivering, which otherwise increases metabolic heat. In severe cases, intubation and ventilation with neuromuscular blockade might be necessary. Definitive treatment occurs in the PICU, requiring close monitoring for multiorgan complications (15). Adolescents who experience exertional heatstroke, often from sports activities, may have better outcomes if immediately treated, though mortality remains significant. Survivors may suffer lasting neurological damage, particularly if core temperature rises above 42°C.

Some medications or medical conditions predispose for heatstroke due to poor temperature management. Among them are cardiovascular medication influencing volume status and vasodilation, SSRI's, TCA and anti-epileptic medications decreasing sweating or urine production. Paediatricians should be more aware and warn their patients considering the current predictions of yearly recurring heat waves (16).

Indirect impacts of heat on children

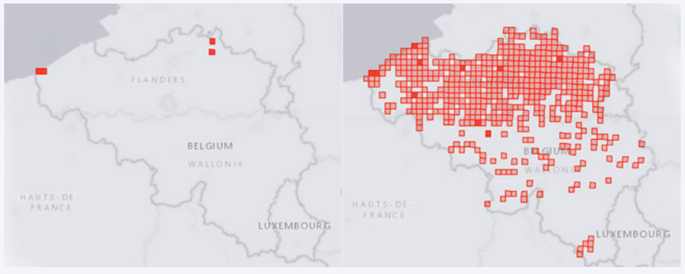
Indirect health effects **include an increased transmission of vector-borne diseases**, such as those spread by mosquitoes, ticks, or fleas. Climate change alters temperature and rainfall patterns, expanding the habitats of these vectors and increasing their activity. This topic is discussed elswhere in this issue.

Extreme heat **reduces productivity and raises accident risk**. In very hot weather, work and learning tasks become difficult, sometimes forcing schools or institutions to close.

Heat can also **indirectly affect health services**. During heatwaves, emergency department (ED) visits among children rise, particularly in infants. Asthma is often the leading cause, though heatwaves are also linked to a rise in unintentional injuries. Deaths and hospitalizations related to extreme heat typically occur rapidly—on the same day or within a few days—so timely interventions after a heat alert are essential. However, heat can also disrupt health services by affecting electricity supply and transport, further endangering public health.

Heatwaves are frequently associated with **dangerous air pollution episodes**.

FIGURE 6: Ambrosia sightings in 2002 (left) and 2025 (right). *(Source: waarnemingen.be)*



The following section examines the effects of climate change on pollen, the phenomenon of thunderstorm asthma, and the interaction between heat and air pollution.

1. *Pollen allergy in a changing climate*:
Both the production of larger amounts of pollen as well as the increased duration of the pollen season due to new species blooming later in the year are leading to more severe symptoms. Take Ambrosia (ragweed) as an example. Originally from North America, it has spread from South to North Europe over the past 25 years (Figure 6). Ragweed's pollen potency is far stronger than grass pollen: as few as 10 grains/m^3 air can trigger symptoms like those caused by 50 grass pollen grains/m^3 air. Ambrosia is also a superspreader: a single plant can emit one billion grains. Ragweed pollen can cause severe hay fever, and even skin contact with the flowers may cause symptoms. Allergies to ragweed pollen already affect 50 million people in the US alone. The late flowering of the plant, in September and October, extends the pollen season by at least 2 months (17).

2. *Supercharged pollen*:
Although still rare, events of supercharged pollen or "thunderstorm asthma" are increasing and triggered by several climate factors. The most significant recent event of supercharged pollen occurred in Melbourne (18). On Nov 21, 2016, it was the first hot day of the year when a severe thunderstorm moved to Melbourne in the late afternoon. Within 1 hour, the health care sector noticed a peak in patients with asthma-related symptoms. The demand for ambulances was so high that they could not timely respond to patients stuck at home. ED presentations increased by 58%, and the number of people presenting with respiratory symptoms increased by 672%! Asthma-related admissions increased by 992%, with 30 ICU admissions. Five ICU patients died due to neurological complications associated with cardiac arrest. The other 5 deaths were out-of-hospital deaths either while awaiting emergency transport, or who could not be resuscitated by ambulance services (18). A newspaper rightfully talked about "an event equivalent to a terroristic attack" (19).

In June 2023, a thunderstorm in London caused a similar sharp increase in children presenting with wheeze at a paediatric ED. Strikingly, 57% occurred in children without prior asthma, though many had a history of eczema or hay fever (44%). Of all presentations, 59% were severe and 6% life-threatening. No intubations or deaths were reported (20).

"Thunderstorm asthma" describes acute asthma attacks triggered by thunderstorms, particularly when pollen counts are high. How thunderstorms trigger asthma is not fully understood. The theory is that cold air downdrafts generate strong winds, stirring up (grass) pollen grains and fungal spores. They get carried high into the clouds, where moisture causes them to swell and break apart into smaller fragments, massively increasing the number of allergen particles in the air. Lightning may also enhance their rupture. The smaller particle size makes it easier for the fragments to go deep into the airways, leading to severe bronchospasm in susceptible individuals (18,20). Pollen levels seem to spike during the first 20-30 minutes of a thunderstorm. Younger people seem to be particularly affected.

Notably, having asthma is not the strongest predictor of risk. Instead, allergic rhinitis (hay fever) appears to be a more reliable indicator (18). Preventive measures include forecasting risks, early warning systems, and limiting outdoor exposure during high pollen conditions. In addition, adherence to inhaled corticosteroids and the use of allergen immunotherapy before or during storm seasons may reduce the risk (18,20).

As climate change worsens weather patterns and increases pollen production, the risk of thunderstorm asthma is likely to rise.

3. *When pollution and heat meet*:
Alerts on heat waves and air pollution often come together, because heat exacerbates air pollution through several mechanisms:

- *Increased primary emissions*. High temperatures raise energy demand, particularly for air conditioning, resulting in greater emissions. Heat also facilitates the occurrence of wildfires, which release pollutants that spread over wide areas (21).
- *Formation of secondary pollutants*: Sunlight and heat accelerate chemical reactions that convert NO (emitted from vehicles and industry) and volatile organic compounds (VOC's, originating from gasoline, paints, and cleaning agents) into ground-level ozone. While stratospheric ozone protects against harmful ultraviolet radiation, ground-level ozone is a toxic respiratory irritant that aggravates asthma and other pulmonary conditions. Most urban smog observed today is ground-level ozone (21,22).

  Furthermore, heat drives the formation of ultrafine particles (a mixture of solid and liquid droplets suspended in the air, discussed elsehwere in this issue) that penetrate deep into the lungs and even the bloodstream. Despite representing only a small proportion of particular matter ($PM_{2.5}$ mass, these ultrafine particles are highly toxic and increasingly recognized as a major determinant of air-pollution-related morbidity (23).
- *Atmospheric stagnation*. Heatwaves are often associated with high-pressure weather systems that trap pollutants near ground level, leading to higher pollutant concentrations. Almost no Belgian city currently meets the WHO target for particulate matter. Air quality in Ghent, Antwerp, and Brussels is worse than in most other European cities (24).

  Children are more susceptible to air pollution and may be more exposed than adults too:
- Their lungs are growing, and the epithelial barrier is more permeable.
- Their developing immune system is less efficient, strengthening the effects of pollution.
- They breathe faster and inhale more air/kg of body weight, resulting in higher doses of pollution
- They breathe air closer to the ground where traffic-related pollutants are concentrated.
- They inhale mostly through their mouths, allowing pollutants to penetrate deeper into the lower respiratory tract

Air pollution is linked to many adverse health effects in children, including an increased risk of upper airway infections and otitis media (25); exacerbation of asthma (26); impaired lung function and postnatal lung development, particularly due to short-term exposure to ozone and nitrogen dioxide, and long-term exposure to $PM_{2.5}$ (27). Emerging evidence also links air pollution to harmful effects on the developing brain. Its ultrafine particles can enter the bloodstream and trigger neuroinflammation or even reach the brain via the olfactory nerve, as magnetite does, causing oxidative stress tied to neurodegenerative disorders. Other pollutants, such as polycyclic aromatic hydrocarbons, harm brain regions essential for neuronal communication and children's cognitive development (28).

Air pollution can also affect the foetus: exposure during the 2nd trimester, when airways develop, is associated with a significantly increased risk of childhood asthma. Continued exposure during the first 2 years of life increases the risk even further. Pregnant women should be advised to minimize exposure to air pollution, just as they are advised to avoid (second-hand) smoking (29).

Heat waves and air pollution are a deadly combination. In Europe, air pollution is estimated to cause more than 1,200 deaths annually in children under 18, and this number is likely to increase with global warming. Beyond mortality, it contributes substantially to morbidity, leading to school absenteeism, chronic respiratory disease, and long-term impairments (30).

Conclusion

Global warming is an immediate threat to global health, particularly for our children. Rising temperatures intensify air pollution, increase water and food insecurity, and amplify the risks of infectious diseases and natural disasters. Even under optimistic scenarios (global warming to be held at 2°C by 2100), billions of people will face chronic flooding, water scarcity, and deteriorating living conditions. If global warming reaches 3°C or

higher, sweating might no longer be enough to keep the human body from overheating in certain regions.

Addressing this crisis relies on 3 strategies: *mitigation* or reducing GHG emissions; *adaptation* or learning to live with the consequences; and *innovation* to engineer our way around the problem. Of these, mitigation attacks the source of the problem. At the present rate of consumption, oil, gas, and coal reserves are projected to decline dramatically by 2080 according to the International Energy Agency; fossil fuels must be replaced anyway. Advances in renewable energy, shifts in public policy, and individual behavioural changes all demonstrate that solutions are within reach.

Nevertheless, the temperature will hardly drop at all over the first thousand or so years after emissions cease, reflecting mostly the effects of heat storage in the oceans. In the absence of technology for removing CO_2 from the atmosphere, we will have to live with (adapt to) altered climate for many thousands of years. We could build dikes, restore wetlands and the diversity of forests, paint roofs with white reflective paint or support green rooftops, increase tree cover and green spaces to battle the heat island effect in our cities, stop deforestation, eat a plant-based diet, have one fewer child, and implement heat action plans to make societies more resilient.

Paediatricians have a role in this process: advocating for children's health, preparing for climate-related emergencies by developing protocols and heat action plans, raising awareness by providing anticipatory guidance to caregivers on managing heat exposure, and integrating the health consequences of climate change into clinical practice and medical education. Every action, no matter how small, will contribute to safeguarding the health and future of our children. We cannot and should not wait any longer: the momentum for change is here—and the responsibility to act is ours. Start today.

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Beyfortus® wordt terugbetaald voor alle preterm geboren baby's tijdens hun eerste RSV-seizoen*, voor alle term geboren kinderen indien de moeder geen maternale vaccinatie heeft gekregen tijdens hun eerste RSV-seizoen, én voor kinderen die kwetsbaar blijven tijdens hun tweede RSV-seizoen**.

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▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg worden 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. Hulpstoffen met bekend effect: Dit middel bevat 0,1 mg polysorbaat 80 (E433) in elke doseringseenheid van 50 mg (0,5 ml) en 0,2 mg in elke doseringseenheid van 100 mg (1 ml). 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. - Kinderen tot 24 maanden oud die kwetsbaar blijven voor ernstige RSV-ziekte tijdens hun tweede RSV-seizoen (zie rubriek 5.1). Beyfortus dient te worden gebruikt in overeenstemming met officiële aanbevelingen. DOSERING EN WIJZE VAN TOEDIENING Dosering Zuigelingen tijdens hun eerste RSV-seizoen. 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 vanaf de geboorte voor zuigelingen die tijdens het RSV-seizoen zijn geboren. Voor diegenen die buiten het seizoen geboren zijn, dient Beyfortus idealiter te worden toegediend voorafgaand aan het RSV-seizoen. 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 bloottselling 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). Kinderen die kwetsbaar blijven voor ernstige RSV-ziekte tijdens hun tweede RSV-seizoen De aanbevolen dosis is een enkelvoudige dosis van 200 mg intramusculair toegediend als twee injecties (2 x 100 mg). Beyfortus dient idealiter te worden toegediend voorafgaand aan aanvang van het tweede RSV-seizoen. Voor personen die een hartoperatie ondergaan met cardiopulmonale bypass, kan zodra de persoon 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 tijdens het eerste RSV-seizoen 50 mg of 100 mg te zijn, afhankelijk van het lichaamsgewicht, of 200 mg tijdens het tweede RSV-seizoen. 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, tijdens het eerste RSV-seizoen of 100 mg tijdens het tweede RSV-seizoen om de rest van het RSV-seizoen te dekken. 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. Zijn er twee injecties nodig, gebruik dan twee verschillende injectieplaatsen. Zie rubriek 6.6 voor instructies inzake speciale hanteringsvereisten. 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 bijwerkingen 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 en tijdens het toezicht na het in de handel brengen. 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). Immunsysteemaandoeningen · Niet bekend · Overgevoeligheid a Bijwerkingen uit spontane melding Huid- en onderhuidaandoeningen · Soms – Rash b Rash is gedefinieerd door de volgende gegroepeerde voorkeurstermen: rash, maculo-papulaire rash, vlekkerige rash Algemene aandoeningen en toedieningsplaatsstoornissen · Soms – Injectieplaatsreactie ; Pyrexie c Injectieplaatsreactie is gedefinieerd door de volgende gegroepeerde voorkeurstermen: injectieplaatsreactie, injectieplaatspijn, injectieplaatsverharding, injectieplaatsoedeem, zwelling van injectieplaats. Zuigelingen met een verhoogd risico op ernstige RSV-ziekte in hun eerste seizoen. De veiligheid is onderzocht in MELLEY 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 (n=614) of palivizumab (n=304) kregen. Het veiligheidsprofiel van nirsevimab bij zuigelingen die nirsevimab ontvingen in hun eerste RSV-seizoen was vergelijkbaar met het vergelijkende geneesmiddel palivizumab en consistent met het veiligheidsprofiel van nirsevimab bij voldragen en premature zuigelingen GA ≥ 29 weken (D5290C00003 en MELODY). Zuigelingen die kwetsbaar blijven voor ernstige RSV-ziekte in hun tweede seizoen De veiligheid werd beoordeeld in MEDLEY bij 220 kinderen met chronische longziekte van prematuriteit of hemodynamisch significante congenitale hartziekte die nirsevimab of palivizumab kregen in hun eerste RSV-seizoen en vervolgens nirsevimab kregen in hun tweede RSV-seizoen (180 proefpersonen kregen nirsevimab in zowel seizoen 1 als 2, 40 kregen palivizumab in seizoen 1 en nirsevimab in seizoen 2). Het veiligheidsprofiel van nirsevimab bij kinderen die nirsevimab kregen in hun tweede RSV-seizoen was consistent met het veiligheidsprofiel van nirsevimab bij voldragen en premature zuigelingen GA ≥29 weken (D5290C00003 en MELODY). De veiligheid werd ook onderzocht in MUSIC, een open-label onderzoek zonder controlegroep met enkelvoudige dosis bij 100 immuungecompromitteerde zuigelingen en kinderen ≤24 maanden die nirsevimab ontvingen in hun eerste of tweede RSV-seizoen. Dit omvatte deelnemers met ten minste een van de volgende aandoeningen: immunodeficiëntie (gecombineerd, antilichaam of andere etiologie) (n=33); systemische behandeling met hoge doses corticosteroïden (n=29); orgaan- of beenmergtransplantatie (n=16); gebruik van immunosuppressieve chemotherapie (n=20); andere immunosuppressieve behandeling (n=15) en HIV-infectie (n=8). Het veiligheidsprofiel van nirsevimab was consistent met wat werd verwacht voor een populatie van immuungecompromitteerde kinderen en met het veiligheidsprofiel van nirsevimab bij voldragen en premature zuigelingen GA ≥29 weken (D5290C00003 en MELODY). Het veiligheidsprofiel van nirsevimab bij kinderen tijdens hun tweede RSV-seizoen was consistent met het veiligheidsprofiel van nirsevimab dat werd waargenomen tijdens hun eerste RSV-seizoen. Voldragen en premature zuigelingen die hun eerste RSV-seizoen beginnen. De veiligheid van nirsevimab werd ook beoordeeld in HARMONIE, een gerandomiseerd, multicenter open-labelonderzoek bij 8.034 voldragen en premature zuigelingen (GA ≥29 weken) die hun eerste RSV-seizoen begonnen (en niet geschikt waren voor palivizumab), die nirsevimab (n=4.016) of geen interventie (n=4.018) kregen ter preventie van ziekenhuisopname voor onderste luchtweginfectie (lower respiratory tract infection, LRTI) door RSV. Het veiligheidsprofiel van nirsevimab toegediend in het eerste RSV-seizoen was consistent met het veiligheidsprofiel van nirsevimab in de placebogecontroleerde onderzoeken (D5290C00003 en MELODY). 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 worden verzocht alle vermoedelijke bijwerkingen te melden via: België: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten: www.fagg.be – Afdeling Vigilantie: Website: www.eenbijwerkingmelden.be – e-mail: adr@fagg-afmps.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: 04/2025. Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau http://www.ema.europa.eu

* Beyfortus® wordt vergoed voor baby's die geboren zijn sinds 19/02/2025 (einddatum van het RSV-seizoen 2024-2025) voor hun eerste RSV-seizoen.
** Beyfortus® wordt vergoed voor jonge kinderen (<2 jaar) die een hartoperatie met extracorporele circulatie ondergaan tijdens hun eerste of tweede RSV-seizoen, of voor jonge kinderen (<2 jaar) die kwetsbaar blijven voor ernstige ziekte door RSV tijdens hun tweede RSV-seizoen (zoals beschreven in de aanbevelingen van de HGR (advies 9760)).

Referentie:
1. Beyfortus® SKP, April 2025.

Sanofi Belgium MAT-BE-2501425-V1.0-01/2026

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The Impact of Air Pollution on Children's Health

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Keywords
Air Pollution ; Children ; Respiratory Health ; Cognitive Function ; Endothelium.

Abstract
Air pollution poses a major environmental risk to our health. Particulate matter affects more people than any other pollutant and is therefore commonly used as a proxy indicator for air pollution. Children are of particular interest, since they are uniquely vulnerable to the effects of exposure to air pollution.

Little is known about the effects of air pollution in healthy children as studies often focus on an adult or elderly population, or children with an underlying condition such as asthma. Additionally, the large variation in study design across available research leads to inconsistent results. This review will give an overview of existing studies on the effect of air pollution in children.

Overall, evidence can be found, supporting the detrimental effects of exposure to air pollution on certain health outcomes. As such, negative associations were found between both children's respiratory health and neurocognitive functions and exposure to air pollution. Moreover, a possible link could be unveiled between endothelial dysfunction and cardiovascular, respiratory or neurocognitive effects in response to exposure to air pollution. A future challenge remains to generalize study designs as much as possible. Acute respiratory effects, neurocognitive changes or effects on endothelial function in children in relation to PM exposure are still scarcely studied in healthy children, especially based on high resolution personal monitoring data. Furthermore, there is still insufficient evidence for causal associations.

General introduction

"The United Nations General Assembly has formally declared access to a clean, healthy, and sustainable environment a universal human right, especially for children. In 2023, the United Nations Committee on the Rights of the Child emphasized the children's right to a clean, healthy, and sustainable environment. ***Yet, it is a right that goes unfulfilled for billions of people"*** *(1).*

It is clear that air pollution is a major environmental risk factor to our health (2). According to the World Health Organization (WHO), air pollution forms the second leading cause of deaths from noncommunicable diseases such as asthma, cardiovascular problems and respiratory diseases including lung cancer, even for children (1, 2). In 2020, air pollution was even officially recognized as the direct cause of a young girl's death in the United Kingdom—the first time it had been explicitly identified as such (3).

Air pollution

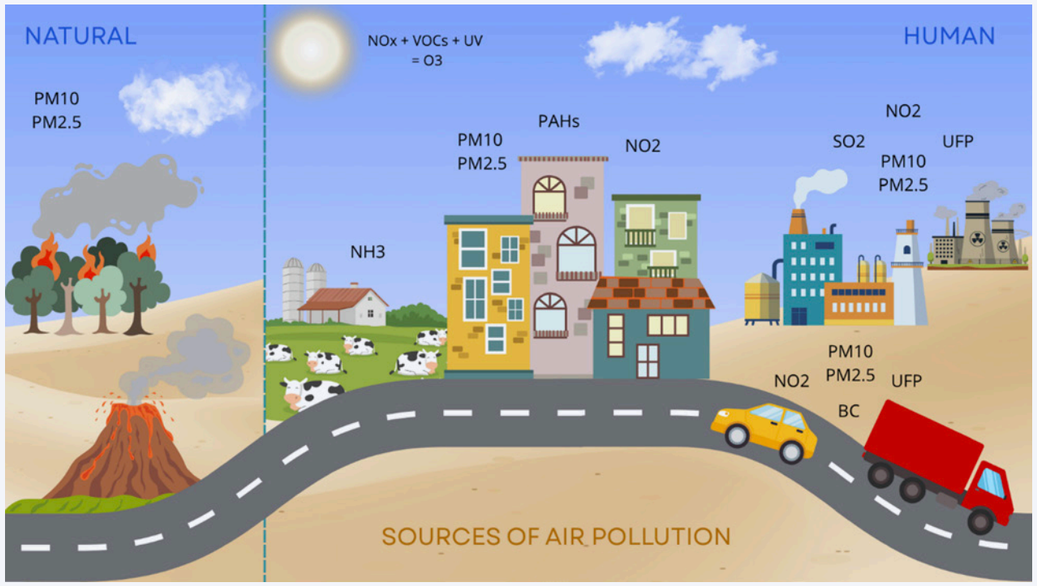
Air pollution is a complex matter, and different types of pollution exist. Pollutants are often linked and considerable interactions between them complicates determining the effects of a single pollutant. Air pollutants that affect the public health include particulate matter (PM), ozone (O3), nitrogen dioxide (NO2), polyaromatic hydrocarbons, sulphur dioxide (SO2) and ammonia (NH3). They are shown in Figure 1, with the corresponding major sources. Among these, PM, NO2 and O3 exert the greatest health impact, and they contribute to premature death (4). Even though in the EU, air pollution related deaths decreased by 45% between 2005 and 2022, PM2.5 still contributed to an estimated 239,000 premature deaths in 2022, while O3 and NO2 contributed to an estimated 70,000 and 48,000 premature deaths (4). In Flanders, about 3500, 1800 and 800 premature deaths were attributable to PM2.5, O3 and NO2 respectively (5).

PM, affecting more people than any other pollutant, is considered a major air pollutant by the WHO. It is commonly used as proxy indicator for air pollution (2). PM is classified according to the aerodynamic diameter of its particles: PM10, PM2.5 and ultrafine particles (UFPs) are the main fractions (Figure 2). PM10 includes particles ≤ 10 µm in diameter, originating from natural sources (e.g., Saharan or volcanic dust) or human activities such as fuel combustion for industry, agriculture or road transport. PM2.5 refers to finer particles (≤ 2.5 µm), produced directly by combustion processes or formed secondarily through atmospheric reactions between gases such as NH3 from livestock and traffic nitrogen oxides (NOx). UFPs, with a diameter ≤ 0.1 µm, can also be emitted directly into the atmosphere or formed from gaseous precursors. These particles are inherently unstable and, similar to PM2.5, can grow into larger particles through coagulation or condensation. Transportation and industry are important sources (6).

Black carbon, a major component of soot, is an important constituent of PM. It is a primary pollutant mainly produced by incomplete combustion from traffic, industry, heating and biomass burning and is often used as a proxy for traffic exhaust (7). In areas dominated by combustion-derived pollution, PM can contain substantial amounts (up to 80–90% of the UFP mass) of black carbon and organic carbon. Metals and polyaromatic hydrocarbons are other important constituents of PM (6).

Nitrogen oxides mainly consist of NO2 and nitric oxide (NO). NO is emitted into the atmosphere and immediately thereafter, NO2 is formed as a result of chemical reactions with e.g. ozone. The large, and growing body of scientific evidence linking NO2 with various health outcomes has shown that short-term exposure to NO2 can irritate the airways and aggravate existing respiratory conditions (2). A major source of NO2 is traffic exhaust. As such, NO2 is a common pollutant in cities and the highest levels are observed in high-income, urbanized and densely populated areas. NO2 is therefore, like black carbon, used as a proxy indicator for traffic pollution. Burning of fuels in power plants or industry are additional sources of NO2 (1).

FIGURE 1: The main sources of air pollutants that are known to affect public health: particulate matter (PM), ozone (O3), nitrogen oxides, polyaromatic hydrocarbons (PAH's), sulphur dioxide (SO2) and ammonia (NH3).



Episodes of intense air pollution are often referred to as smog. O3 is a major component of so called 'ozone smog' or 'summer smog'. Whereas the major component during 'winter smog' is PM (8). O3 is synthesized by a photochemical reaction with exhaust gases such as NO2 and volatile organic compounds, in the presence of UV sun radiation, especially in wind still weather conditions. The highest ground-level levels of O3 therefore occur during periods of sunny, warm weather (9). Exposure to excessive levels of O3 can affect breathing, provoke coughing and wheezing, trigger asthma, reduce respiratory function or lead to lung disease (2).

The interplay between air pollution and climate change

Greenhouse gases, such as CO2, methane and O3 in the atmosphere absorb radiation and as such trap heat in a way the planet can no longer lose it, causing global warming. Over the last 150 years, human activities are almost entirely responsible for the increase in greenhouse gases in the atmosphere (10, 11). The burning of biomass and fossil fuels (for electricity, heat, or transportation) as important sources of air pollution, also contribute to the emission of these greenhouse gases. Black carbon is also suggested as an important contributor to global warming (7). Hence, the continuous use of biomass or fossil fuels not only enriches air pollutant concentrations, it also aggravates the impact on our climate. Meanwhile climate change and its consequences enhance air pollution: more severe and prolonged droughts, drier lands, wildfires and dust storms (12). Additionally, summers become warmer and more heatwaves occur, which in turn accelerates the formation of O3 due to a more vigorous catalysation of e.g. NO2 (9).

Air quality management

Overall, global and European air quality has improved in recent decades due to declining emissions. In Flanders for example, 2024 was a favourable year due to both rainy weather and reduced emissions. Emissions from industry and energy sectors are declining, while households (heating of buildings) and traffic are increasing sources of PM, polyaromatic hydrocarbons and NOx. Agriculture remains the predominant source of NH3 (13).

Nevertheless, there are no safe levels of air pollution according to the WHO: even very low levels of PM2.5 can cause adverse health effects (2). In other words, concentrations should be kept as low as possible. Therefore, air quality guidelines are in place (table 1). While the WHO sets strict guidelines to protect public health, the European Commission has adopted less stringent standards in its legislation, under the Ambient Air Quality Directive. The Ambient Air Quality Directive contains emission limits for pollutants such as PM10, PM2.5, NO2, O3, SO2, CO, Pb, and benzene. Black carbon has only recently been included in air quality management, but no specific guidelines exist yet. The European Commission proposed a revised Ambient Air Quality Directive, introducing stricter targets to be achieved by 2030. The new limits for PM2.5 and NO2 remain twice as high as WHO recommendations but should still represent substantial progress. Member states are required to implement these targets into national law, within two years. Additionally, the EU Zero Pollution Action Plan targets a toxic-free environment by 2050, aiming to reduce air, water, and soil pollution to levels no longer harmful to human health or ecosystems (14).

Particulates toxicity

Determinants of particulates toxicity

PM is a complex mixture of particles that vary in mass, number, size, shape, surface area, chemical composition as well as reactivity, acidity, solubility and origin (6). Particulates behaviour in our respiratory system and their potential to cause adverse health effects is directly linked to their size, chemical characteristics and surface area to interact with human tissue (6). Particles from different combustion

TABLE 1: Air quality guidelines.

European Union (EU) air quality standards = Limit values for the protection of human health to be attained by 1 January 2030 (8). and World Health Organization (WHO) global air quality guidelines (2). The dashes indicate the absent guidelines.

	PM_{10}		$PM_{2.5}$		NO_2		UFP's	BC
	EU	WHO	EU	WHO	EU	WHO		
1 hour	-	-	-	-	200 µg/m³ [a]	-	-	-
24 hour	45 µg/m³ (b)	45 µg/m³	25 µg/m³ (b)	15 µg/m³	50 µg/m³ [b]	25 µg/m³	-	-
Annual	20 µg/m³	15 µg/m³	10 µg/m³	5 µg/m³	20 µg/m³	10 µg/m³	-	-

[a] Not to be exceeded more than 3 times per calendar year (8). - [b] Not to be exceeded more than 18 times per calendar year (8).

sources can vary in chemical composition, which makes some particles more relevant to human health than others (6). One epidemiological study including children with asthma for example, reported weaker associations between an airway inflammation marker and particle mass, compared to specific PM components (black carbon and organic compounds in particular) (6, 15). Furthermore, water-soluble gases (such as SO2) are likely to react with the mucus layer of the upper airways, while less soluble gases (such as NO2) more often reach the alveoli. Regarding particulates, the smaller the particles (i.e. PM2.5, UFP or black carbon) the deeper they can penetrate into the lungs (to the alveoli and terminal bronchioles) and the further they can migrate through the body via entering the bloodstream (16). In this context, UFPs are considered the greatest risk to our health. They are small enough to enter the bloodstream (even end up in brain tissue) inducing inflammation and potentially promoting cardiovascular, respiratory and cognitive problems. In contrast, larger particles, e.g. PM10 remain in our airway system (6). Apart from penetrating deeper into the lung, smaller particles also have a greater surface area on a mass basis, allowing more toxic chemicals to adsorb onto their surfaces compared to larger particles (6).

Mechanisms of toxicity

Air pollutants possess the ability to act directly as pro-oxidants of proteins and lipids, or as generators of free radicals such as reactive oxygen species (ROS). In the human body, free radicals (including ROS) are continuously generated during normal metabolism and they play a crucial role in cellular processes (17, 18). However, when concentrations increase considerably, for example due to exposure to exogenous components, excess reactive oxygen species can result in a state of oxidative stress. (18, 19). Exposure to air pollution was already associated with increased levels of reactive oxygen species, and oxidative stress has been associated with various diseases, including heart attack, stroke, chronic inflammatory disease, Alzheimer and even cancer (17, 18).

The body's immune system can be activated by pollutants, resulting in elevated cytokine expression and stimulation of an inflammatory response. As such, oxidative stress and the induction of inflammatory responses (through deposition in the lungs, or systemic inflammation due to translocation of particles to the blood circulation) are common suggested cellular mechanisms by which most pollutants exert their adverse health effects (18). Since research results showed that PM could carry heavy metals and polyaromatic hydrocarbons, the presence of these components may also contribute to PM toxicity (20-22).

Endothelial function

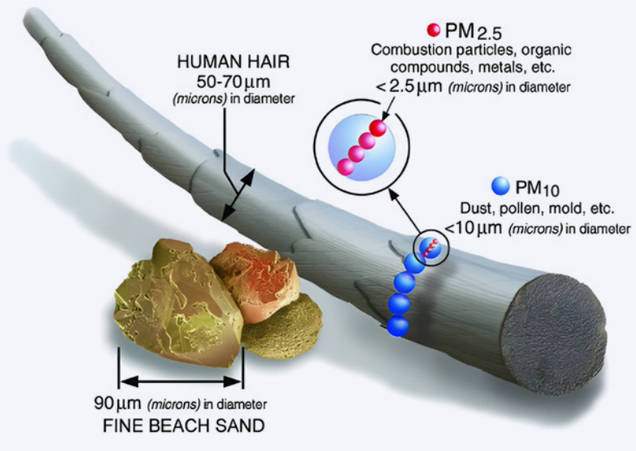
These suggested underlying mechanisms, oxidative stress and inflammatory responses, potentially provoke endothelial dysfunction. Endothelial dysfunction is an early predictor of cardiovascular disease (23). Furthermore, it is hypothesized that particulates affect the cerebral microvasculature resulting in a decreased perfusion and thus insufficient oxygen availability. Hence, a possible link could be unveiled between endothelial dysfunction and cardiovascular, respiratory or neurocognitive effects in response to exposure to air pollution.

The vascular endothelium, aligning the inside of our blood vessels, is an interesting target for studying the effects of air pollution since the smallest particles can enter the bloodstream. Endothelial function can be assessed using various methods. First, (surrogate) blood markers for endothelial function are often measured, with endothelin-1, a vasoconstrictor and inflammatory mediator, as most common reported marker. Secondly, different methods exist to directly assess the vascular function. These include assessing the retinal microvasculature, a proxy for the systemic microcirculation, measuring the flow-mediated dilation of the brachial artery and application of peripheral arterial tonometry.

Despite the variation in studies, findings are pointing in the same direction: evidence supports the association between exposure to air pollutants and signs of endothelial dysfunction. Exposure to traffic-related air pollution, particularly UFPs, has been linked to a reduced endothelial function in adults (24, 25). However, evidence in children remains limited. Hashemi et al. reported that exposure to PM10 and passive smoking impaired the flow-mediated dilatation of the brachial artery (hence reduced the endothelial function) in healthy children. Both PM10 and passive smoking were also inversely associated with the basal brachial artery diameter (26). In the same study population, Kelishadi et al. found that PM10 was associated with a decrease of serum NO levels (a potent vasodilator) and an increase in C-reactive protein (CRP), an inflammatory marker) (27). Similarly, Prunicki et al. observed elevated CRP and other immune markers in relation to air pollution (28), while Calderón-Garcidueñas et al. reported higher plasma endothelin-1 levels among children chronically exposed to PM2.5 in Mexico City (29, 30).

PM was also found to affect the retinal microvasculature in children. However, results are inconsistent and appear to depend on the duration of exposure (e.g. recent versus chronic exposure or prenatal versus postnatal exposure) and on the interaction between pollutants (e.g. PM2.5 and Ox (the combined oxidant capacity of O3 and NO2)) (31-33). Provost et al., found that short-term exposure to PM2.5 was associated with narrower retinal arteriolar diameters and wider venular diameters, consistent with the findings of other studies in both children and adults (27, 34). Whereas Luyten et al. found that exposure was associated with a widening of the retinal arterioles (32). Korsiak et al. reported that arteriolar narrowing was associated with PM2.5 only when Ox concentrations were elevated. No clear associations between PM2.5 or Ox and venular diameter were found here (33).

FIGURE 2: Size comparisons for PM particles (United States Environmental Protection Agency – available from: https://www.epa.gov/sites/default/files/2016-09/pm2.5_scale_graphic-color_2.jpg)



Size comparisons for PM particles

Air pollution as an environmental threat to our health

Worldwide, 99% of the population (including hundreds of millions of children) live in areas with levels levels exceeding international guidelines exceeding international guidelines (35, 36). Yet, the most vulnerable groups of the population (such as children, elderly, or people living in developing countries) are disproportionately affected by exposure to air pollution. Inhalation is the main route of exposure: breathing polluted air causes adverse effects to our health, targeting certain organs and systems. The effect of exposure on our respiratory function (volume/flow) is therefore of interest. Since evidence is growing that exposure to air pollution can disrupt cognitive development, an additional important health concern is the effect of PM on brain function.

Children experience some of the greatest health effects due to exposure.

Children are a uniquely vulnerable part of the population, so their exposure to air pollution is of particular concern. (37). Their immune system, neuropsychological abilities and lungs are not fully developed, which may lead to different health responses as compared to adults or even affect the development of lungs and cognition (37). Children have a relatively larger lung surface and breathe more air per mass of body weight compared to adults. They spend more (active) time outside as well, sometimes during peak traffic times. Furthermore, young children play closer to the ground, where PM is often more concentrated (17, 38). Chronic exposure to high levels of air pollution during pregnancy can even affect the foetus and is associated with low birth weight, preterm or even still birth (39, 40). If left untreated, some of these health impacts may have lifelong consequences. Social and economic effects (such as school attendance and performance, health costs and productivity potentially affecting income, poverty and inequities) could occur as well.

Respiratory effects

Air pollution has been widely recognized as a contributor to a range of adverse respiratory effects, ranging from allergic reactions and airway irritation to breathing difficulties, wheezing, coughing, asthma, chronic inflammation, and even lung cancer. Commonly used parameters for assessing respiratory function include forced expiratory volume in one second (FEV1), which reflects airflow through the large and medium airways and forced vital capacity (FVC), which indicates lung size. In addition to these physiological measures, many studies evaluate respiratory health through the prevalence of respiratory diseases (e.g., asthma, infections) and symptoms such as coughing, wheezing or hospitalizations (35).

To date, relatively few research exists on acute effects on the respiratory function, especially considering healthy children. Exposure studies that exist, report on long(er)-term rather than acute effects while other studies are restricted to adult participants. Research also often focuses on vulnerable groups such as asthma patients (41-43). Weeda et al. for example, reviewed the effects of climate variables, including temperature and air quality, on children's respiratory health. Most studies examined the relationship between air quality and the risk of asthma, (asthma-related) emergency department visits, and other respiratory infections (44). Although findings varied, most reported an increased risk of asthma associated with higher levels of air pollutants such as PM2.5, NO2, and O3. Similarly, Boogaard et al. reported positive associations between NO2 and other traffic-related pollutants with asthma onset and acute lower respiratory infections in children in their review (45). Elevated pollutant levels were also linked to higher rates of childhood pneumonia and combined respiratory disease–related hospitalizations, as well as increased all-cause respiratory emergency department presentations linked to PM2.5 and PM10 exposure (46-49).

Schultz et al. reviewed studies investigating the effects of traffic-related pollutants on children's RF. Despite some inconsistencies, most of the studies reported a negative impact of traffic-related air pollution on RF (35). Exposure to PM10 and NO2 during both early life and over the lifetime was found to be negatively associated with RF, while others observed stronger associations with current exposure at children's home addresses rather than at birth. Lifetime and past-year exposure to black carbon and PM2.5 were primarily linked to reduced FVC, whereas exposure to PM10 and NO2 during the first year of life was associated with lower FEV1. These results align with Fuertes et al., who observed a strong effect from early life exposure to PM10 (42). Similarly, Bergstra et al. reported that exposure to industry-related pollutants, including PM2.5 and NO_x, was associated with reduced RF (50).

Neurocognitive functions

Elevated concentrations of PM are suggested to negatively affect cognitive functions, such as the ability to think and make decisions, and even affect cognitive development (37, 51). Cognitive functions are essential for learning and achievement. These functions develop significantly during childhood, especially at primary school age. Child and adolescent exposure to air pollution is therefore of special concern, since brain development continues until the second decade of life (16). Inflammatory responses were observed in the brain regions related to executive function after exposure to traffic-related air pollution (52). Evidence was also found for the breakdown of the blood–brain barrier, and thus impairment of its integrity, after exposure in children (53). Likewise, fine PM (especially UFPs) can translocate to the olfactory bulb and migrate to the olfactory cortex, causing tissue damage and local

inflammation (neuroinflammation and damage of neural tissue) after inhalation through the nose (17, 54).

The term neurocognitive functions encompasses a wide and diverse range of cognitive processes and neural mechanisms, making it a highly broad and multifaceted concept. This is reflected in the variety of cognitive outcomes tested in literature, as reported in different review papers: Clifford et al. broadly described three categories: 1] measurements of cognitive function (including intelligence, memory and learning, visual-motor coordination, executive function and attention, and global cognition); 2] measures of neurodevelopment; and 3] tools to identify age-related decline (55). Gartland et al. described two main categories, namely school attainment and executive function, which mainly encompasses working memory and attention (17). Thompson et al. defined a wide range of cognitive functions, including general cognition; intelligence, IQ and reasoning; attention, working memory & executive function and memory and learning (56).

Studies suggest that PM2.5 affects attention and academic achievement. However, findings relating to attention were mixed: higher levels of indoor PM2.5 were associated with increased inattention across one year, whereas Alvarez-Pedrerol et al. found no significant effect (57, 58). PM10 is suggested to have effects on attention, reasoning, and test scores, even though the evidence is limited compared to PM2.5. While working memory seemed to be the main outcome affected by PM2.5, no effects were reported for PM10. In a cross-sectional study in Belgium, Saenen et al. reported a negative effect of acute and chronic exposure on selective attention, and on sustained attention (chronic exposure only), rather than on the short-term memory in healthy children (37). Regarding NO2, the limited evidence suggests a potential specific effect on working memory, while no impact on attention has been observed (17, 59, 60). Other studies, however, reported mixed findings of the impact of NO2 on cognitive outcomes (17). Lastly, evidence also supports the potential effect of elemental carbon/black carbon and UFPs on attentional outcomes, as well as the association between long-term black carbon exposure and a decreased cognitive function in primary school children (61, 62).

Exposure studies comparison

To date, inconsistencies persist across studies due to variations in study design, exposure assessment, and reported pollutants. Study designs range from retrospective to cross-sectional and longitudinal studies, each using different methods to estimate exposure. For example, some studies compared children living in areas with varying levels of air pollution, measured at central monitoring stations or at schools (35). Other exposure estimates included traffic indicators, such as traffic density or proximity to highways. Modelling individual data using land use regression models or dispersion models was also used. Reported pollutants differ as well, with PM2.5 being the most reported pollutant, followed by PM10, NO2 and O3 (44). Further variability arises from differences in pollutant combinations, emission sources (including traffic-; fire-; or industry-related air pollution), duration and the window of exposure (prenatal, early-life, recent or chronic exposure). Health outcomes also vary across studies. Despite the amount of research available, it remains challenging to draw consistent conclusions. However, most evidence supports the negative health impact of air pollution.

Conclusions

Described above are the effects of air pollution on respiratory function and neurocognitive outcomes, and the potential role of endothelial (dys-)function. The focus was set on children, since they are uniquely vulnerable to effects of air pollution. Although, effects from exposure to air pollution are well documented, it is important to point out that the evidence resulting from this research is of small to moderate certainty and often not strong enough to draw firm conclusions. The findings are also far more nuanced than presented here and should therefore be interpreted with caution.

A future challenge is to specify and harmonize the research methodology as much as possible, and to encourage its widespread use. In addition, more work is required to disentangle the impact of different exposures, the potential mechanisms, and the context in which they occur (56). Acute respiratory effects, neurocognitive changes or effects on endothelial function in children in relation to PM exposure are still scarcely studied in healthy children, especially based on high resolution personal monitoring data (51). Furthermore, there is still insufficient evidence for causal associations (37, 55, 63). Hence, there is a clear need for further experimental research.

Reducing air pollution can improve quality of life and save children's lives by lowering the risk of respiratory infections like pneumonia and asthma. It also reduces pregnancy and childbirth complications, supports healthy child development, and contributes to sustainable development and climate change mitigation.

Conflict of interest

The authors have no conflicts to declare. Funding was provided by the Research Foundation Flanders (FWO), FWO strategic basic fellowship (1SD4924N). This funding had no influence on the content or development of this article.

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Important: L'allaitement maternel est l'alimentation idéale pour les bébés. Information uniquement destinée au corps (para-)médical. **Références:** **1.** Bruzzese E et al. Clinical Nutrition, 2009;28:156–61. **2.** Arslanoglu S et al. Journal of Nutrition, 2007;137:2420–4. **3.** Chatchatee P et al. J Pediatr Gastroenterol Nutr, 2014;58(4):428–37. **4.** Arslanoglu S et al. J Nutr, 2008;138:1091–5. **5.** Chua M et al. JPGN, 2017;65:102–6. **6.** Reverri EJ et al. Nutrients, 2018;10,1346. *Les vitamines C et D soutiennent le développement du système immunitaire **Structure identique Human Milk Oligosacharides ***Plus similaire à la composition du microbiote intestinal des bébés nés par voie vaginale. Basé sur des recherches combinant des oligosaccharides prébiotiques scGOS:lcFOS (9:1) et Bifidobacterium breve M16-V. ****Basé sur des recherches sur les oligosaccharides prébiotiques scGOS:lcFOS (9:1). *****Basé sur la recherche sur les oligosaccharides prébiotiques scGOS:lcFOS (9:1) ou 2'-FL • **8/2025 V.U.: E.R.: Danone Belux S.A. – Quai des Usines 160 – 1000 Bruxelles**

The Impact of Climate Change on the Neurodevelopment of Children: A Scoping Review

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Keywords

Children ; climate change ; neurodevelopment

Abstract

Objective:

Climate change introduces environmental stressors that may affect the developing brain. Children are particularly vulnerable due to biological sensitivity and social exposure. This review summarizes evidence on climate-related impacts on neurodevelopment.

Methods:

A scoping review was conducted focusing on four major exposures: air pollution, extreme temperatures, natural disasters, and endocrine-disrupting chemicals (EDCs). Findings across cognitive, behavioral, and neurobiological outcomes were synthesized.

Results:

Air pollution is linked to structural brain alterations, disrupted functional connectivity, and higher risks of autism, ADHD, and cognitive delay. Extreme heat and cold are associated with poorer language and cognitive performance, sleep disturbances, and behavioral problems. Natural disasters influence development through prenatal stress, trauma, and unstable environments. Increased EDC exposure contributes to neuroinflammation, oxidative stress, and epigenetic changes. Socioeconomically disadvantaged children show the greatest vulnerability.

Conclusion:

Climate change presents a significant risk to child neurodevelopment through interacting environmental and psychological pathways.

Introduction

Climate change, as defined by the United Nations, refers to long-term alterations in global temperature and weather patterns. The World Health Organization (WHO) further emphasizes that climate change affects multiple determinants of human health, such as clean air, safe drinking water, adequate nutrition, and secure shelter, posing a severe threat to public health and potentially reversing decades of progress in global health outcomes. Climate change affects both natural and human systems, including the functioning of healthcare systems. Currently, 3.6 billion people live in regions with high vulnerability to climate change, and populations in these areas have experienced mortality rates from extreme weather events fifteen times higher than those in more resilient regions over the past decade. Health impacts arise through various pathways, including extreme weather events, food system disruption, and increases in zoonotic, food-, water-, and vector-borne diseases (1).

Beyond physical and environmental consequences, awareness of climate change can negatively influence the psychological well-being of children, with anxiety and worry being the most frequently reported emotional responses. In addition to these psychological effects, climate change may also influence the neurodevelopment of children and adolescents. Neurodevelopment involves the formation and maturation of the brain beginning in the prenatal period, and environmental factors play a crucial role in shaping these processes. Disruptions during sensitive periods, such as those associated with synaptogenesis, may lead to lasting impairments. Due to their cognitive and physiological developmental stage, children and adolescents are particularly vulnerable to adverse consequences of climate change, including exposure to traumatic events, nutritional deficiencies, environmental toxins such as air pollution, and temperature extremes (2, 3).

The purpose of this review is to summarize current knowledge on how climate change affects neurodevelopment in children.

Methods

A scoping review methodology was adopted to address the research objectives of this study. This approach is appropriate given that the aim of this study is to summarize what is currently known about the impact of climate change on neurodevelopment and to highlight areas requiring further research. We followed the Arksey and O'Malley framework, which consists of five stages: identifying the research question, conducting a systematic search, selecting relevant studies, charting the data, and synthesizing and reporting the results (4). The guiding research question for this review was: "What is known about the effects of climate change on neurodevelopment in children and adolescents?"

Inclusion and exclusion criteria

This review included studies involving (unborn) children and adolescents up to 18 years of age, in accordance with the WHO definition of a child. Qualitative, quantitative, and mixed-method studies were eligible. In studies that included both adults and children, only those reporting child-specific data were retained. No geographic restrictions were applied, since the aim was to provide a global overview of the available evidence. The search was limited to publications in English and Dutch, with no restrictions on publication date. Eligible studies examined the relationship between climate change and neurodevelopmental outcomes in children and adolescents, including environmental exposures such as air pollution, nutritional stressors, temperature changes, and climate-related traumatic events that may affect brain development or psychological functioning. No formal quality assessment was performed, as the primary aim of this scoping review was to map and summarize the available evidence.

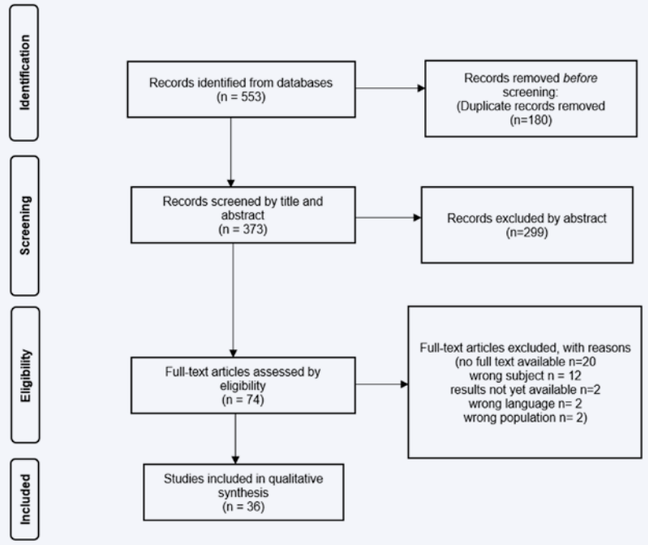
Search strategy

Searches were conducted in six academic databases (PubMed, Web of Science, GreenFILE, Cochrane Evidence-Based Medicine, Embase, and Scopus) in October 2025. The full search terms are presented in Table 1.

Study selection process

All identified records were imported into EndNote (version 2025). The references were then uploaded into the systematic review platform Rayyan, where duplicates were removed. Titles and abstracts were independently screened by two reviewers according to the predefined inclusion and exclusion criteria. Articles that met the eligibility criteria were subsequently assessed through full-text screening, and reasons for exclusion were documented. A third reviewer was not required, as any disagreements were resolved through discussion. The screening process and study selection are illustrated in the PRISMA flow diagram (Fig. 1).

FIGURE 1: Article selection Prisma flow diagram



Data extraction

Data were manually extracted by one reviewer and verified by a second reviewer for accuracy. Extracted information included: author(s), year of publication, study location, study aim, population characteristics, sample size, methodology, and key findings (Table 2).

Synthesis

A narrative synthesis approach was used to summarize the findings across the included studies, drawing on textual descriptions to compare and integrate evidence.

Results

The studies included in this review demonstrate that climate change, through exposure to extreme heat, ambient air pollution (e.g., PM2.5, NO2) , endocrine disruptive chemicals (EDCs) and natural disasters, can affect neurodevelopment in children.

TABLE 1: Search terms

Search number	Search terms
#1	('child*') OR ('adolescent*') OR ('teen'*) OR ('youth') OR ('young people') OR ('school children') OR ('schoolchildren*') OR ('school age'*) OR ('school-age'*) OR ('infant'*) OR ('newborn'*) OR ('neonate'*) OR ('toddler'*) OR ('early childhood') OR ('young child')
#2	noft('neurodevelopment'*) OR noft ('brain development') OR noft (cognitive development')
#3	Noft ('climate change') OR noft ('global warming') OR noft ('environmental change') OR noft ('climate crisis')

[1]. PM2.5 = particulate matter, particles ≤ 2.5 µm; NO2 = nitrogen dioxide

TABLE 2: Data extraction

Paper	Country	Research purpose/question	Research type and population (sample size)	Important findings
Odo DB, Yang IA, Dey S, Hammer MS, van Donkelaar A, Martin RV, et al. A cross-sectional analysis of long-term exposure to ambient air pollution and cognitive development in children aged 3–4 years living in 12 low- and middle-income countries. Environ Pollut. 2023;318.	Benin, Burundi, Cambodia, Chad, DRC, Honduras, Jordan, Rwanda, Senegal, Timor-Leste, Togo, Uganda	Is annual average exposure to PM2.5 associated with delays in indicators of cognitive development among children aged three to four years?	Cross- sectional study with children 3-4 years old living in low- and middle-income countries (n=57647).	Findings suggest that exposure to ambient PM2.5 is cross sectionally associated with indicators of cognitive delay in young children living in LMICs. There was between-country variation in the effects of PM2.5 on cognitive delay.
Thompson R, Stewart G, Vu T, Jephcote C, Lim S, Barratt B, et al. Air pollution, traffic noise, mental health, and cognitive development: A multi-exposure longitudinal study of London adolescents in the SCAMP cohort. Environ Int. 2024;191.	United Kingdom	Is ground-level ozone exposure in relation to adolescent executive functioning?	Longitudinal cohort with adolescents from 39 different schools (n=7744).	Strong evidence indicates detrimental associations between ground-level ozone exposure and executive functioning during adolescence, alongside supportive evidence for associations between various other environmental exposures (like noise pollution) and psychological outcomes.
Barbalat G, Guilbert A, Adelaïde L, Charles M-A, Hough I, Launay L, et al. Impact of early life exposure to heat and cold on linguistic development in two-year-old children: findings from the ELFE cohort study. Environ Health Global Access Sci Sour. 2025;24(1).	France	What is the effect of ambient temperature on linguistic development in children?	Cohort study with 2-year-old children (n=12163).	Exposure to night-time heat during the second trimester of pregnancy, as well as exposure to daytime and night-time heat during the first seven months postpartum, was associated with lower vocabulary production scores on the MB-CDI at two years of age.
Zhuo H, Warren JL, Bellia G, Wang P, Chen K, Liew Z, et al. High ambient temperature during pregnancy and offspring cerebral palsy: A population-based study in California. https://doi.org.10.1101/2025.05.21.253228071.	United States	To examine whether prenatal exposure to high ambient temperatures is associated with an increased risk of cerebral palsy in offspring.	Case control study with children with cerebral palsy (n=5938) and control (n=1.092.313).	Prenatal exposure to higher ambient temperatures was associated with an increased risk of childhood cerebral palsy, particularly during early pregnancy (gestational weeks 0–3). These associations remained robust across sensitivity analyses and showed a positive trend with cumulative exposure throughout gestation.
Trombley J. Fine particulate matter exposure and pediatric mental health outcomes: An integrative review. J Nurs Scholarsh. 2023;55(5):977–1007.	The studies were conducted in United States (5), England and Wales (4), China (3), Denmark (2), Taiwan (1), South-Korea (1), and Sweden (1)	Is exposure to fine particulate matter (PM2.5) potentially correlated with poor mental health outcomes among children and adolescents aged 18 or younger?	Integrated review: included studies covered both children and adolescents, with sample sizes ranging from 130 to over 1,4 million participants.	Evidence suggests a possible association between early-life exposure to fine particulate matter and the development of autism in children, particularly during the first three years of life/ Findings for ADHD were mixed.
Brumberg HL, Karr CJ. Ambient air pollution: Health hazards to children. Pediatrics. 2021;147(6),	United States	What are the health hazards of ambient air pollution for children?	Policy commentary and review of multiple studies; national-level data.	Summarizes multiple systematic reviews showing that prenatal and postnatal exposure to traffic-related air pollution (TRAP) and PM2.5 increases the risk of autism spectrum disorder (ASD), ADHD, and lower cognitive function. Identifies oxidative stress, inflammation, endocrine disruption, and epigenetic changes as biological pathways linking pollution to neural injury.
Payne-Sturges DC, Marty MA, Perera F, Miller MD, Swanson M, Ellickson K, et al. Healthy Air, Healthy Brains: Advancing Air Pollution Policy to Protect Children's Health. Am J Public Health. 2019;109(4):550–4	United States	Effect of combustion-related air pollution on neurodevelopment in children.	Policy commentary and review of diverse US cohorts: includes epidemiological and animal studies.	Combustion-related air pollutants (PM2.5, NO_2, PAHs) are linked to reduced IQ, developmental delays, ADHD, and structural brain changes. Climate change exacerbates exposure via wildfires and heat.
Nunhes ML, Cunha AJLA. Neurodevelopment and climate change. J Pediatr. 2025;101: S34–S9.	Brazil	Impact of climate change on neurodevelopment and mental health in children and adolescents.	Narrative review based on recent literature and global data.	Climate change affects neurodevelopment through air pollution–induced neuronal loss, glial inflammation, and altered microbiota, linking these to ADHD, autism, and anxiety. Vulnerable groups (e.g. children, Indigenous communities) are disproportionately affected. Early life exposure is critical.
Malaspina D, Howeel EA and Spicera J. Intergenerational Echoes of Climate Change. JAMA Psychiat. 2020;77(8):778–80.	United States	How do extreme temperatures during pregnancy affect neurodevelopment and psychiatric risk in offspring?	Narrative review of >40 studies.	Prenatal exposure to extreme heat or cold increases risk of adverse pregnancy outcomes and long-term psychiatric disorders. Effects are amplified in low-resource urban areas due to heat islands and lack of access to cooling. Climate change may perpetuate intergenerational health inequities.
Veras MM, Saldiva PHN. Impact of air pollution and climate change on maternal, fetal and postnatal health. J Pediatr. 2025;101: S48–S55.	Brazil	What are the effects of air pollution and climate change on gestation, fetal development and postnatal health?	Narrative review of 86 systematic reviews.	Neurodevelopment is negatively influenced by prenatal and early life exposure to air pollution. Changes in structural morphology and impairments on intellective functioning, memory and learning, attention and executive functions, verbal language, numeric ability, and motor and/or sensorimotor functions are also affected.
Perera F. Pollution from Fossil-Fuel Combustion is the Leading Environmental Threat to Global Pediatric Health and Equity: Solutions Exist. Int J Environ Res Public Health. 2017;15(1).	United States	Review the data on the health impacts of fossil fuel pollution, highlighting the neurodevelopmental impacts and describe available means to achieve a low-carbon economy.	Commentary review.	Emphasizes synergistic effects between air toxics and climate change, identifying epigenetic and neuroinflammatory mechanisms as pathways of damage to the developing brain.
Yu T, Zhou L, Xu J, Kan H, Chen R, Chen S, et al. Effects of prenatal exposures to air sulphur dioxide/ nitrogen dioxide on toddler neurodevelopment and effect modification by ambient temperature. Ecotoxicol Environ Saf. 2022;230.	China	What are the effects of prenatal exposure to SO2 or NO2 on toddler neurodevelopment and the effect-modification by ambient temperature.	A prospective birth-cohort with a total of 184,546 parents or guardians of children.	Prenatal increased exposure to SO2 and NO2 from industrial, transportation, and building sources was strongly associated with higher odds of ADHD symptoms (ORs 1.79–5.71, p<0.001). This association was stronger in boys, children younger than 12 years of age, those exposed to passive smoking, and those who were non-breastfed.
Bonthrone AF B, Piyasena C, Counsell SJ. The Effects of Climate Change on Children's Health. Pediatr Clin North Am. 2025;72(5):991–1001.	United States	What are the neurodevelopmental and educational sequelae of climate change on children?	Narrative review of 84 articles.	Rising ozone and particulate matter levels (linked to climate change) worsen asthma and indirectly affect oxygen delivery to the brain, which can impair cognitive development. Children exposed to floods, wildfires, and heat experience higher rates of PTSD, anxiety, and depression. The importance of food security after birth is evidenced by studies documenting that malnutrition during infancy and childhood is associated with less favourable neurodevelopmental outcomes.
Buthman JL, Bernmanhia T, Huang JY, Huang P, Miller JG, Uy JP, et al. Exposure to Fine Particulate Matter During Pregnancy Is Associated with Hippocampal Development in Offspring. BP: GOS. 2025;5(4):100490.	Singapore	Does prenatal exposure to fine particulate matter (PM2.5) affect hippocampal volume development in children from early to middle childhood, and is this related to later emotional or behavioural problems?	Cohort study with 325 mother-child dyads.	Late gestational PM2.5 exposure (weeks 36–40) was associated with slower bilateral hippocampal volume growth from ages 4.5 to 10.5 years in 325 children (Singapore GUSTO cohort). Faster right-hemisphere hippocampal growth predicted more externalizing and attention problems at age 10, reflecting neurobehavioral dysregulation.
Kidd SA, Gong J, Massazza A, Bezgrebelna M, Zhang Y, Hajat S. Climate change and its implications for developing brains - In utero to youth: A scoping review. J Clim Change Health. 2023;13.	Netherlands	What are the major considerations of the peer-reviewed literature that address climate change as it relates to brain development and health from early development through to youth populations?	Scoping review of 40 articles, with an upper age limit 24 years.	Changing climate patterns and weather extremes have substantial and wide-ranging effects on developing brains. These relationships occur within complex systems with both direct (e.g., hyperthermia, brain injury) and indirect (e.g., vector borne illness, malnutrition) effects, indexing as a function of the weather variables involved and geographic contexts alongside population, socioeconomic, and cultural characteristics. It is a consistent observation that individuals and populations lacking resources and experiencing inequities, as in other climate-health impact relationships, have the poorest outcomes.
Padmanabhan S, Tharan O. Impact of Climate Change on Neurodevelopmental Disorders in Pediatrics. J Res Appl Sci Biotechnol. 2024;3(1):368–82.	United States	What are the causal mechanisms by which climate change impacts neurodevelopmental disorders in children, what are the related health consequences, and what protective and policy strategies can mitigate these effects?	Narrative review with articles about children. No specific sample size is reported.	The review identifies several neurodevelopmental outcomes linked to climate-related environmental stressors: - ADHD and learning disabilities associated with air pollution (PM2.5, ozone). - Autism spectrum disorder (ASD) linked to exposure to heavy metals (mercury, lead) and phthalates. - Developmental delays related to pesticide exposure and heat stress. - Behavioural and emotional issues resulting from psychosocial stressors (displacement, food insecurity, family stress).
Yu Hg. Effects of extreme temperature on childhood cognitive development: evidence from China. Educ Econ. 2024.	China	What are the long-term effects of extreme temperature during infancy on school-aged children's cognitive development in China?	Quantitative, observational study using longitudinal survey data of 2894 children aged 10-16 years, born between 1995-2011, across 159 counties in China.	One additional low-temperature day during infancy lowers word test score by 0,2 points and math test score by 0,1 points. Boys are more affected by moderately cold days (-5-0°C), while girls are more affected by severely cold days (<-5°C). Children in southern China and those from unsupportive home environments are more vulnerable. Gender-specific mechanisms include physiological vulnerability in boys and gender-biased resource allocation disadvantaging girls.
Briker S, Tran KT, Visoki E, Gordon JH, Hoffman KW, Barzilay R. Association Between Extreme Heat and Externalizing Symptoms in Pre- and Early Adolescence: Findings from the ABCD Study. J Am Acad Child Adolesc Psychiatry. 2025;3(3):713–24.	United States	What are the associations between extreme heat and externalizing symptoms or suicidal behaviour among US preadolescents?	Longitudinal cohort (N= 8,120, mean age 9.89 years).	Each increase in days ≥90°F is significantly associated with higher externalizing symptom counts (aggression, impulsivity, hyperactivity) in U.S. children aged 9–12 (N=8,120). Importantly, the association remained significant when covarying for individual demographics and multiple geocoded neighbourhood characteristics.

Paper	Country	Research purpose/question	Research type and population (sample size)	Important findings
Zundel CG, Ely S, Brokamp C, Strawn JR, Jovanovic T, Ryan P, et al. Particulate Matter Exposure and Default Mode Network Equilibrium During Early Adolescence. Brain Connect. 2024;14(6):307–18.	United States	What is the impact of particulate matter (PM2.5) on resting-state functional connectivity (rsFC) of the default mode network (DMN) and three key attention networks: dorsal attention, ventral attention, and cingulo-opercular?	Longitudinal cohort with 9–10-year-old children (n = 11,876) and caregivers.	PM2.5 exposure was associated with disrupted maturation of the default mode network (DMN) and attention networks, both crucial for cognitive and emotional regulation.
Webb D. Critical Periods in Cognitive and Socioemotional Development: Evidence from Weather Shocks in Indonesia. Econ J. 2024;134(660):1637–65.	Indonesia	What are the critical periods during childhood when weather shocks affect long-term cognitive and socioemotional development in rural Indonesia?	Quantitative, longitudinal observational study with >30,000 children born between 1988-2000.	There is a critical period the age of 2 where exposure to adverse weather conditions (drought or excess rainfall) leads to significant declines in adult cognitive ability. Poor early nutrition is linked to reduced dendritic growth and myelination, aligning with recognized neurobiological pathways of developmental impairment.
Assari S, Zare H. Extreme Heat Exposure Is Associated with Higher Socioeconomic Disadvantage and Elevated Youth Delinquency. J Soc Mat Hum Eng Sci. 2024;3(1):15–28.	United States	What are the association between extreme heat exposure and delinquency among children and what are the potential mediating roles of neighbourhood socioeconomic status?	Cross-sectional study with participants that were 9-10 years old at baseline. (n=11 878).	Exposure to extreme heat is associated with increased individual delinquency among children. This can be attributed to several factors, including physiological stress responses to heat, which can impair cognitive functioning and self-regulation. Mental health may also worsen under heat extremes.
Parenteau AM, Hang S, Swartz JR, Wexler AS, Hostinar CE. Clearing the air: A systematic review of studies on air pollution and childhood brain outcomes to mobilize policy change. Dev Cogn Neurosci. 2024;69.	United Kingdom	Synthesize empirical evidence linking outdoor air pollution to brain outcomes in children.	Systematic review of 40 studies, which included measures of air pollution and brain outcomes at various points in development.	Air pollution exposure is associated with a range of structural brain alterations in children, including alterations in cortical thickness and surface area, white matter volume, and subcortical volume. Associations between pollution exposure and structural MRI measures are specific to the region examined, the type of pollutant, and the timing of exposure. Air pollution exposure is associated with alterations in brain metabolites, although no consistent associations with certain metabolites have been detected. Large studies have linked air pollution exposure to childhood CNS tumour incidence. Early development (e.g., prenatal period, early childhood) appears to be a vulnerable window of exposure. The pollutants of most concern seem to be PM2.5 and traffic-related pollutants.
Assari S, Zare H. Extreme Heat Exposure and Adolescent Cognitive Function. Open J Neurosci. 2025;3(1).	United States	What is the association between extreme heat exposure and cognitive outcomes among 9–10-year-old children?	Cross-sectional study with participants that were 9-10 years old at baseline. (n=11 878).	Children exposed to extreme heat had slightly lower cognitive function scores, even after adjusting for other factors.
Assari S, Zare H. Extreme Heat Exposure is Associated with Lower Learning, General Cognitive Ability, and Memory among US Children. Open J Neurosci. 2025;3(1):10–22.	United States	What is the relationship between extreme heat exposure and various domains of cognitive function in children.	Cross-sectional study with participants that were 9-10 years old at baseline. (n=11 878).	Extreme heat exposure is significantly associated with lower learning, memory, and general cognitive ability in U.S. children (ages 9–10).
Assari S, Najand B, Zare H. Heat Exposure Predicts Earlier Childhood Pubertal Initiation, Behavioral Problems, and Tobacco Use. Glob J Epidemiol Inf Dis. 2025;5(1).	United States	Does exposure to extreme heat predict earlier pubertal onset in children, and is early puberty associated with behavioural problems and tobacco use?	Cross-sectional study with participants that were 9-10 years old at baseline. (n=11 878).	This study highlights a significant association between extreme heat exposure and early puberty initiation at ages 9–10, with subsequent links to behavioural problems and tobacco use.
Anderko L, Pennea E. Climate Changes Children's Health: Improving Clinical Practice to Address Changing Health Needs. J Nurse Pract. 2022;18(4):395–8.	United States	Translate evidence on climate change impacts on children into anticipatory guidance for pediatric nurse practitioners.	Clinical review of studies with children and adolescents in pediatric care.	Links climate stressors (heat, floods, wildfire smoke, CO_2) to asthma, allergies, vector-borne disease, neurodevelopmental and mental health effects.
Granes L, Essers E, Ballester J, Petricola S, Tiemeier H, Iniguez C, et al. Early life cold and heat exposure impacts white matter development in children. Nat Clim Change. 2024;14(7).	Netherlands	Does exposure to cold and heat during early life affect white matter microstructure in children?	Longitudinal cohort study of children from the Generation R birth cohort (n = 2681).	Cold exposure during pregnancy and infancy, and heat exposure during infancy and toddlerhood, are associated with reduced myelination. No associations were found for FA. Children in low SES neighbourhoods were more vulnerable.
Bellanger M, Demeneix B, Grandjean P, Zoeller RT, Trasande L. Neurobehavioral Deficits, Diseases, and Associated Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union. J Clin Endocrinol Metabol. 2015;100(4):1256–66.	EU (France, Denmark, US authorship)	To estimate the neurodevelopmental burden and economic costs in Europe that can be reasonably attributed to exposure to endocrine-disrupting chemicals (EDCs).	Quantitative model + expert panel synthesis.	EDC exposures in Europe contribute substantially to neurobehavioral deficits and disease, with a high probability of €150 billion costs/year.
Denicola N, Lasher E, Bakenra A, Joglekar R, Zhang J, Hasenburg A, et al. FIGO committee opinion: Environmental drivers of obstetric health and early childhood development. Int J Gynecol Obstetr. 2025.	Global, FIGO (International Federation of Gynaecology and Obstetrics)	To provide a comprehensive synthesis of scientific evidence on how environmental toxicants—including air pollution, endocrine-disrupting chemicals (EDCs), heavy metals, and climate-related stressors—affect reproductive, perinatal, and early childhood outcomes.	Systematic review	Prenatal air pollution exposure (especially PM2.5 and NO_2) is consistently linked to autism spectrum disorder and cognitive impairment. Heavy metals (lead, mercury, cadmium) remain potent prenatal neurotoxins causing lifelong deficits.
Lafortune S, Laplante DP, Elgbeili G, Li X, Lebel S, Dagenais C, et al. Effect of Natural Disaster-Related Prenatal Maternal Stress on Child Development and Health: A Meta-Analytic Review. Int J Environ Res Public Health. 2021;18(16).	Canada	To quantify the effects of prenatal maternal stress (PNMS) caused by natural disasters on multiple domains of child development and health.	Meta-analytic systematic review of 37 studies (qualitative synthesis), 30 studies (meta-analysis).	Prenatal stress disrupts neurodevelopment. Consistent deficits in cognitive, motor, socio-emotional, and behavioural domains mirror the adverse neurodevelopmental outcomes observed in climate-stress-affected populations.
American College of Obstetricians and Gynaecologists, Practice GCoO. Reducing Prenatal Exposure to Toxic Environmental Agents: ACOG Committee Opinion, Number 832. Obst Gynae. 2021;138(1): e40–e54.	USA	To integrate more recent literature regarding reducing prepregnancy and prenatal toxic environmental exposures.	Clinical guidance document, no defined sample size.	Consistent deficits in cognitive, motor, socio-emotional, and behavioural domains mirror the adverse neurodevelopmental outcomes observed in climate-stress-affected populations.
Lin L-Z, Chen J-H, Yu Y-J, Dong G-H. Ambient air pollution and infant health : a narrative review. eBioMedicine. 2023;93.	China	To summarize recent evidence on how ambient air pollution affects infant health outcomes, including prenatal and early postnatal exposures.	Systematic review, no defined sample size.	Prenatal exposure to $PM_{2.5}$ and NO_2 is associated with lower psychomotor, cognitive, and language scores at 15–24 months.
Yu T, Zhou L, Xu J, Kan H, Chen R, Chen S, et al. Effects of prenatal exposures to air sulphur dioxide/ nitrogen dioxide on toddler neurodevelopment and effect modification by ambient temperature. Ecotoxicol Environ Saf. 2022;230.	China	To determine how prenatal exposure to sulphur dioxide (SO_2) and nitrogen dioxide (NO_2) affects toddler neurodevelopment, and to examine whether ambient temperature modifies these effects.	Prospective birth cohort study with 225 mother–child pairs.	Elevated prenatal exposure to ambient sulphur dioxide (SO_2) and nitrogen dioxide (NO_2) was linked to poorer neurodevelopmental outcomes in early childhood. The sensitive periods of vulnerability appeared to occur during the first and third trimesters for SO_2, and primarily during the third trimester for NO_2. Moreover, temperature acted as an effect modifier, as lower average temperatures throughout pregnancy intensified the adverse influence of SO_2 exposure on toddlers' language acquisition and adaptive behaviour development.
Conroy RM, Golden J, Malone C. Rethinking professional boundaries: The climate crisis and brain health. BJPsych Bull. 2025;49(1).	Ireland	How does the climate crisis—particularly air pollution—impact brain health, and what professional and disciplinary shifts are needed within healthcare to address this challenge effectively?	Conceptual and advocacy-oriented editorial. No primary data or specific population studied.	Noise pollution (from transport) is associated with poorer cognitive performance and school attainment in children. Exposures in utero to fine particulate matter and nitrogen dioxide are associated with deficits in cognitive and psychomotor development in children. These effects are evident as early as 15 months.
Polemiti E, Hese S, Schepanski K, Yuan J, Schumann G. How does the macroenvironment influence brain and behaviour—a review of status and future perspectives. Mol Psychiatry. 2024;29(10):3268–86.	Germany and China	To provide a comprehensive overview of the existing evidence between the macroenvironment and the structure and functions of the brain, with a particular emphasis on its implications for mental illness.	Systematic narrative review	Air Pollution is associated with structural brain changes, linked to increased risk of depression, anxiety, schizophrenia, and cognitive decline. Prenatal and early-life exposure affects neurodevelopment (e.g., corpus callosum, limbic system, prefrontal cortex). High temperatures and humidity are associated with increased risk of depression, anxiety, suicide, and mental health-related hospitalisations. Extreme weather events (e.g., floods, droughts) linked to PTSD, depression, and anxiety. Limited neuroimaging evidence: simulated heat exposure linked to altered activation in PFC and impaired cognitive performance
Landrigan PJ, Fuller R, Fisher S, Suk W, D Sly PD, Chiles TC, et al. Pollution and children's health. Sci Total Environ. 2019; 650:2389–94.	United States	Comprehensive analysis of pollution and its effect on human health and global economy.	Review of articles which included children (0-19 years old).	Environmental pollution is a major contributor to child mortality. Notably, two-thirds of these fatalities occurred in children under the age of five. The burden of pollution-related mortality is disproportionately borne by low- and middle-income countries, which account for approximately 92% of these deaths. The primary causes are respiratory and gastrointestinal illnesses, largely resulting from exposure to polluted air and contaminated water sources. Beyond acute disease, pollution has also been increasingly linked to a growing number of non-communicable diseases (NCDs) in children, reflecting a concerning upward trend in chronic health conditions. Addressing pollution through preventive strategies presents a significant opportunity to reduce disease burden and promote healthier developmental outcomes in children worldwide.

This section provides a concise overview of the associations identified between these climate-related factors and child neurodevelopment.

Air pollution

At the neuroanatomical level, the hippocampus appears particularly vulnerable to air pollution. Prenatal exposure to PM2.5 during the third trimester has been associated with reduced hippocampal volume growth. Altered hippocampal development may have behavioural consequences; for example, a larger right hippocampal volume has been linked to increased externalizing symptoms around age of ten (2).

Prenatal and postnatal exposure to traffic-related air pollution and PM2.5 has also been associated with higher risks of autism spectrum disorder, attention deficit/hyperactivity disorder (ADHD), and lower IQ. Several mechanisms have been proposed to explain these effects. Prenatal PM2.5 exposure is linked to decreased levels of synapsin I, a synaptic protein essential for neurotransmitter release, potentially disrupting neural communication (5-8). Attention and behavioural difficulties may also arise from altered maturation of the default mode network and attention networks, both critical for cognitive and emotional regulation (9).

Beyond cognitive functions such as memory and learning, motor and sensorimotor abilities have also been shown to be adversely affected by air pollution exposure (10,11).

Although more research is needed, evidence from a London-based longitudinal cohort indicates that increases in outdoor ozone exposure may impair executive function development in adolescence (12). Importantly, rising levels of ozone and particulate matter, exacerbated by climate change, can worsen respiratory conditions such as asthma and reduce oxygen availability to the brain, further compromising cognitive development (13).

Extreme temperatures

Heat exposure during early development, particularly from the second trimester of pregnancy to seven months postpartum, has been associated with poorer language outcomes in young children (14). Even heat exposure during the very early prenatal period (weeks 0-3) has been linked to an increased risk of cerebral palsy (15).

In a U.S. cohort of 8,120 children aged 9–12 years, it was found that a higher number of days with temperatures above 32.2 °C was linked to an increase in externalizing behaviours (16). Exposure to extreme heat has also been linked to higher levels of individual delinquency and tobacco use among children, potentially due to physiological stress responses that impair cognitive functioning and self-regulation (17,18). Altered prefrontal cortex activation and reduced cognitive performance may offer additional explanatory pathways (19). Furthermore, extreme heat exposure has been associated with reduced learning, memory, and overall cognitive performance in children aged 9-10 years (20,21). Not only heat but also cold temperatures during pregnancy and the postnatal period has been associated with reduced myelination (22).

Natural disasters

Natural disasters constitute a major climate-related stressor affecting neurodevelopment through both direct physiological stress mechanisms and indirect pathways, such as disrupted nutrition, housing instability, and reduced access to healthcare. Adequate nutrition in the postnatal period is essential, and early childhood malnutrition is strongly linked to adverse neurodevelopmental outcomes (13). A critical developmental window appears to be around age two, when exposure to drought, flooding, or other extreme weather events can have long-term neurocognitive consequences, including reduced cognitive abilities in adulthood. Insufficient nutrition during this period may impair dendritic formation and myelination, key processes supporting healthy neurodevelopment and learning (23).

In addition to nutritional deficits, the psychosocial stressors associated with natural disasters, such as displacement, food insecurity, and heightened family stress, have been linked to emotional and behavioural difficulties in affected children (24).

Endocrine disrupting chemicals

EDCs, including phthalates, bisphenols and per- and polyfluoroalkyl substances (PFAS), can interfere with thyroid hormone signalling, a process essential for normal brain maturation. Environmental shifts associated with climate change, such as rising temperatures and extreme weather events like floods and heatwaves, may further increase human exposure to these compounds. EDC exposure has been shown to trigger neuroinflammation, oxidative stress, and epigenetic alterations, ultimately disrupting neurodevelopment and impairing cognitive functioning. According to the FIGO Committee Opinion, exposure to EDCs contributes substantially to the burden of neurobehavioral disorders in Europe, with societal costs estimating to exceed €150 billion annually (6,25).

Discussion

The objective of this review was to map the existing evidence on the effects of climate change on neurodevelopment. The literature indicates that several climate-related domains, including temperature changes, air pollution, and natural disasters, affect neurodevelopment through multiple biological and psychosocial pathways. A consistent finding across studies is that individuals with lower socioeconomic status and limited resources are disproportionately affected by climate change and its neurological consequences. Although climate change encompasses various subdomains, we restricted our focus to studies explicitly addressing “climate change”. This strategy enabled a coherent overview of its diverse impacts, while acknowledging that some relevant studies may not have been captured, for example, those focusing exclusively on “air pollution” or “heat waves”. Given the broad scope of the topic, narrowing the search to climate change terminology also reduced the total number of articles requiring screening.

Another important consideration is that the term “neurodevelopment” is interpreted variably across studies. While it may refer to anatomical brain development or developmental disorders, some authors include broader mental health outcomes. Articles that addressed mental health without linking outcomes to brain development or climate-related exposures were therefore excluded. Likewise, we did not include specific diagnostic terms such as “autism” or “ADHD”, which likely resulted in the omission of certain relevant publications.

It is also essential to recognize that climate change represents only one of many environmental factors influencing neurological development. Exposure to toxic chemicals, plastics, light and noise pollution, urbanization, socioeconomic disadvantage, and reduced access to green spaces can all significantly affect brain development (6). As discussed above, climate change may exert substantial effects on neurodevelopment, contributing to increased psychological, social and economic burdens for children and society. These impacts should be considered in future policymaking, with particular attention to vulnerable populations who bear the greatest risk. Further research, both international and locally focused, is necessary to strengthen the evidence base. For instance, in Belgium, it would be valuable to investigate whether climate change-related exposures are associated with differences in the prevalence of neurodevelopmental disorders between urban and rural regions. Such findings could guide policy and resource allocation.

In conclusion, climate change is likely to have long-term consequences for child development, extending beyond physical health to influence cognitive functioning, social participation, and overall well-being.

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

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Infectious Diseases Threats in a Changing Climate

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Keywords
Climate Change ; Communicable Diseases, Emerging ; Waterborne Diseases ; Foodborne Diseases ; Vector-borne Diseases ; Europe.

Abstract
Background
Factors related to human activity, such as international travel, globalisation, trade, urbanisation and the disruption of ecosystems and biodiversity, have a significant impact on the epidemiology of infectious diseases. Climate change is an additional factor which often amplifies this impact. It is estimated that climate change has exacerbated over half of all infectious diseases worldwide, contributing to 60–80% of emerging infectious diseases.

Objective:
The aim of this narrative review is to provide a concise overview of infectious disease threats linked to climate change, with a focus on Europe.

Methods:
A literature search was conducted in PubMed using the keywords 'climate change', 'infectious diseases' and 'Europe', with results limited to publications from the last 5 years. Additional information was obtained from the websites of the European Centre for Disease Prevention and Control, the European Commission, the European Food Safety Authority, the World Health Organization, the US Centers of Disease Control and Prevention, and Google Scholar.

Results:
The eco-epidemiology of existing and emerging infectious diseases in Europe is impacted by global warming, changing rainfall patterns and extreme weather events resulting from climate change, either directly or indirectly. This article reviews the risk of a new pandemic and of waterborne, foodborne, vectorborne diseases.

Conclusion:
The eco-epidemiology of infectious diseases is complex and influenced by various factors, including climate change. A coordinated, multisectoral approach is required from a One Health perspective to ensure proactive preparedness.

Introduction

Climate change includes rising global temperatures, shifting precipitation patterns, an increased number and intensity of heat waves, as well as more frequent extreme weather events, such as floods, droughts, wildfires and storms. Climate change will continue at least through this century and probably far beyond (1). Since the 1980's Europe has been warming twice as fast as the global average, making it the fastest warming continent on earth (2).

Climate change is a major additional factor that modifies and usually amplifies the influence of other human-activity-related factors on the eco-epidemiology of infectious diseases. These factors include international travel, globalisation, trade exchange, deforestation, land use, close interaction with livestock, population growth, urbanisation and migration. Together with biodiversity loss, climate change, is an important driver of the spread, emergence and persistence of infectious diseases (3, 4). It is estimated that 58% of all infectious diseases reported to have impacted humanity worldwide have been exacerbated by climate change, particularly waterborne and vector-borne diseases (5). Furthermore, it is estimated that 60–80% of newly emerging diseases are of zoonotic origin (6).

The two most important climate factors influencing the emergence of infectious diseases are temperature and precipitation (7). It is estimated that the mean annual temperature in Europe may increase by between 2 and 7°C by 2100. Annual mean precipitation is projected to increase in the north and decrease in the south. Northern and Central Europe are likely to experience more frequent and intense extreme precipitation events (8). Southern Europe is projected to experience more frequent and prolonged droughts, higher risk of wildfires, and increased pressure on water resources.

Although climate change is not the only factor, it is assumed that it can have a direct and indirect influence on the epidemiology of infectious diseases (5, 7-10). Direct influences include extreme weather events, such as outbreaks following water contamination after heavy rainfall or flooding, foodborne infections due to food spoilage during heatwaves, the geographic expansion of pathogens and vectors, increased pathogen replication and transmission. Indirect influences include population displacement or migration due to water and food insecurity, or conflicts. Increased indoor activity and overcrowding also facilitate the spread of airborne or diarrhoeal diseases.

Nevertheless, the most significant global threat is the potential emergence of a new pandemic, which may be influenced by climate change.

Methods

A literature search was conducted in PubMed using the keywords 'climate change', 'infectious diseases' and 'Europe', with results limited to publications from the last 5 years. Additional information was obtained from the websites of the European Centre for Disease Prevention and Control, the US Centres of Disease Control and Prevention the European Commission, the European Food Safety Authority, the World Health Organization, and Google Scholar. Following an initial selection, 364 records were retained, and 90 after the final selection.

Pandemic threat

While any pathogen X could initiate a new pandemic, the WHO believes that a respiratory influenza virus is the most likely candidate (11, 12). The genome of the influenza virus, which consists of eight separate RNA segments, is susceptible not only to mutations during replication but also to segment exchange during co-infection with two different virus strains, potentially creating a new virus. If this new virus can transmit between humans, it has the potential to cause a pandemic. Airborne respiratory pathogens have a significant advantage in terms of speed and extent of transmission. Respiratory manoeuvres like coughing or sneezing can spread thousands of infectious respiratory particles (IRPs). Depending on their size and environmental conditions these IRPs can remain suspended for a long time and can be carried by air currents (13). They can infect many individuals without direct contact with the primary source. The risk of transmission is particularly high in crowded or poorly ventilated spaces. Moreover, in a globalised world, everyone is only a plane ride away from each other (14).

Pandemics often start with pathogen transmission from animals to humans. The highly pathogenic type A H5N1 avian influenza virus is currently a source of great concern.

At the end of the 1990s, an H5N1 epidemic broke out in poultry in Asia, likely introduced by migrating wild birds. The virus was capable of crossing species and infecting humans who were in close contact with sick poultry, causing severe illness with a high mortality rate. However, human-to-human transmission was rare. Since the end of the 2000s, the virus has spread to other continents. Next, it expanded its host range, likely due to adaptive mutations in viral proteins that facilitate infection of terrestrial and marine carnivorous mammals. These animals become infected by ingesting infected birds or through exposure to a contaminated environment (15-17). Mammal-to-mammal transmission was observed in 2022 among farmed minks in Spain. A second larger fur farm outbreak (71 farms) occurred in 2023 in Finland that affected mink, arctic foxes and raccoon dogs. The same year, large numbers of sea lion carcasses washed up on beaches along the coasts of Peru and Chile when the H5N1 avian influenza virus outbreak in marine mammals surged (18). The first confirmed detection of H5N1 avian influenza in U.S. dairy cattle was announced in 2024 (19, 20). As of 28 July 2025, the infection has been detected in 1,063 herds across 17 states. It is believed that the cows became infected via feed contaminated with faeces from migrating wild birds. Disease symptoms in cattle are usually mild. Bovine-to-bovine spread occurs within herds. There is also evidence that the virus can spread from dairy cattle premises to nearby poultry facilities. In November 2024, the H5N1 virus was detected in two pigs on a farm where poultry and livestock were mixed, representing the first time the virus had been found in US swine. Between March 2024 and October 2025, the United States reported 70 human infections with highly pathogenic avian influenza H5N1, including two children (21). Of these, 41 were linked to exposure to infected dairy cattle, 24 to commercial poultry, 2 to backyard poultry, and 3 to unidentified sources of exposure. While symptoms were generally comparable to classic flu symptoms, serious illness has occurred and one infected person with underlying health conditions has died. So far, no cases of human-to-human transmission have been observed in the U.S..

The ability of the H5N1 virus to spread across species demonstrates both its remarkable adaptability and the serious threat it poses as a potential source of the next pandemic, underscoring the urgent need for a One Health (an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems) approach. Climate change may amplify this risk by altering the migration patterns and behaviours of wild birds, disrupting ecosystems, and bringing humans and animals into closer contact — conditions that facilitate viral adaptation and interspecies transmission. In addition, rising temperatures and humidity fluctuations can influence human behaviour, indoor crowding, and the environmental persistence of IRPs, further shaping the dynamics of disease spread.

Waterborne infections

Heavy rainfall and flooding

Pluvial and fluvial floods are the most common types of natural disaster in Europe (22), and these are expected to become more frequent across all European regions (23). In 2024, Europe experienced its most extensive flooding since 2013. Beyond the immediate risk of injury or drowning, exposure to hazardous chemicals, infrastructure loss, and long-term psychological and economic consequences, floods also increase the risk of infectious diseases. Flooding is associated with waterborne, rodent-borne and vector-borne diseases, which typically occur sequentially over time. Floodwater-borne infections typically occur acutely (0–7 days), rodent-borne infections in the mid-term (1–4 weeks), and vector-borne infections in the longer term (4 weeks to several months) (24). The greatest risk to children is posed by floodwater-borne gastrointestinal infections and vector-borne infections.

> Extreme rainfall on 14 and 15 July 2021 caused flooding in Belgium, Luxembourg and Germany. The worst-hit areas were western Germany and eastern Wallonia in Belgium, particularly the provinces of Liège and Luxembourg. 31,563 households were flooded in 209 municipalities, affecting more than 100,000 people, and there were 37 deaths and 6 missing persons (25, 26).
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> The Walloon health officer conducted a retrospective analysis of the impact of flooding on a number of targeted notifiable diseases. Covid-19 (the pandemic was still happening), legionellosis, leptospirosis and Shiga toxin-producing *Escherichia coli* (STEC). Although underreporting occurred due to an overwhelming workload and communication difficulties for practitioners, as well as limited access to primary care for the population, an increase in reports of all these diseases was observed in the weeks following the flood.
>
> A cluster of 10 STEC cases was identified. 6 children (range 2 – 17 years) developed a haemolytic uremic syndrome (27). Surveillance questionnaires linked the infection to contaminated tap water.

Floodwater-borne infections result from the contamination of water supplies with animal or human excreta carried in soil washed away by flooding and/or from malfunction or destruction of sewage systems.

In general, flooding increases the risk of gastrointestinal infections, including bacterial infections caused by *Campylobacter* spp., *Escherichia coli* (including Shiga toxin-producing *E. coli*), *Salmonella* enterica serotypes, and Shigella spp.; viral infections caused by norovirus, rotavirus, and hepatitis A virus; and parasitic infections caused by *Cryptosporidium* spp. and *Giardia lamblia* (25). Children are particularly vulnerable to severe disease progression and complications arising from gastrointestinal infections. Contaminated water can also lead to contamination of food. Malfunction or destruction of distribution lines, as well as cooling and cooking systems, can contribute pathogen transmission via food. In addition, population displacement and overcrowding in temporary shelters increase the risk of infection transmission.

A lack of garbage collection and management increases the rodent population, thereby raising the risk of leptospirosis. Rodents shed *Leptospira* in their urine, and flooding prevents it from being absorbed into the soil or evaporating. *Leptospira* can then persists in the water or mud (25). Humans may become infected through contact with contaminated water or mud via mucous membranes or damaged skin, or by drinking contaminated water or inhaling small droplet nuclei. Warm and humid conditions also promote the *Leptospira* survival (28).

Stagnant water left behind after flooding promotes mosquito breeding, potentially increasing the risk of mosquito-borne diseases. This risk also depends on the presence of pathogens in human and non-human reservoirs, as well as the competence of mosquito vectors (i.e., their ability to harbour and transmit a pathogen). For example, West Nile virus (WNV) is transmitted by Culex species mosquitos, whereas dengue and chikungunya are transmitted by Aedes species. Heavy rainfall and floods in Europe have already been associated with WNV outbreaks (Czech Republic) and chikungunya cases (France) (29, 30). As the geographical range of the tiger mosquito (Aedes albopictus) in Europe steadily expands, along with cases of imported and locally transmitted dengue and chikungunya, flooding may further promote the expansion and risk of these diseases.

Flooding can also increase the risk of *legionellosis*. Floodwaters may disperse Legionella bacteria from their natural habitat, depositing them in soil or sediment. Humans can become infected through aerosols generated when cleaning these areas, for example with high-pressure jet cleaners. Damage to water supply infrastructure may further elevate the risk of infection.

Risks related to the increase in global temperature

Pathogens can contaminate freshwater bodies - lakes, ponds, rivers, streams, canals or artificial reservoirs - through direct release of sewage or wastewater, or via excreta from livestock or wild animals washed in by rain. Pathogens may also infiltrate groundwater through soil fertilised with organic fertilisers or via seepage from contaminated surface water. In Europe, 60–70% of soils are degraded, and 62% of freshwater bodies are in poor ecological condition (2). Apart from industrial pollution, the main pressures on surface and groundwater come from the use of fertilisers and pesticides in agriculture. Furthermore, nitrogen and phosphorus fertilisers stimulate bacterial growth and replication. Climate change can increase pressure on farmers to use more fertilizers and pesticides. Rising global temperatures also promote the development of bacteria such as *Salmonella* and *E. coli*, *Leptospira*, *Legionella* and toxin-producing cyanobacteria, as well as the survival of protozoa such as *Cryptosporidium* oocysts. A major concern is the evidence linking climate change to the development and spread of antimicrobial resistance (31-34).

Freshwater bodies are commonly used for recreational activities such as swimming, boating, and fishing. During longer and warmer summers, recreational freshwater activities are likely to increase, along with the bacterial load in contaminated water, thereby raising the risk of waterborne infections. Drinking water can be extracted from either groundwater or surface water. The main challenges in ensuring the safety of public drinking water systems are water purification, disinfection, storage, and distribution. Biofilms often form in old, corroded metal or rough-walled concrete pipelines. These consist of various bacteria and fungi, including *Pseudomonas aeruginosa*, non-tuberculous *Mycobacteria*, *Legionella* and *Aspergillus fumigatus*, even in chlorinated drinking water. Higher temperatures, especially in summer, increase biofilm formation and microorganism concentrations (35-37). Biofilms and *Legionella* are often associated with infections linked to public drinking water (38). Infections from private drinking water supplies, such as wells or springs, are typically caused by enteric pathogens — bacteria, viruses, or protozoa — present in contaminated groundwater or surface water.

Due to climate change and the resulting increase in sea surface temperatures, the risk of vibriosis in coastal waters is rising, particularly during warm periods.

> An eleven-year-old boy is on holiday at a holiday park near the Oosterschelde estuary. As it is a hot summer, he goes swimming and plays in the water every day. One day, he steps on a sharp shell and gets a small cut on his ankle. However, this didn't stop him from continuing to play in the water. The next morning, his ankle was red, swollen and painful, and he had a fever of 39°C. Fortunately, the doctor who examined him was aware of the presence of *Vibrio* spp. in the waters of the Oosterschelde and recognised a potential *Vibrio* wound infection with cellulitis. Given the potential severity of *Vibrio* infections, she decided to hospitalise him. A blood sample and a swab of the wound were taken for culture and he was started on intravenous antibiotics (ceftriaxone plus ciprofloxacin). Three days later, the wound culture tested positive for *Vibrio alginolyticus*, which is known to cause milder disease. He was discharged on a course of oral ciprofloxacin.

Vibrio spp. are naturally found in brackish coastal waters where saltwater and freshwater mix. They are traditionally detected during the summer in the Baltic Sea, where the lower salinity favours their growth. Such conditions are becoming increasingly common in other parts of Europe due to climate change. *Vibrio* spp. have been found in other regions, including the North Sea, and their range is expected to expand to additional coastal areas (39). These are non-cholera *Vibrio* spp., such as *V. vulnificus*, *V. parahaemolyticus* and *V. alginolyticus*. *V. vulnificus* can cause septicaemia, severe wound infections and diarrhoea; *V. parahaemolyticus* can cause diarrhoeal disease following the consumption of seafood; and *V. alginolyticus* can cause wound infections and otitis externa. A 2012 study by the National Reference Centre in Belgium (Centre

Hospitalier Universitaire de Liège) also demonstrated the presence of *Vibrio* in recreational waters, particularly in the northern part of the country (40).

Foodborne infections

Contamination of food with pathogenic microorganisms can occur at any point along the food chain. At the production stage, pathogens may originate from animal faeces, contaminated soil or water. At the processing stage, improper handling or cross-contamination can introduce pathogens. At the distribution stage, poor temperature control can augment pathogen replication. At the retail stage, poor hygiene practices and cross-contamination further increase the risk. Finally, during food preparation, undercooking and improper hygiene can contribute to the presence of pathogenic microorganisms.

Many of the pathogens that cause foodborne infections are transmitted from animals to humans. In Europe, in 2023, the five most frequently reported zoonoses were all foodborne: campylobacteriosis, salmonellosis, yersiniosis, listeriosis, as well as infections caused by Shiga toxin producing *E.coli* (STEC) (41). For these five bacteria combined, 247574 cases of foodborne infections were reported in 2023, representing a 12.5% increase compared to 2022 (220089 cases) and a 22.3% increase compared to 2021 (202446 cases). Foodborne infections can lead to outbreaks of severe diarrhoea, with children being particularly vulnerable. We could not find any figures on the number of children with foodborne infections in Europe. According to the WHO, 30% of foodborne infection-related deaths occur in children worldwide (42).

Rising global temperature, along with more frequent heat waves and heavy rainfall linked to climate change, threaten food security. Higher global temperatures can stimulate the replication and/or survival rates of bacteria in the environment and in food (e.g. *Salmonella*, *E. coli* and *Campylobacter*), and can also accelerate toxin production by toxin-producing bacteria (e.g. *Staphylococcus aureus* or STEC) (43, 44). A warmer climate may additionally expand the geographic range of certain pathogens, such as *Vibrio* spp. in seafood.

Prolonged hot summers or heatwaves can lead to water shortages. When water is scarce, untreated wastewater may be used for irrigation, contaminating crops (43, 45). Such wastewater often contains high levels of enteric bacteria and protozoa, including *Giardia lamblia* and *Cryptosporidium*, as well as viruses such as hepatitis A virus, norovirus and rotavirus. Extended periods of high temperatures or heatwaves can also place considerable strain on the cold chain. Overall, prolonged heat and heatwaves driven by climate change represent a significant risk factor for foodborne infections.

The consequences of heavy rainfall have already been discussed.

Models predict that foodborne infections and outbreaks will increase in Europe - particularly in the central and southern regions – driven by higher temperatures and more frequent extreme weather events (43, 44).

Arthropod vector-borne infections

The recent emergence of 'tropical' vector-borne diseases in Europe is a captivating phenomenon. The vectors - *Aedes albopictus* (the tiger mosquito) and, to a lesser extent, *Aedes aegypti* – along with the pathogens they harbour - dengue, chikungunya and Zika viruses – have been introduced to the continent through human travel and global trade. Climate change has created increasingly favourable conditions for the establishment and spread of arthropod vectors, like mosquitoes, ticks and sandflies, by altering the habitat and life cycle. This has facilitated their geographical expansion towards higher latitudes and altitudes (46, 47).

Rising temperatures accelerate vector development and reproduction, increase population density, biting rates, and human contact, and shorten the intrinsic incubation period of pathogens, all factors that elevate the risk of human disease (28, 46, 48). However, temperature increases also have limitations. Optimal conditions for the development of pathogens and vectors are relatively narrow; for example, *Ae. albopictus* transmits dengue and chikungunya most efficiently at daily average temperatures of 24–26 °C, though transmission can occur between 12–30 °C (49). As a result, the future spread of vector-borne diseases may differ from the current situation and predictions (10, 50).

Table 1 provides an overview of current arthropod-borne diseases in Europe (51).

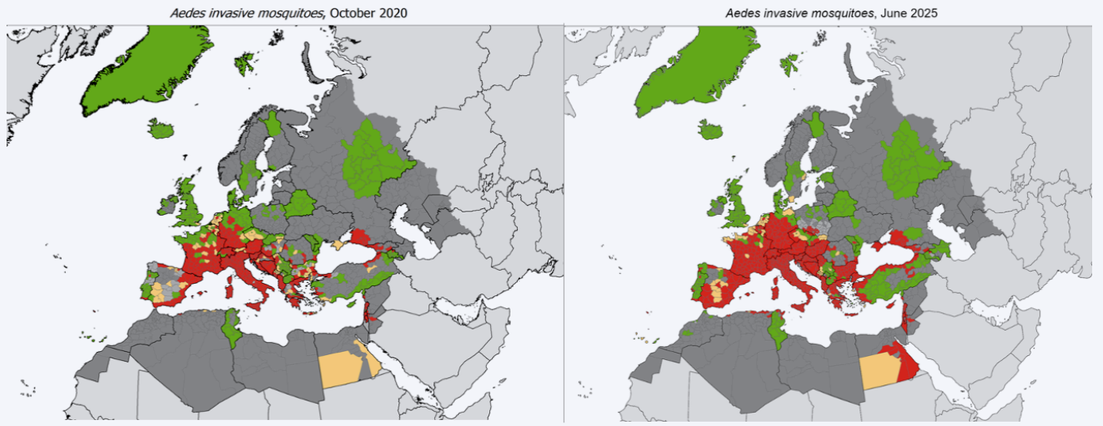
The European Centre for Disease Prevention and Control (ECDC) defines an invasive vector species as 'introduced' when it has been detected without evidence of established populations, and as 'established' when there is evidence of reproduction and overwintering. *Aedes* mosquitoes are now established and introduced in a large part of Europe (Figure 1) (52). Northern Europe is relatively spared but climatic projections suggest that *Ae. albopictus* will expand in the coming decade. These mosquitoes are both diurnal and nocturnal, adapted to urban and inhouse environments. Vertical transmission of the dengue virus - and probably the chikungunya and Zika viruses - from infected female mosquitoes to their offspring has been documented (53). Once infected, these mosquitoes remain infectious and are capable of transmitting the virus to multiple individuals. Additionally, European species can survive winter by hibernating as eggs in diapause (54).

TABLE 1: Overview of the most current arthropod-borne diseases in Europe.

Disease	Vector	Pathogen	Main host reservoir	Reported cases in EU/EEA in 2023 [x]
Dengue virus disease	*Aedes* spp. mosquito	*Orthoflavivirus (4 serotypes)*	Humans	5510
Chikungunya	*Aedes* spp. mosquito	*Alphavirus*	Humans	337
West Nile virus disease	*Culex* spp. mosquito	*Flavivirus*	Birds	742
Zika virus disease	*Aedes* spp. mosquito	*Flavivirus*	Humans	80
Malaria	*Anopheles* spp. mosquito	*Plasmodium spp.*	Humans	7245
Tick borne encephalitis	*Ixodes* spp. ticks	*Flavivirus*	Small rodents	3578
Lyme neuroborreliosis	*Ixodes* spp. ticks	*Borrelia spp.*	Small rodents	1497
Lyme disease (non-neurological)	*Ixodes* spp. ticks	*Borrelia spp.*	Small rodents	No registration
Leishmaniasis	*Phlebotomus* spp. sandflies	*Leishmania spp.*	Dogs and rodents	No registration

x European Centre for Disease Prevention and Control. Surveillance Atlas of Infectious Diseases. 2023 (EU/EEA = European Union and European Economic Area)

FIGURE 1: Expansion of the Aedes mosquitoes in Europe over five years, from October 2020 to June 2025. Red = established, yellow = introduced, green = absent. Source: ECDC invasive mosquito maps, available from https://www.ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/invasive-mosquito-maps.



Mosquito-borne diseases

> A seven-year-old girl was admitted to Cesena Hospital (Emilia-Romagna, Italy) at the end of summer 2007 with a persistent high fever (40°C) for three days. She reported severe pain, particularly in her lower limbs, which prevented her from walking or sleeping. Clinical examination revealed a rash on her face, but no other specific abnormalities. A week earlier, her grandfather had experienced a high fever, joint pain, epigastric pain and vomiting, all of which resolved spontaneously within a few days. One month before, at the end of June, an imported case of chikungunya had been reported in a traveller returning from Kerala, India (55). The first locally acquired case was reported at the beginning of August. Ultimately, 330 locally acquired cases of chikungunya were notified to public health authorities, including 12 in children and adolescents up to 19 years of age, with the girl being one of them (56). PCR testing of her blood confirmed the presence of the virus.

This first large outbreak of autochthonous chikungunya warned us of the potential for invasive vectors and pathogens to become established in temperate climates when conditions are favourable.

Most chikungunya cases in Europe also involve travellers infected abroad. However, local outbreaks are increasing: Italy reported 330 and 270 cases in 2007 and 2017; and in 2025, France and Italy recorded 700 and 353 indigenous cases, respectively (57). Climatic conditions likely contributed: experienced wetter-than-average conditions in March 2025 and a hotter, longer summer, creating favourable conditions for mosquitoes (58). While direct attribution to climate change is uncertain, the transmission of chikungunya by *Aedes albopictus* has increased by 46.3% since the mid-20th century (59).

Chikungunya typically causes a sudden high fever, vomiting, muscle pain, a maculopapular rash and often severe joint pain. However, compared to adults, joint involvement is less frequent in children. Instead, neurological manifestations such as headaches, altered sensorium and irritability are more common. Prolonged, debilitating inflammatory arthritis, a common complication in adults, is less common in children (60).

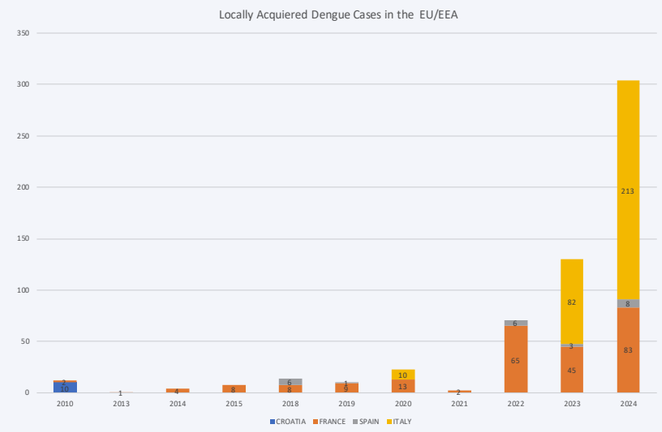
Dengue is the fastest-spreading mosquito-borne disease worldwide (4). Climate suitability for dengue transmission, measured by the basic reproduction number (R_0), has increased significantly for both *Ae. albopictus* and *Ae. Aegypti*, by 46.3% and 10.7% respectively, between 1951–1960 and 2016–2023 (59). The risk of dengue rose by approximately 13% for each 1°C increase in temperature (28). A study has estimated that, by the end of the century, half of the world's population could be at risk of contracting dengue fever (61).

Most dengue virus infections are asymptomatic. If symptoms are present, dengue typically presents with a sudden high fever, severe headache, retro-orbital pain, muscle and joint pain, nausea, vomiting, rash and haemorrhagic manifestations. In severe cases, it can progress to dengue haemorrhagic fever, which is characterised by plasma leakage and may progress to dengue shock syndrome. Importantly, infection with one serotype provides no lasting immunity against the others (there are 4 serotypes). Reinfection with a different serotype is possible and often results in more severe illness, making secondary infections a major public health concern.

Globally, children are the age group most affected by dengue. The younger the child, the more serious the disease. Children are at greater risk of developing symptoms, haemorrhagic dengue fever with plasma leakage and shock. Dengue has a higher mortality rate in children (62-64).

Dengue is not currently endemic in Europe ; most cases are travel-related, with 9603 cases reported in the EU/EEA (European Union / European Economic Area) in 2024, representing all four dengue virus serotypes (51, 65, 66). Where *Aedes* mosquitoes are established, viraemic travellers can trigger local transmission, leading to sporadic cases or outbreaks. Over the past 15 years, the majority of locally acquired cases have been reported in France, Italy and Spain. As Figure 2 illustrates, the number of cases has steadily increased, suggesting that sporadic local outbreaks may be evolving into a substantial and growing arboviral threat.

FIGURE 2: Number of locally acquired dengue cases in Europe.



As of today, the majority of cases of Zika virus disease in Europe are travel-related. Only three autochthonous, vector-borne cases have been reported in France, all in 2019 (67). A modelling study, assuming competence of the European *Ae. albopictus* population for transmitting the Zika virus, identified potential areas for autochthonous transmission, including Italy, southern France, the southern and eastern coasts of Spain, the western regions of the Balkans, and southern and northern Greece (68). However, it is now believed that European *Ae. albopictus* mosquitoes are relatively less competent at transmitting the Zika virus (67). But things might change.

About 25% of people infected with the Zika virus experience clinical symptoms, which include low-grade fever, conjunctivitis, maculopapular rash and arthralgia of the small joints. The virus has neurotropic properties and has been associated with Guillain-Barré syndrome, myelitis and meningoencephalitis. The virus is notorious for causing microcephaly and developmental disorders in babies following intrauterine infection. The course in children infected postnatally is similar to that in adults.

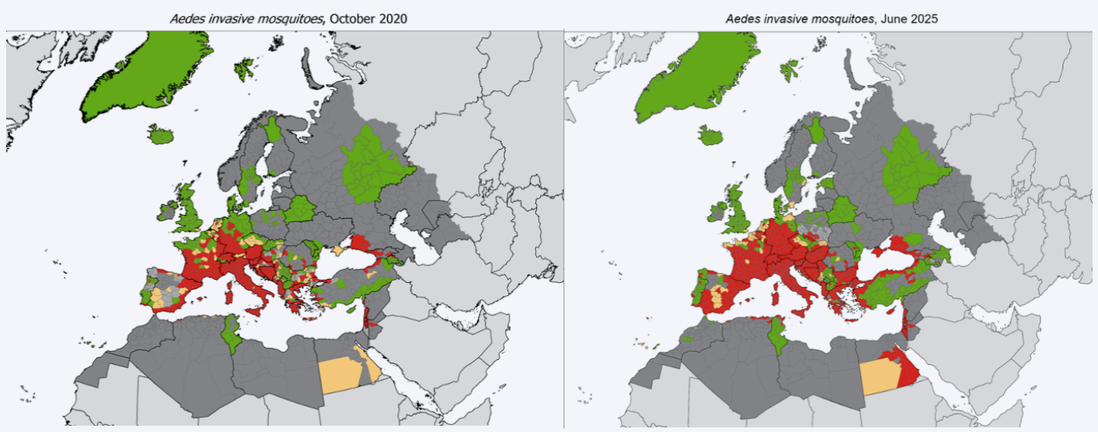
West Nile virus (WNV) is the most widely distributed arbovirus globally. The virus is transmitted by *Culex* spp., a mosquito species native to Europe. Birds are the primary hosts. but humans and other mammals, particularly horses, can be infected by a mosquito bite. In humans, infection is asymptomatic in approximately 80% of cases. Symptomatic infections may present as West Nile fever, a febrile illness, or as West Nile neuroinvasive disease, which affects the central nervous system and can present as meningitis, encephalitis or acute flaccid paralysis. Meningitis is more frequent in children than in adults (69). The circulation of WNV in Europe has been detected since the 1950s. In 2025, Belgium reported three WNV outbreaks in wild birds to the EU Animal Diseases Information System (ADIS) for the first time ever (70). Notably, infected birds are often identified before human cases, highlighting their role as sentinels for virus circulation (10).

Rising temperatures and altered rainfall patterns are facilitating the northward expansion of mosquito vectors, as illustrated for the *Culex pipiens* group in Figure 3. At the same time, migratory birds are shifting their wintering and breeding grounds further north and adjusting their migration routes, aiding the virus's geographical spread. Higher temperatures also promote WNV genetic diversification and adaptation, enhancing transmission potential (71). As a result, the virus's basic reproduction number (R_0) increased by 4.3% in the 2014–2023 period compared with 1951–1960 (59).

According to US Centers for Disease Control and Prevention (CDC) data, WNV is less commonly reported in children than in adults (5%) (72). However, given the many prolonged outdoor activities that children engage in during the summer months, they are also at risk of infection. As infection often presents asymptomatically and WNV may not be systematically considered in cases of "viral meningitis" during the summer months, the true incidence may be underestimated.

Malaria is one of the five leading causes of death in children worldwide (73). Malaria is strongly influenced by climate change,

FIGURE 3: Expansion of *Culex pipiens* group mosquitoes in Europe between 2020 and 2023. Red = present, green = absent. Source: ECDC. Native mosquitoes maps, available from: https://www.ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/native-mosquito-maps.



which affects mosquito vector distribution and expands suitable transmission zones. Since the mid-20th century, an additional 17.1% of global land has become suitable for *Plasmodium falciparum* transmission and 21.8% for *Plasmodium vivax* (28, 59).

Malaria was once endemic in Europe. Native *Anopheles* mosquitos can still transmit malaria, and although most current cases are travel-related, a few locally acquired 'airport malaria' cases have occurred (74, 75). If conditions become favourable, malaria could re-establish local transmission cycles, but it remains impossible to predict whether it will become endemic again in Europe.

Tick-borne diseases

Climate change - particularly in terms of temperature, rainfall and humidity - affects the geographic distribution and behaviour of ticks. Shifts and expansions to higher latitudes (northwards) and altitudes have already been reported (76, 77). Shorter winters and longer springs and autumns further extend the period of tick activity (3, 78). Rising temperature and humidity also increase tick biting rates and enhance oviposition and larval survival (46). Tick abundance is additionally influenced by host availability, which is shaped by land use and land-use changes, including human outdoor activity, agricultural and livestock practices, and deforestation.

> In May 2024, a six-year-old girl presented with a six-day history of fever, diarrhoea and myalgia. Initial clinical and blood tests revealed mild thrombocytopenia, leukopenia and elevated creatine kinase levels. No clear cause of the fever was identified. The fever subsided after three to four days.
>
> Four days later, the fever recurred and she had arthralgia. She was admitted to hospital. Blood tests were normal, but meningeal signs developed on day 4, with cerebrospinal fluid (CSF) analysis showing leukocytosis. Intravenous cefotaxime was initiated. After seven days, tick-borne encephalitis virus (TBEV) IgM was detected in her CSF. Her symptoms resolved and she was discharged with no residual effects. A follow-up brain MRI scan showed no abnormalities. This is the first reported case of locally acquired TBEV infection in a child in Belgium (79). Three autochthonous adult cases had been described in 2021 (80).

Ticks transmit a broad range of pathogens, including viruses, bacteria and parasites. *Ixodes ricinus* is the most widespread tick in Europe (Figure 4) and the primary vector for *Borellia burgdorferi* sensu lato, which causes Lyme disease and neuroborreliosis, as well as for tick-borne encephalitis virus (TEBV), a *Flavivirus* (76). Tick-borne encephalitis is characterised by a biphasic fever. During the first phase, symptoms such as fever, tiredness, arthralgia, myalgia, headache and gastrointestinal symptoms predominate. Following an afebrile period of approximately seven days, the fever recurs with neurological manifestations. Nevertheless, two-thirds of infected individuals are not symptomatic, and some exhibit only the initial phase..

The second most common tick in Europe is *Dermacentor reticularis*, a vector for various pathogens including *Coxiella burnetti* (Q-fever) and *Ricktesia* spp. (tick-borne lymphadenopathy) (81). The ECDC also monitors *Hyalomma marginatum*, a vector for the Crimean-Congo haemorrhagic fever (CCHF) virus, a *Bunyavirus*. This thick is widely distributed across North Africa and Asia and is present in southern and eastern Europe. CCHF virus considered an emerging pathogen in Europe (82).

Sandfly-borne diseases

Different sandfly species can transmit *Leishmania* spp. parasites. *Leishmania* is an obligate intracellular parasite that infects macrophages. The species present in Europe belong to the so-called 'Old World' group. *L. major, L. tropica* and *L. aethiopica* cause cutaneous leishmaniasis, which is the mildest form and presents as painless nodules or ulcerative lesions. *L. aethiopica* can also cause mucocutaneous disease, characterised by destructive lesions of mucous membranes and cartilage in the nose, mouth, and pharynx. The most severe form, visceral leishmaniasis, is caused in Europe by the parasite *L. donovani infantum* and manifests with intermittent fever, anaemia, hepatosplenomegaly, and weight loss (83). Because of its non-specific systemic symptoms and cytopenias, visceral leishmaniasis is often initially mistaken for haematological malignancy.

The main reservoir of *Leishmania* in Europe is domestic dogs, although a range of other animals - including rodents, horses, birds and reptiles - can also harbour the parasite (28). The continued spread of *Leishmania* across European countries has been facilitated in part by the frequent and largely uncontrolled movement of infected pet dogs, but human migration from endemic regions may also contribute to the parasite's spread (8). Children and young adults appear to be at the greatest risk of infection.

Leishmaniasis is endemic in southern Europe (84). In Europe most *Phlebotomus* sandfly species are distributed in around the Mediterranean basin, although *P. perniciosus* is also found in parts of France and Germany (see VectorNet phlebotomine sandfly maps (85)). Sandflies are thermophilic, thriving in environments where average temperatures consistently exceed 15°C (83). As a result, global warming is expected to influence their distribution, potentially making more northern regions increasingly suitable for their establishment. In recent years, sporadic locally acquired cases of leishmaniasis have been reported in central European countries, including Germany, Austria, and England.

Personal protection measures against arthropod vector- borne diseases

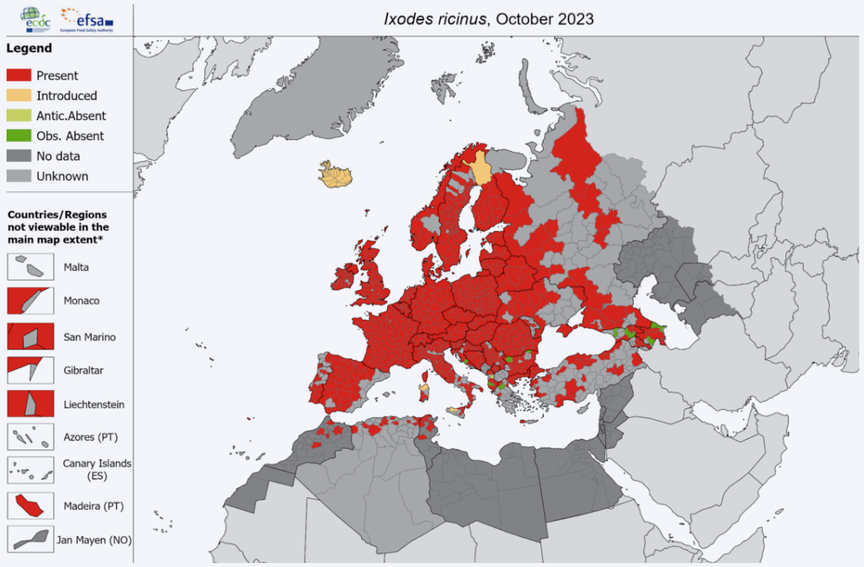
Personal protection against arthropod vectors generally includes wearing clothing that minimises exposed skin, applying insect repellents outdoor, and, when appropriate, using insecticides and impregnated bed nets indoors. Reducing mosquito breeding sites in residential areas is also essential measurement in vector control; this involves eliminating standing water in items such as buckets, uncovered rain barrels, plant saucers, and clogged gutters.

Vaccines are recognized as a critical tool for climate adaptation strategies. Immunisation protects against several climate-sensitive infectious diseases, strengthens health system resilience and serves as an important enabler of climate adaptation, particularly for vulnerable communities (86). Currently, licensed vaccines exist for several climate-sensitive diseases, including tick-borne encephalitis (TBE), dengue, chikungunya. TBE vaccine is an inactivated virus, whereas the dengue and chikungunya vaccines are live attenuated virus vaccines. Each vaccine has specific indications (for example, dengue vaccination is recommended only for children aged six years and older with confirmed previous dengue infection) which are out of the scope of this article but guidance on vaccine indications can be consulted on the website of the Institute of Tropical Medicine in Antwerp (www.wanda.be) or in the Superior Health Council Vaccination Reports (87).

Conclusion

The eco-epidemiology of infectious diseases is increasingly influenced by changes in human behaviour, including urbanisation, travel, land use changes, biodiversity loss and climate change.

FIGURE 4: Distribution of *Ixodes ricinus* in Europe. Source: ECDC. Tick maps, available from: https://www.ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/tick-maps.



These changes together increase the risk of diseases caused by both indigenous and introduced pathogens, the emergence of antimicrobial resistance, and potential pandemic outbreaks. While infectious disease threats linked to these changes affect everyone, children—especially the youngest—are the most vulnerable, not only because of their heightened biological susceptibility but also because they will be exposed to the evolving consequences of a changing climate for many more years.

A concerted One Health approach is imperative to address this serious threat. The WHO defines One Health as an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. In July 2021, the WHO established the One Health Initiative to coordinate the adoption of the One Health approach in national, regional, and international health policies (88). The EU and Belgium are collaborating on this initiative. The one health approach includes, for example, implementing interdisciplinary collaboration and data sharing, enhancing surveillance of diseases, vectors and pathogens and incorporating climate data. It also implies the need for shared research agendas on the impact of biodiversity loss on health. Policies should be implemented to control and prevent vector-borne diseases, for example through vector control strategies and vaccine development and administration. At the level of paediatricians, climate change issues should be integrated into medical education and training. Paediatricians could educate parents and children about the health risks associated with climate change issues. When working with vulnerable families, climate change should be integrated into practice by asking about housing and food storage issues, and the availability of safe water and by providing anticipatory guidance (89, 90).

Let us hope that we can help make the world a safer place for children.

Statements

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

Artificial intelligence (AI): Le Chat – Mistral AI was used to formulate suggestions (with source references) for detailed questions that arose during the writing process. DeepLwrite was used when there was doubt about English syntax or word choice. ChatGPT was used to improve language.

Due to the large number of references and the limited page count of the printed journal, the editors have decided to publish the references only in the online version. This is available via the journal's website https://belgjpaediatrics.com. The article can also be found on Google Scholar (https://scholar.google.com/).

Prix public	
4mg / ml	
50 ml	€ 16,49
180 ml	€ 22,06

DÉNOMINATION DU MÉDICAMENT : Tiorfix nourrissons et enfants 4 mg/ml suspension buvable. **COMPOSITION QUALITATIVE ET QUANTITATIVE** : Racécadotril 4 mg. Chaque ml de suspension buvable contient 4 mg de racécadotril. Le flacon de 50 ml contient 168 mg de racécadotril, correspondant à 112 doses-kg. Le flacon de 180 ml contient 660 mg de racécadotril, correspondant à 440 doses-kg. Chaque dose-kg correspond à 1,5 mg/kg/dose. Excipients à effet notoire : Chaque dose-kg de suspension buvable contient : 1,13 mg de benzoate de sodium, 0,84 mg de sodium, 225 mg de saccharose et 1,06 mg de propylène glycol. Pour la liste complète des excipients, voir rubrique 6.1 du Résumé des caractéristiques du produit (RCP). **FORME PHARMACEUTIQUE** : Suspension buvable. Suspension de couleur blanche à blanc cassé. **INDICATIONS THÉRAPEUTIQUES** : Tiorfix nourrissons et enfants 4 mg/ml est indiqué en complément de la réhydratation orale et des mesures diététiques dans le traitement symptomatique des diarrhées aiguës du nourrisson et de l'enfant de plus de 3 mois et pesant 7 kg et plus, lorsque la réhydratation orale et les mesures diététiques seules ne suffisent pas à contrôler l'état clinique et lorsqu'un traitement causal n'est pas possible. Si un traitement causal est possible, le racécadotril peut être administré en traitement complémentaire. **POSOLOGIE ET MODE D'ADMINISTRATION** : Tiorfix nourrissons et enfants 4 mg/ml est administré par voie orale en association avec une réhydratation orale (voir rubrique 4.4 du RCP). **Posologie :** Population pédiatrique : *Réservé au nourrisson et à l'enfant de plus de 3 mois et pesant de 7 kg à 52 kg* : La posologie usuelle est établie en fonction du poids corporel de l'enfant. Elle est de 1,5 mg/kg/prise (qui correspond à une dose-kg). Le premier jour : une première prise d'emblée puis selon l'heure de la première prise, jusqu'à un maximum de 3 prises réparties dans la journée, en comptant dans ces 3 prises la première prise d'emblée. Les prises doivent se faire de préférence au début des trois principaux repas. Les jours suivants : 3 prises réparties dans la journée, de préférence au début des trois principaux repas. La posologie journalière maximale est de 3 prises. Le médicament s'administre au moyen d'une seringue pour administration orale (graduée en kg de poids corporel) qui délivre une dose de 1,5 mg de racécadotril par graduation indiquée en kg. Pour chaque prise : • Nourrissons et enfants jusqu'à 26 kg : remplir la seringue jusqu'à la graduation indiquant le poids de l'enfant. • Enfants entre 27 et 38 kg : remplir une première fois la seringue jusqu'à la graduation 13 kg et donner la suspension à l'enfant. Puis remplir une deuxième fois la seringue jusqu'à atteindre un total égal au poids de l'enfant et donner à nouveau la suspension à l'enfant. • Enfants entre 39 et 52 kg: remplir une première fois la seringue jusqu'à la graduation 26 kg et donner la suspension à l'enfant. Puis remplir une deuxième fois la seringue jusqu'à atteindre un total égal au poids de l'enfant et donner à nouveau la suspension à l'enfant. • Au-delà de 52 kg, il convient d'utiliser des formes pharmaceutiques plus adaptées. Durée du traitement : Le traitement sera poursuivi jusqu'au retour de deux selles moulées consécutives, sans dépasser 7 jours. Aucune étude clinique n'a été menée chez les nourrissons de moins de 3 mois. **Mode d'administration :** Voie orale. 1 : Agiter vigoureusement le flacon pour homogénéiser la suspension avant l'emploi. 2 : Ouvrir le flacon en tournant et en appuyant sur le bouchon sécurité-enfant. 3 : Introduire à fond la seringue dans l'embout de prélèvement. 4 : Pour remplir la seringue, tenir le flacon « tête en bas » ; bien maintenir la seringue en place et tirer doucement et régulièrement le piston jusqu'**à la graduation nécessaire en kg**. 5 : Remettre le flacon « tête en haut » et retirer la seringue. 6 : Introduire la seringue dans la bouche de l'enfant sans enfoncer et administrer la totalité de la suspension en appuyant doucement et progressivement sur le piston. Après chaque utilisation, démonter la seringue pour administration orale, la rincer à l'eau et la sécher. L'usage de cette seringue pour administration orale est strictement réservé à l'administration de Tiorfix nourrissons et enfants 4 mg/ml. Populations particulières : Aucune étude n'a été menée chez les enfants souffrant d'insuffisance hépatique ou rénale (voir rubrique 4.4 du RCP). **CONTRE-INDICATIONS :** Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP. **EFFETS INDÉSIRABLES :** Les essais cliniques conduits sur Tiorfix granulés pour suspension buvable, une autre forme pharmaceutique pour nourrissons et enfants au cours de la diarrhée aiguë ont fourni des données de sécurité d'emploi chez 860 nourrissons et enfants traités par du racécadotril et 441 traités par du placebo. Les effets indésirables présentés dans la liste ci-dessous ont été observés plus fréquemment avec racécadotril qu'avec placebo au cours des essais cliniques ou ont été rapportés pendant la période de commercialisation. Les effets indésirables sont repris selon les classes principales de systèmes d'organes MedDRA. Au sein de chaque classe de systèmes d'organes, les effets indésirables sont présentés par fréquence. Au sein de chaque groupe de fréquence, les effets indésirables sont présentés par ordre décroissant de gravité. La fréquence des effets indésirables a été définie selon la convention suivante : très fréquent (≥ 1/10), fréquent (≥ 1/100, < 1/10), peu fréquent (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000), très rare (< 1/10 000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Des réactions cutanées indésirables graves (SCAR), notamment des syndromes d'hypersensibilité médicamenteuse avec éosinophilie et symptômes systémiques (DRESS), ont été rapportées avec le traitement par racécadotril (voir rubrique 4.4 du RCP). Infections et infestations : Peu fréquent : amygdalite. Affections de la peau et du tissu sous-cutané (voir rubrique 4.4 du RCP) : Peu fréquent : rash, érythème. Fréquence indéterminée : urticaire, angioœdème (œdème de Quincke), œdème de la langue, de la face, des lèvres ou des paupières, érythème polymorphe, érythème noueux, rash papuleuse, prurit, prurigo, toxidermie, syndrome d'hypersensibilité médicamenteuse avec éosinophilie et symptômes systémiques (DRESS). Affections du système immunitaire : Fréquence indéterminée : choc anaphylactique. **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, www.afmps.be. Division Vigilance : Site internet : www.notifieruneffetindesirable.be – e-mail : adr@fagg-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 :** Bioprojet Pharma, 9 rue Rameau, 75002 Paris, France. **NUMÉRO(S) D'AUTORISATION DE MISE SUR LE MARCHÉ :** BE661445. LU : 2024080213 – 0964282 (50 ml) – 0964296 (180 ml). **MODE DE DÉLIVRANCE** : Médicament sur prescription médicale. **DATE DE MISE À JOUR DU TEXTE :** 04/2024. Version 06/2024_2

1. Lehert P. et al., Digestive and Liver Disease 2011; 43. 707-713 - **2.** Baumer et al. Effects of acetorphan, an enkephalinase inhibitor, on experimental and acute diarrhoea, Gut, 1992, 33, 753-758
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065-09-2025 BEFR, Septembre 2025

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In Our Own Backyard: An Unusual Case of Atraumatic Purpuric Rash in a School-Aged Girl

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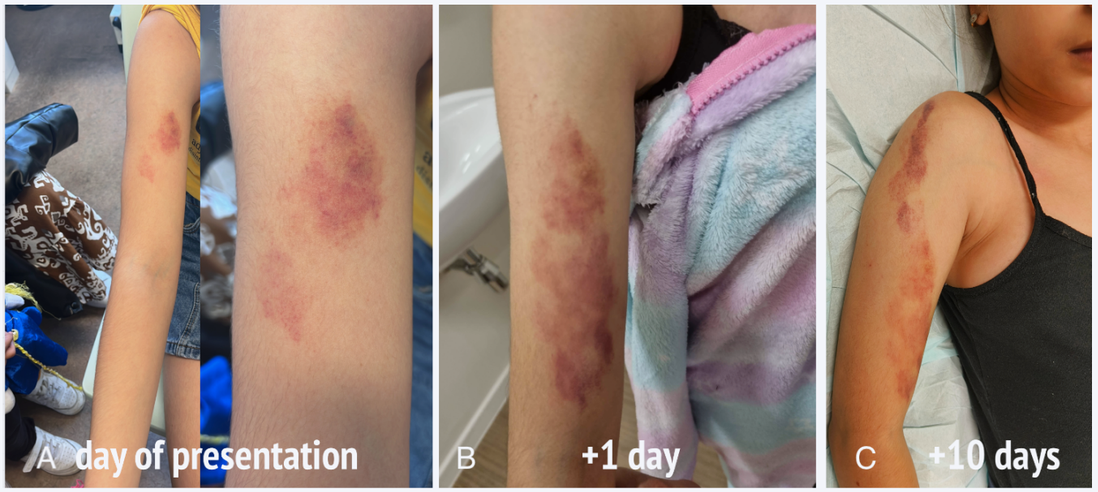
Keywords
Purpura, muscle weakness, venoms, autochthonous acquisition.

Pictures of the rash on the upper arm on the day of presentation (A), after one day (B), and after ten days (C).



A 10-year-old girl presented to our outpatient clinic with a 3-day history of sudden-onset, atraumatic and worsening pain in her right upper arm, coinciding with an expanding purpuric rash covering her right biceps area. In addition, she experienced loss of strength in her right hand making it difficult, for example, to tie her shoelaces.

She was afebrile, generally well, had no travel history nor notion of any recent insect, tick or spider bite. Past medical history was otherwise unremarkable.

Clinical examination revealed a poorly demarcated non-blanching purpuric rash which expanded over the next few days as shown in figure 1a. At the centre of the lesion a small puncture wound was found which was believed to be a bite or sting mark. Upper limb strength and reflexes were normal and symmetrical although mild allodynia was noted on palpation of the lesion. Because of the reassuring clinical exam and assumed insect bite, the patient was sent home with topical steroids and antiseptics and a follow-up appointment.

The next day she presented to the Paediatric Emergency Department because of expansion of the skin lesions (figure 1b), further clinical exam remained unchanged. At this point, because of the rapid expansion of the lesion, additional work-up was performed: venous doppler ultrasound of the right upper limb including the vena jugularis interna and vena subclavia, was unremarkable without signs of thrombophlebitis or deep venous thrombosis. A complete blood count with differentiation showed no abnormalities except for a marked eosinophilia (1.31 x10E9/L), CRP was < 0.4 mg/dL. APTT/PT were within normal range, as were serum creatinine, sodium, potassium and ALT/AST levels. Glucose-6-phosphate dehydrogenase function was tested and found to be normal.

Because of further expansion of the lesion (figure 1c), a paediatric consultation at a tertiary care hospital combined with a dermatology consult, led to a punch biopsy of the lesion, showing vasodilatation and perivascular oedema with limited lymphocytic infiltration, findings possibly consistent with urticaria or urticarial vasculitis. Additional bloodwork showed absence of antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCAs), with normal complement levels (C3, C4) and normal urine biochemistry.

What is the diagnosis?

The initial presentation in this case, with acute-onset purpuric rash and a central eschar can point to a wide variety of illnesses. In our region, such a presentation is most commonly related to a traumatic event. Nevertheless, atraumatic differential diagnosis includes vasculitides (such as leukocytoclastic vasculitis, Henoch-Schönlein purpura), infectious causes (localized or systemic bacterial or viral illnesses, or rickettsial infection-though rare in Belgium), coagulopathies or thrombosis, and more rarely, an insect bite reaction.

A history of travel, absent in this case, would significantly alter the differential diagnosis and would include viral haemorrhagic fevers, leptospirosis, myiasis, contact dermatitis caused by tropical fauna or flora, and spider bites (particularly from *Loxosceles)*. Rickettsial disease would also be much higher on the list. Although there was no travel history, it was noted that her bedroom window faced a car-tyre transfer facility next door and that the family had noticed a lot of spiders in the house lately. Following a clinical discussion with the experts from the Institute of Tropical Medicine a tentative diagnosis of a *Loxosceles* spider bite was made (with a central eschar visible in figure 1a).

Although the lesion stabilized and diminished over the next four weeks, a flare-up was noted two months later with recurrence of both the skin lesion and the subjective neurologic complaints. Two more flare-ups were noted in the following six months, with good response to colchicine, previously started because of ongoing signs of small-vessel vasculitis.

Loxosceles spiders are not native to Belgium. There are more than 130 species of which *L. reclusa* is most commonly associated with serious envenomation. It has a limited habitat in the Southeast of the US. Other species in Central and South America (Brazil, Argentina, Mexico) are more often linked to necrotic bites. *L. refuscens* is the only species endemic to Europe; its habitat is limited to part of the Mediterranean basin . The effect of its venom in humans is not well characterized; from 1939 onwards, only seven confirmed cases of an *L. refuscens* bite in humans have been reported in literature (1-3). In half of the verified cases of *Loxosceles* bites in humans, systemic effects (such as fever or nausea and even acute renal failure, haemolysis or pulmonary oedema) have been described referred to as viscerocutaneous loxoscelism. Although rare, the venom can have both necrotic and neurotoxic effects, possibly causing the pain and (perceived) muscle weakness in this case. In 75% of cases necrotic lesions of the skin developed with spontaneous healing in around half of them, known as necrotic cutaneous loxoscelism (4). However, it is assumed that the vast majority of bites, especially of *Loxosceles refuscens,* are self-limiting.

As the bite itself is not painful and therefore often unnoticed, it remains a challenge to confirm the diagnosis. Similarly in our patient, the diagnosis of loxoscelism could not be excluded, but it remains unproven. Loxoscelism can only be confirmed if the spider captured at the time of the bite, is identified as a *Loxosceles* species. Without the spider, the diagnosis remains presumptive.

Apart from a challenging diagnosis, treatment remains difficult as well. There is no evidence-based therapy available although studies have examined the use of antivenoms, vaccines, antibiotics and surgical interventions. Current recommendations are to clean the bite wound and apply cold compresses. In addition, there should be adequate pain management, whereas antibiotic administration, corticosteroids and antihistamines can be considered (1, 5). Although symptoms in most cases resolve within 1-8 weeks, chronic- non-healing ulcers or recurrent skin lesions such as vasculitis have been documented.

Loxosceles spiders can easily reside in human buildings, which facilitates their spread by human activities (5). In fact, the role of humans in this highly invasive species' spread beyond its initial natural boundaries appears to be much greater than previously anticipated. In addition, high proportions of spider populations adapt to new climates, possibly facilitated by human urbanization generating favourable microenvironments (4). Recent reports already described a case of Loxoscelism in the north of Italy and in the south of France (1, 6).

Given this, it is easy to think that *Loxosceles* spiders, like the Asian tiger mosquito (cfr. Sciensano surveillance), may be transported via goods like car-tyres from endemic to non-endemic areas such as Belgium (7). Climate change with increasingly mild winters can favour survival of these 'accidental' travellers in non-endemic regions resulting in cases of loxoscelism without an actual travel history in the patient (4).

Statement

The parents of the child gave consent for this case to be published.

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Impact of a Protocol Change on Antibiotic Prescription for Acute Otitis Media in Children: A Retrospective Study in a Belgian Paediatric Emergency Department

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Keywords

Antibiotic Treatment ; Public Health ; Otitis Media

Abstract

Introduction

Acute otitis media (AOM) is a major driver of antibiotic use in children, though most cases are self-limiting. In October 2023, a revised protocol was introduced to align with national antibiotic stewardship guidelines. This study evaluated the impact of the protocol change on antibiotic prescribing and identified factors associated with prescription decisions.

Methods

We conducted a retrospective cohort study of children aged 3 months to 16 years diagnosed with AOM during two six-month periods: before (PRE) and after (POST) protocol implementation. Patients with comorbidities, prior antibiotic use, or incomplete records were excluded. Logistic regression was used to assess the effect of the protocol and clinical variables on systemic and local antibiotic use.

Results

Of 1,868 visits, 1,669 were included (905 PRE, 764 POST). Systemic antibiotic prescriptions decreased significantly from 59.0% to 46.6% ($p < 0.001$). POST-period presentation was associated with lower odds of systemic antibiotic use (OR = 0.59; 95% CI: 0.43–0.81). Factors increasing systemic antibiotic use included younger age and clinical red flags. Five-day treatment courses rose from 16.2% to 45.2%, while delayed prescriptions increased modestly. Overall local antibiotic use remained stable. Older children were more likely to receive local treatment.

Conclusion

The revised protocol significantly reduced systemic antibiotic use and encouraged shorter, more targeted treatments. Further education is needed to limit unnecessary local antibiotic use.

Introduction

Acute otitis media (AOM) is one of the most common paediatric infections and a leading reason for antibiotic prescription in children (1,2). Though typically self-limiting, AOM accounts for a high proportion of unnecessary antibiotic use, contributing to antimicrobial resistance and avoidable side effects (3,4). International guidelines, including those from the Belgian Antibiotic Policy Coordination Committee (BAPCOC) and the World Health Organisation (WHO), have increasingly emphasized watchful waiting and restricted indications for antibiotic therapy in uncomplicated AOM cases (5,6).

Recommendations for immediate antibiotic therapy in children with acute otitis media (AOM) vary across national guidelines. The American Academy of Pediatrics (AAP; USA) recommends antibiotics for all children under 6 months, those with severe symptoms (fever ≥39°C or significant otalgia), otorrhea or bilateral AOM in children under 2 years. The Haute Autorité de Santé (HAS; France) advises antibiotics for all children under 2 years or in case of severe symptoms or otorrhea regardless of age. The National Institute for Health and Care Excellence (NICE, UK) and the Nederlands Huisartsen Genootschap (NHG, The Netherlands) recommend antibiotics for systemically unwell children, and favours observation for those with otorrhea or bilateral AOM in children under 2 years. All guidelines agree on treating severe cases immediately, but differ in age thresholds and how bilateral involvement and otorrhea influence management. A more conservative, watchful-waiting strategy is emphasized in UK and Dutch guidelines compared to the US and French guidelines (7-10).

At the Queen Fabiola Children's University Hospital (HUDERF), the local protocol for AOM management (Appendix 1 and 2) was revised in October 2023 to reflect stricter prescribing criteria and encourage shorter antibiotic courses. Following the BAPCOC guidelines, indications for antibiotic therapy have been limited to patients younger than 6 months, those with comorbidities, or

those presenting with « red flags » (Appendix 3) (5). The duration of treatment has also been reduced to 5 days for all children, and the sole indication for topical antibiotics is in children with tympanostomy tubes and otorrhea. This study aimed to evaluate the impact of protocol change on prescribing behaviour and to identify clinical factors associated with systemic and local antibiotic prescriptions in children presenting with AOM.

The protocol has been revised by the infectious diseases team in collaboration with the ear-nose-throat (ENT) team. The revised protocol was disseminated to all relevant clinicians, including paediatricians, ENT specialists, and residents in paediatrics, emergency medicine, and surgery. Communication took place through multiple channels: the protocol was circulated by email, presented during a departmental "grand tour" meeting, and uploaded to our hospital's online protocol database (ENNOV ®). In addition, a printed version was integrated into the emergency department's (ED) protocol map, which is updated with each new protocol release and systematically reviewed every three months to ensure accuracy and accessibility.

Materials and Methods

Study design and setting:

This was retrospective, non-interventional, monocentric cohort study based on the review of electronic medical records from the paediatric emergency department (ED) of HUDERF (Brussels). Two 6-month periods were analysed: pre-intervention group (PRE; 01/11/2022 to 30/05/2023) and post-intervention group (POST; 01/11/2023 to 30/05/2024).

Our paediatric ED is staffed by a fixed team of paediatric emergency physicians, paediatricians, and general practitioners/family medicine physicians. The resident pool includes emergency medicine residents (general track), paediatric residents, and family medicine residents. Night shifts are covered by residents in emergency medicine, paediatrics, and surgery, under supervision of the attending staff.

In this study, a diagnosis of acute otitis media (AOM) was reserved for children meeting internationally accepted criteria, ensuring that only true AOM cases were included. AOM was defined as the presence of middle ear effusion with signs of acute inflammation, such as a bulging, opaque, or erythematous tympanic membrane, often with visible purulent fluid. Cases presenting with isolated tympanic membrane redness, without effusion or other otoscopic signs of acute infection, were not classified as AOM (7).

Inclusion and exclusion criteria:

Patients aged 3 months to 16 years with a final diagnosis of AOM were included. Exclusions applied to patients with comorbidities (immunodeficiency, craniofacial anomalies, Down syndrome), prior antibiotic use, concurrent infections (e.g., pneumonia, tonsillitis), hospitalization, or incomplete clinical records. Patients below the age of 3 months (90 days) were excluded because they are not included in our local treatment protocol for AOM and are treated according to our fever below the age of 3 months protocol.

Data collection:

For each included patient, demographic data, clinical signs, and prescribing details were extracted. Variables included age, fever duration and intensity, presence of red flags, purulence, bilateral involvement, prescriber type, and antibiotic details (agent, route, duration, delayed vs immediate). Given the retrospective nature of the study, not all clinical variables were documented for every patient (for example, fever characteristics were occasionally missing from the medical record). Patients with missing data were not excluded from the overall cohort but were omitted from specific subanalyses involving the unavailable parameter.

TABLE 1: Demographic and clinical characteristics for both groups.

Factor	n	PRE	n	POST	p
Age (years)	905	2,8 (1,4-4,8)	764	3 (1,4-5,0)	NS
Sex (male %)	905	55,6	764	53,7	NS
Tympanostomy tube (%)	905	1,9	764	2,8	NS
Any fever (%)	891	67	756	61,8	NS
Highest reported fever (°C)	538	39,3 (39,0-40,0)	432	39,3 (38,9-40,0)	NS
Fever duration (h)	556	48 (24-96)	449	48 (24-96)	NS
Otalgia (%)	905	53,4	753	59,5	NS
Unilateral pain (%)	905	43,3	753	46,2	NS
Bilateral pain	905	10,1	747	13,4	0,035
Otorrhea (%)	905	26,4	763	27,2	NS
Red flags (%)	905	3,5	764	3,1	NS
Bilateral AOM (%)	905	32,5	764	32,3	NS
Purulent AOM	905	76,2	764	72,9	NS

TABLE 2: Logistic regression table for factors associated with the probability of systemic antibiotic use. Nagelkerke R^2: 0.23 indicating that 23% of antibiotics prescription rate is due to these variables.

Factor	OR	95% CI	p
POST period	0.59	0.43-0.81	0.0008
Younger age	0.85 per year	0.79-0.91	< 0.0001
Longer fever duration	1.005 per hour	1.00-1.01	0.0016
Highest reported fever	1.35 per °C	1.07-1.69	0.0103
Bilateral AOM	2.33	1.68-3.23	< 0.0001
Red flags	5.05	1.51-16.91	0.0087
Purulent AOM	3.21	2.28-4.54	< 0.0001

Manuscript preparation:

Translation from French to English of the preliminary version of the article was generated with the support of ChatGPT (OpenAI, June 2025 version, https://chat.openai.com), based strictly on the content of the original dissertation. All statistical interpretation and written content were critically reviewed, corrected, and approved by the authors to ensure accuracy and fidelity to the source material.

Statistical analysis:

Univariate comparisons between PRE and POST groups were conducted using chi-square, t-tests, or Mann-Whitney U-tests as appropriate. Multivariable logistic regression was used to identify factors associated with systemic and local antibiotic prescriptions. Statistical analysis was performed using JASP (v0.19.3) and MedCalc (v23.1.3).

Ethics:

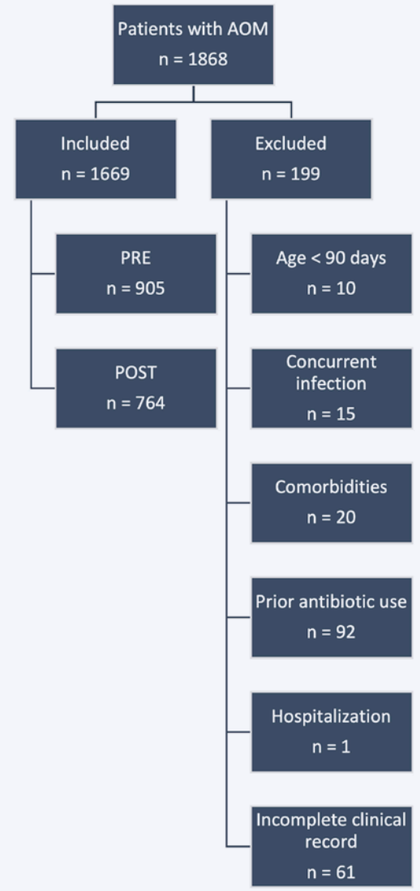
The study was approved by the HUDERF ethics committee (CEH 40/24).

Results

Population:

A total of 1,669 AOM cases were included (905 PRE, 764 POST) (Figure 1). In the pre-intervention period, 23 children were younger than 6 months, 312 were between 6 and 24 months, and 570 were older than 24 months. In the post-intervention period, these numbers were 14, 272, and 478 respectively, difference between age distribution is not significant. The distribution of prescriber type differed significantly between the two periods ($x^2 = 63.9$, $p < 0.0001$), mainly due to a difference between the number of patients treated by emergency medicine residents (175 vs. 71), while general practitioners were more frequently involved in the post-intervention period (152 vs. 81). The proportions of patients seen by the staff physicians (101 vs. 85) and paediatric residents (548 vs. 456) remained stable across both periods. Demographic and clinical characteristics were comparable between groups (Table 1).

FIGURE 1: Study flow diagram illustrating patient inclusion and exclusion criteria.



Systemic antibiotic prescriptions:

Systemic antibiotic use decreased significantly in the POST period (59.0% vs 46.6%, $p < 0.001$). Most prescriptions were for amoxicillin (95.9%). The proportion of delayed prescriptions increased from 0.88% to 3.4% ($p < 0.001$). The proportion of 5-day treatments increased significantly post-intervention (from 16.2% to 45.2%, $p < 0.0001$).

Subgroup analysis according to cut-of-ages in the BAPCOC guidelines, showed a decrease in systemic antibiotic prescription rate in all age categories. In infants under 6 months of age, systemic antibiotics were prescribed in 100% of cases during the PRE period and 76.2% in the POST period. Although this reflects a numerical decrease, no statistical comparison could be performed due to the absence of untreated cases in the PRE period. Differences for the age groups 6 to 24 months (79,9% vs. 69,8%, $p = 0.0054$) and above 24 months (43,5% vs. 32,2%, $p = 0.0002$), and pairwise comparison between all age groups for every

FIGURE 2: Subgroup analysis according to cut-of-ages. Differences for the age groups 6 to 24 months and above 24 months, and pairwise comparison between all age groups for every period were statistically significant.

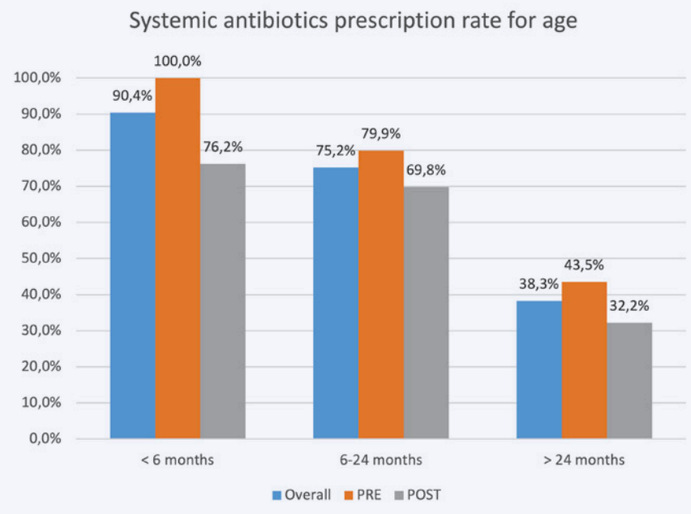


FIGURE 3: Pairwise comparison for treatment duration between both periods.

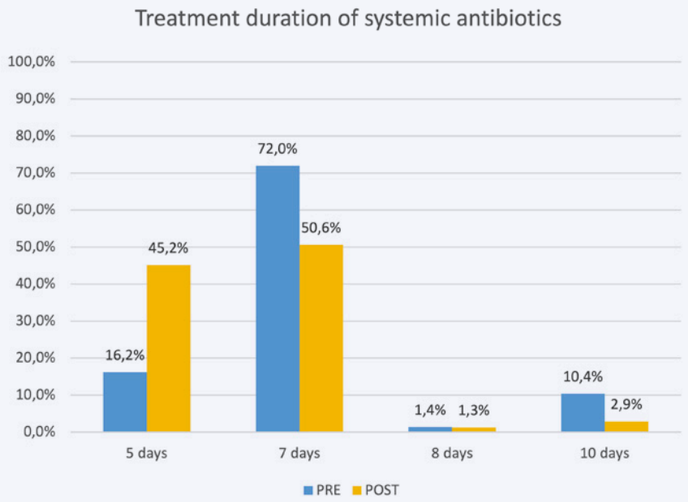


TABLE 3: Logistic regression table for factors associated with the probability of local antibiotic use. Nagelkerke R^2: 0.10 indicating that 10% of antibiotics prescription rate is due to these variables. There is no significant difference between the two periods.

Factor	OR	95% CI	p
POST period	1.24	0.92-1.66	NS
Older age	1.14 per year	0.79-0.91	0.0001
Shorter fever duration	0.99 per hour	0.99-1.00	< 0.0001
Bilateral AOM	0.64	0.47-0.87	0.0047
Purulent AOM	0.54	0.39-0.74	0.0002

period (p = 0.001) were statistically significant (Figure 2).

Treatment duration:

The proportion of children prescribed, for whom a 5-day course of antibiotics was prescribed, more than tripled following the protocol revision, increasing from 16.2% in the PRE period to 45.2% POST period (p < 0.0001). Conversely, the use of 7-day treatment courses significantly declined, from 72.0% to 50.6% (p < 0.0001) (Figure 3).

Factors associated with systemic antibiotic use, as identified with logistic regression, are described in table 2 (Table 2; Figure 4).

Local antibiotic prescriptions:

Overall local antibiotic prescription rates rose modestly (35.0% to 40.7%, p = 0.017), with a significant shift from ciprofloxacin and combination drops toward chloramphenicol/dexamethasone.

Factors associated with local antibiotic use, as identified with logistic regression, are described in table 3 (Table 3; Figure 5);

There was no significant difference in the use of local antibiotics between both periods (POST period: OR 1.24 (95% CI 0.92-1.66, NS)).

Prescriber behaviour:

General practitioners (GPs and GP trainees) at our ED prescribed fewer systemic antibiotics than (resident) paediatricians and emergency physicians (46.4% vs 53.8%, p = 0.034). Specialist prescribing significantly decreased after the protocol update (58.7% to 47.2%, p < 0.0001), while no significant change was observed in GP prescribing.

Discussion

This study confirms that a structured protocol change at HUDERF reduced systemic antibiotic prescriptions in children with AOM. We were encouraged to observe a significant reduction in systemic antibiotic prescriptions following the implementation of the revised protocol, indicating a positive shift toward more judicious use.

Although clinical severity indicators (younger age, high/long fever, bilateral/purulent AOM, red flags) seemed to drive systemic antibiotic use, overall prescription rates remain high, particularly in age groups where a more conservative approach is often justified. Notably, 69.8% of otherwise healthy children aged 6 to 24 months and 32.2% of children over 2 years still received antibiotics. These figures suggest that, despite progress, there is still room for improvement, especially in reinforcing the appropriateness of watchful waiting in non-severe, uncomplicated cases (11,12).

The revised protocol led to a clear improvement in prescribing practices regarding treatment duration, with a significant increase in the proportion of children receiving the recommended 5-day course. This suggests an ongoing process in adherence to updated guidelines and awareness of the benefits of shorter antibiotic therapy. However, 7-day courses, which are no longer in line with the protocol for children over 2 years without complications, remained the most frequently prescribed duration in the post-intervention period. This persistence may reflect prescriber habit, clinical caution, or a lag in fully adopting the new recommendations. Continued educational efforts and targeted feedback may be needed to further align prescribing behaviour with evidence-based standards.

There was a shift towards local antibiotic use, multivariate analysis suggests this shift reflects substitution for systemic therapy in milder cases (older age, less severe presentation). However, given that local treatment is generally not recommended except in otorrhea with tympanostomy tubes, this highlights a potential area for further clinician education (13).

GPs in our ED consistently prescribed fewer antibiotics, aligning with outpatient care literature (14). Interestingly, the improvement post-intervention was mainly observed among (resident) paediatricians and emergency physicians, suggesting effective internal dissemination and adherence to the new protocol.

Strengths and limitations

This study has several strengths. It is based on a relatively large cohort of paediatric patients, with strict inclusion and exclusion criteria and a clearly defined clinical endpoint. The before-and-after design allowed a pragmatic assessment of the impact of a targeted intervention (a revised prescribing protocol) in a real-world emergency department setting. Detailed clinical data, including fever characteristics and otoscopic findings, enabled robust multivariable analysis of factors influencing prescribing behaviour.

However, the study also has limitations. Its retrospective and monocentric nature restricts generalizability beyond our institution. Prescribing decisions were not always explicitly documented, which may introduce residual confounding. The reliance on clinician diagnosis, without systematic confirmation by otoscopy by an ENT or tympanometry, may affect diagnostic consistency. Finally, some subgroup analyses (e.g., infants < 6 months) involved small sample sizes, limiting statistical power or preventing formal testing.

Conclusion

The implementation of a revised local protocol for AOM at HUDERF significantly reduced systemic antibiotic prescriptions and encouraged shorter treatment durations and delayed prescribing. Clinical severity remained the main driver of prescribing decisions. The persistent use of local antibiotics, even when not strictly indicated, suggests a need for further education targeting both clinicians and caregivers.

Future research should explore long-term sustainability of these trends and the impact on clinical outcomes, parental satisfaction, and resistance patterns.

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

FIGURE 4: Factors associated with systemic antibiotic prescription, logarithmic scale.

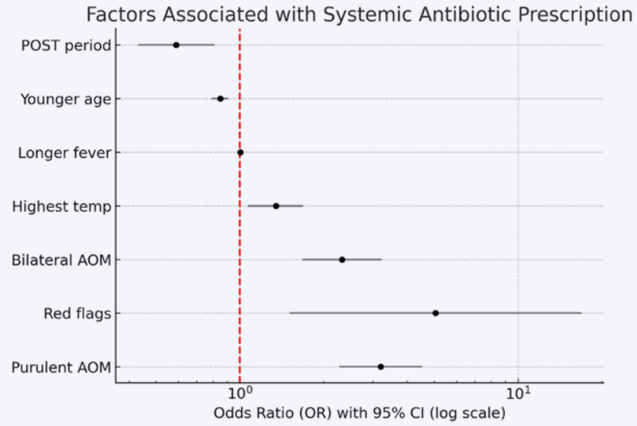
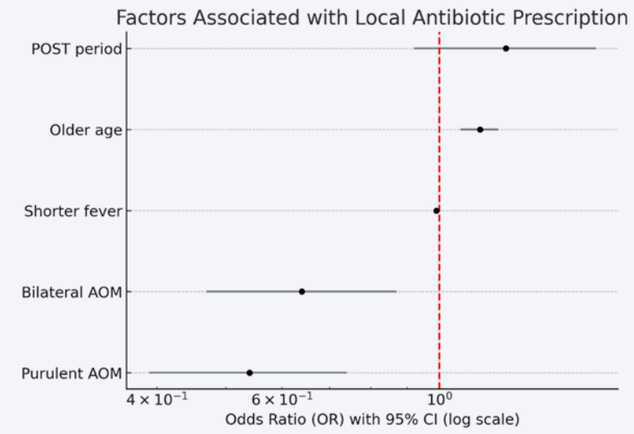


FIGURE 5: Factors associated with local antibiotic prescription, logarithmic scale.



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APPENDIX 1:
Initial protocol (October 2022)

Indications for Immediate Antibiotic Treatment

Immediate antibiotic therapy is recommended for the following categories of children:

- Children under 6 months of age
- Bilateral AOM in children under 2 years of age
- Severe AOM, defined as AOM with:
  - Moderate to severe otalgia
  - Otalgia lasting ≥ 48 hours
  - Temperature ≥ 39°C
- AOM that remains symptomatic (e.g., fever, otalgia) in the presence of purulent otorrhea
- In cases of prolonged purulent otorrhea (> 4 days) or infection with uncommon pathogens, antibiotic treatment is also recommended at a later stage
- Presence of underlying conditions associated with an increased risk of severe AOM (e.g., immunodeficiency, craniofacial anomalies, etc.)
- Recurrent AOM, defined as ≥ 3 episodes within a 6-month period

First-Line Treatment

In children presenting with a new episode of AOM (either a first episode or one occurring more than 3 weeks after the previous episode), without purulent conjunctivitis and without a history of recurrent AOM, amoxicillin 90 mg/kg/day divided into 3 doses, is the antibiotic of choice.

Duration of Antibiotic Therapy

A 10-day antibiotic course is recommended for:

- Children under 2 years of age
- Symptomatic AOM with purulent otorrhea
- Cases of recurrent AOM

A 5-7 day course may be prescribed for:

- Children over 2 years of age, without tympanic membrane perforation and without a history of recurrent AOM

APPENDIX 2:
Current protocol (October 2023)

Immediate oral antibiotic therapy is recommended in the following cases:

- Children under 6 months of age
- Presence of comorbidities such as (but not limited to):
  - Immunodeficiency
  - Craniofacial anomalies
  - Down syndrome

In all other cases:

50-80% of all cases of AOM cases resolve spontaneaously within 3 days, 90% within 7 days.

- If no otorrhea is present, and/or the child is 2 years and older: No antibiotics
- If otorrhea is present and/or the child is 6-24 months old, consider management based on the overall clinical situation and choose between:No antibiotics
- Delayed oral antibiotic prescription
- Immediate oral antibiotic prescription
- Prefer local antibiotic treatment (eardrops) in children with tympanostomy tubes

Antibiotic Regimens

- First-line therapy amoxicillin 80-100 mg/kg/day, divided into 3 doses, for 5 days
- Second-line therapy amoxicillin 40-50 mg/kg/day plus amoxicillin-clavulanate 40-50 mg/kg/day, in 3 divided doses, for 5 days, recommended in case of:
  - Recurrence within 3 weeks
  - Failure of initial treatment
  - Associated purulent conjunctivitis

APPENDIX 3:
Red flags

- Age < 90 days
- Severe pain not relieved by analgesics
- Severe/persistent headaches
- Retro auricular edema/erythema
- Focal neurological signs
- Meningeal signs
- Facial nerve paralysis
- Visual disturbances
- Difficult to arouse
- Excessive crying, irritability
- Loss of interest in play
- Nasal flaring, grunting, increased respiratory effort
- Dry mucous membranes
- Pallor/cyanosis of the skin and mucosa
- Drinking < 50% of unusual intake
- Significantly decreased urine output

Les soins pour
les peaux très sèches à atopiques de toute la famille(*)

99% d'ingrédients d'origine naturelle

93% d'ingrédients d'origine naturelle

Le soin quotidien
anti-grattage
Produit cosmétique

Le traitement SOS
des crises d'eczéma
Sans cortisone
Dispositif médical(1)

Mode d'action 100% naturel

COSMOS ORGANIC

(*) Stelatopia Intense convient aux nourrissons dès 1 mois, aux enfants et aux adultes.
(1) Bitop AG. Lire attentivement la notice. Ce dispositif médical est un produit de santé réglementé qui porte, au titre de cette réglementation, le marquage CE. Date d'élaboration de la publicité : 09/2024

NIEUW
VANAF NU BESCHIKBAAR
UITSLUITEND VERKOCHT IN DE APOTHEEK

Nestlé NAN RICE

1ste lijnsaanbeveling in geval van koemelkeiwitallergie*

✔ Gehydrolyseerde rijsteiwitten
✔ Zonder lactose
✔ Maïszetmeel (1,4g/100ml)
✔ Vezels (0,4g/100ml)
✔ HALAL en 100% vegetarisch
✔ Zonder palmolie

4901-849

*In lijn met de nieuwe ESPGHAN-aanbevelingen. ESPGHAN position paper on the diagnosis, management, and prevention of cow's milk allergy. JPGN. 2024;78(2):386-413.

Dit document is voorbehouden voor gezondheidsspecialisten. Belangrijke informatie voor (para)medici: de Wereldgezondheidsorganisatie (WHO) heeft aanbevolen om zwangere vrouwen en moeders van zuigelingen te informeren over de voordelen en de superioriteit van borstvoeding. In het bijzonder dat borstvoeding de beste voeding is en de beste bescherming tegen ziektes biedt. Moeders moeten ook begeleid worden met de voorbereiding op en de verderzetting van borstvoeding, met de nadruk op het belang van de kwaliteit van hun eigen voeding tijdens de zwangerschap en na de geboorte. Onnodige introductie van gedeeltelijke flesvoeding of andere voedingsmiddelen of dranken zou ontmoedigd moeten worden omdat het een negatieve invloed op borstvoeding kan hebben. Bovendien moeten moeders gewaarschuwd worden dat zij niet terug kunnen komen op hun beslissing om geen borstvoeding meer te geven. Voordat een moeder besluit om flesvoeding te geven, zou ze geadviseerd moeten worden over de sociale en financiële gevolgen van haar beslissing, bijvoorbeeld als een baby exclusief flesvoeding krijgt, dan is meer dan 450 gram per week nodig, dus de familiale omstandigheden en de kosten moeten in overweging worden genomen. Moeders moeten eraan herinnerd worden dat borstvoeding niet alleen de beste voeding, maar ook de meest economische voeding is. Wanneer toch wordt besloten om flesvoeding te geven is het belangrijk om de juiste instructies mee te geven omtrent het gebruik van deze voeding en erop te wijzen dat ongekookt water, niet gesteriliseerde zuigflessen of een onjuiste bereiding de baby ziek kan maken. **Met vriendelijke groeten, Nestlé Babyvoeding.** V.U : Karlien Desmedt, Nestlé Belgilux SA/NV, rue de Birminghamstraat 221-1070 Bruxelles/Brussels, BCE/KBO 0402.231.383. PID3788 September 2025

Autosomal Dominant Polycystic Kidney Disease. KDIGO 2025 Guideline, a Belgian Paediatric Perspective

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Keywords
Polycystic kidney, autosomal dominant ; genotype ; risk factors ; counselling ; child.

Abstract
Autosomal dominant polycystic kidney disease (ADPKD) is traditionally viewed as an adult-onset condition. However, increasing evidence highlights a broad phenotypic and genotypic spectrum in children, including very early-onset cases. Despite the absence of curative therapies, early identification of modifiable risk factors such as arterial hypertension, proteinuria, and obesity may delay progression and improve long-term outcomes. This narrative review provides a Belgian paediatric perspective on the updated KDIGO 2025 guidelines for ADPKD. We discuss the clinical variability of paediatric ADPKD, the role of genotype in disease severity, and the emerging paediatric-specific risk stratification tools to identify children at risk of rapid progression. We further explore the benefits and considerations of screening at-risk children and offer practical recommendations for diagnosis, counselling, and early management. By raising awareness among general paediatricians, we aim to promote timely intervention and structured follow-up for affected children and their families.

Introduction

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is an inherited disorder associated with multiple bilateral kidney cysts and several extrarenal manifestations (1–4). ADPKD is the most prevalent hereditary kidney disease and the fourth most common cause of kidney replacement therapy in adult patients (1). The estimated prevalence of ADPKD is one in 1000 individuals (2,3).

The typical phenotype of ADPKD is characterized by multiple bilateral kidney cysts leading to progressive kidney enlargement. The first clinical symptom is generally arterial hypertension (HTA) while decline in kidney function often occurs later in the disease. Common complications in adults with ADPKD include abdominal discomfort or pain, cyst haemorrhage, gross haematuria, nephrolithiasis and cyst infections (2,3). Extrarenal manifestations of ADPKD may include liver cysts, increased risk of intracranial aneurysms, pancreatic cysts, cardiac valvular disease and abdominal hernias (2,3).

ADPKD is often regarded as a silent disease, as significant kidney cyst enlargement and subsequent decline in kidney function typically occur at an adult age. Progression to kidney failure most commonly takes place after the fourth decade of life. However, ADPKD exhibits a broad clinical spectrum, encompassing paediatric manifestations and, in some cases, the detection of prenatal cysts (1). Therefore, this narrative review aims to outline the phenotypic and genotypic complexity of paediatric ADPKD, identify modifiable risk factors, and discuss the potential benefits and challenges associated with paediatric or adolescent screening in the context of familial ADPKD. Additionally, we provide recommendations for the management of ADPKD in paediatric patients according to the recent KDIGO (Kidney Disease: Improving Global Outcomes) guidelines.

Phenotype complexity

As outlined in the introduction, ADPKD is most commonly recognized as an adult-onset condition. However, its broad phenotypic spectrum also encompasses paediatric presentations, which may range from asymptomatic incidental findings of cyst on ultrasound, to HTA or proteinuria, to symptomatic disease such as pain, enuresis, haematuria or urinary tract or cyst infections (1,5,6). Recent evidence further suggests that kidney cyst formation already starts in utero (7,8).

A recent study on paediatric ADPKD utilized data from multiple registries, including the multinational ADPedKD registry (www.ADPedKD.org), the European Rare Kidney Disease Registry (ERKReg), and the United Kingdom RaDaR registry, encompassing data from 32 countries (1). The study aimed to characterize the genotypic and phenotypic features of ADPKD in the paediatric population (Table 1). The most common mode of presentation in this study was diagnosis through family screening, followed by postnatal incidental findings and clinical signs and symptoms. Since 2000, the prevalence of prenatal diagnosis has increased,

TABLE 1: Genotypic and phenotypic features of ADPKD in the paediatric population.

Mode of presentation	ADPedKD (N=950)	ERKReg (N=596)	RaDaR (N=139)
Family screening	48% (455)	62% (370)	Unknown
Prenatal	14% (129)	2% (13)	11% (15)
Incidental findings	31% (293)	21% (126)	Unknown
Clinical symptoms	8% (73)	15% (87)	Unknown

Adapted from Gimpel et al. 2025 (1). ADPedKD, ADPKD registry; ADPKD, autosomal dominant polycystic kidney disease; ERKReg, European Rare Kidney Disease Registry; RaDaR, National Registry of Rare Kidney Diseases. Mentioned as % (N).

primarily driven by advancements in the accuracy and utilization of prenatal ultrasound imaging. These prenatal cases usually exhibit hyperechogenic, enlarged kidneys rather than the typical cysts seen in classical presentations. Given that not all prenatal cases progress to very early-onset (VEO) ADPKD, counselling at an expert centre is essential to provide accurate prognostic information and prenatal reassurance.

Not only does the mode of presentation vary considerably in paediatric ADPKD, but the age of symptom onset also spans a broad range. VEO-ADPKD is typically diagnosed either in utero, characterized by hyperechogenic, enlarged kidneys and oligohydramnios, or between birth and 18 months of age, when affected infants may present with enlarged cystic kidneys, HTA, and/or reduced estimated glomerular filtration rate (eGFR) (3,4). Children with VEO-ADPKD have been shown to have a higher likelihood of developing HTA and impaired kidney function (eGFR < 90 mL/min/1.73 m²) by adolescence compared to those diagnosed later in childhood (4). Early-onset ADPKD is defined by the emergence of ADPKD-related clinical manifestations between 18 months and 15 years of age (3). A third group comprises children diagnosed with ADPKD who do not meet the previous criteria. The most severe phenotypes observed in childhood are often associated with digenic inheritance involving pathogenic variants in two or more ADPKD-associated genes (4). The genetic basis of ADPKD is further discussed in the following section.

Genotype complexity

The two major genes implicated in ADPKD are *PKD1*, located on chromosome 16, and *PKD2*, located on chromosome 4. These genes encode polycystin-1 and polycystin-2, respectively. Together, *PKD1* and *PKD2* account for over 90% of diagnosed familial ADPKD cases, with *PKD1* being the more prevalent of the two (2,3). The clinical phenotype of ADPKD varies depending on the genes involved. Mutations in *PKD2* are associated with a milder disease course, with affected individuals typically reaching kidney failure approximately two decades later than those with *PKD1* mutations (4,9). Among individuals with *PKD1* mutations, those carrying truncating variants tend to exhibit a more severe phenotype than those with non-truncating variants (4,9).

A small proportion of ADPKD cases are attributed to pathogenic variants in less common genes, for which pathogenicity is well supported (*IFT140, ALG5, ALG9, GANAB, DNAJB11, and NEK8*) (3). Although these genes are associated with distinct phenotypic features, they often show clinical overlap with *PKD1* and *PKD2*-associated disease. For instance, *PKD1*, *PKD2* and *DNAJB11* mutations have all been linked to a substantial risk of progression to kidney failure. In contrast, several additional genes (*ALG6*, *ALG8*, *PKHD1*) have been proposed as potential contributors to cystic kidney disease, but their pathogenicity in the context of ADPKD remains uncertain (3).

VEO-ADPKD represents a rare and particularly severe clinical presentation, occurring in less than 1% of affected families. These cases frequently exhibit an oligogenic inheritance pattern, where the co-inheritance of multiple rare variants, such as compound heterozygous mutations in *PKD1* or *PKD2* or additional mutations in other cystogenes, contributes to an earlier and more severe disease phenotype than typically seen in classical ADPKD (2). Evidence from recent case series demonstrates that children with severe, early-onset cystic kidney disease often carry two rare *PKD1* variants in trans, supporting a dosage effect and a model in which disease severity is modified by the cumulative impact of multiple genetic variants rather than a strictly monogenic mechanism (10). Furthermore, large deletions involving both *PKD1* and the adjacent TSC2 gene can result in a combined phenotype of ADPKD and tuberous sclerosis complex, so called "contiguous gene syndrome PKD1-TSC2", leading to rapid progression to kidney failure in childhood. The identification of concomitant nephropathies in some patients who progress to kidney failure earlier than expected based on their genotype further underscores the complexity of genetic and phenotypic interactions in VEO-ADPKD (2). These findings highlight the importance of comprehensive gene panel analysis using next-generation sequencing for accurate diagnosis, prognosis, and genetic counselling in early-onset cases.

Modifiable risk factors

Several non-modifiable factors influence the disease course of ADPKD, including age at symptom onset, underlying genotype, ethnicity, and sex. However, a number of modifiable factors have been identified that may impact long-term disease progression. These include body weight, blood pressure control, presence of proteinuria, level of physical activity, smoking status, and dietary salt intake (4).

HTA is the most common and earliest clinical feature of ADPKD, typically developing before the age of thirty (4). Early-onset HTA is a key risk factor for progression to kidney failure and is strongly correlated with total kidney volume (TKV) and cyst burden, more than other kidney manifestations (11,12). Since cardiovascular disease is the leading cause of death in ADPKD, it is essential for us as paediatricians to regularly monitor and manage blood pressure to improve long-term outcomes.

HTA is estimated to affect 20-40% of children and adolescents with ADPKD, with a prevalence notably higher than in the general paediatric population (4). A meta-analysis reported HTA in approximately 20% of children with ADPKD (9,11). Data from a recent retrospective international multicentre study, including 310 paediatric ADPKD patients from 22 European centres, revealed even higher prevalence rates using 24-hour ambulatory blood pressure monitoring (ABPM) (13). 24-hour ABPM identified HTA in 31% of patients during daytime, 42% during nighttime, and 35% over the full 24-hour period. Additionally, 52% exhibited non-dipping nocturnal blood pressure patterns, while 18% had isolated nocturnal HTA (13). These findings highlight the clinical value of ABPM in the routine follow-up of paediatric patients with ADPKD.

HTA is one of the earliest treatable manifestations of ADPKD in children and adolescents. Studies have demonstrated a correlation between elevated blood pressure and both total kidney volume and cyst volume in this population (4). Children with ADPKD who develop HTA exhibit faster kidney growth and a more rapid decline in kidney function compared to their normotensive peers (4). Furthermore, blood pressure values in the high-normal range (75th–90th percentile) have been associated with an increased long-term cardiovascular risk (4). In children, blood pressure above the 75th percentile has also been linked to elevations in left ventricular mass index (14).

Proteinuria represents another early and potentially modifiable manifestation of ADPKD in children. Estimates suggest that microalbuminuria affects 20-48% and proteinuria 10–23% of paediatric patients with ADPKD (9,11,15). Both paediatric and adult cohort studies have demonstrated that the presence of proteinuria is associated with a more aggressive course of kidney disease (15). Moreover, proteinuria is recognized as a modifiable risk factor for the progression of chronic kidney disease (CKD) in children (16).

Overweight and obesity are recognized modifiable risk factors in ADPKD. Overweight in children and adolescents is defined as a body mass index (BMI) between the 85th and 95th percentiles for age and sex, whereas obesity is defined as a BMI at or above the 95th percentile. In adult cohorts, a higher body mass index (BMI) has been identified as an independent risk factor of disease progression (17,18). A post-hoc analysis of the TEMPO 3:4 trial demonstrated that overweight and, particularly, obesity were strongly and indepentdently associated with kidney growth in adult patients (17). Also, analysis of participants of the HALT-PKD trials showed an increased risk of progression to kidney failure in adolescents and adults with early-stage ADPKD (18). Although paediatric data on the effect of BMI on children with ADPKD are currently lacking, recent KDIGO guidelines recommend regular assessment of BMI in children and adolescents and emphasize the importance of lifestyle counselling to mitigate potential long-term risks based on adult data (4).

In addition to the importance of monitoring BMI for ADPKD progression, overweight and obesity in childhood also carry other significant long-term health consequences such as increased risk for cardiovascular disease, type 2 diabetes mellitus, hypertension, dyslipidaemia, and non-alcoholic fatty liver disease. The prevalence of childhood obesity is slowly increasing, projections suggest that by 2035 more than 750 million children (age 5–19 years) are expected to be living with overweight and obesity that if no substantial interventions are implemented (19). Early identification through routine BMI screening and addressing social determinants of health are essential to mitigate the adverse outcomes (20).

Stratification models

Risk stratification is becoming an essential component of care in paediatric ADPKD, especially as interest grows in early monitoring and timely intervention. Although adult risk scores such as the PROPKD model incorporate genetic and clinical features, they have not yet been validated in children (12). Also, the Mayo Imaging Classification (MIC) is a well-established tool that uses height-adjusted total kidney volume (htTKV) measured by MRI or CT to predict kidney prognosis and guide clinical trial enrolment for adults with ADPKD (21,22).

TABLE 2: Risk categories according to the Leuven Imaging Classification (LIC) based on height-adjusted total kidney volume measured by 3D ultrasound.

Risk category		Meaning
A	Very low risk	Children with kidney volumes in the normal range for age and minimal risk of progression
B	Low risk	Children with mild kidney enlargement, typically without clinical signs
C	Intermediate risk	Children with moderate kidney growth, sometimes accompanied by early hypertension or microalbuminuria
D	High risk	Significant or extreme kidney enlargement, often associated with *PKD1* mutations, higher blood pressure, and early decline in kidney function
E	Very high risk	

Recently, the Leuven Imaging Classification (LIC) was developed by Breysem et al. in 2023, and validated as a paediatric-specific imaging-based risk model (23). LIC combines 3D ultrasound-derived htTKV with age to assign children into five risk categories (A–E), offering a non-invasive, age-appropriate tool for clinical stratification (Figure 1 and Table 2). These categories help clinicians identify which children may benefit from closer monitoring and early lifestyle or therapeutic interventions. In a large multicentre study, LIC class was significantly associated with both genotype and blood pressure, reinforcing its clinical relevance (24).

Importantly, the LIC relies on 3D ultrasound. Ultrasound is generally more accessible and practical than magnetic resonance imaging (MRI) in paediatric settings, particularly for younger children, however, 3D ultrasound is not yet routinely implemented in clinical practice. Therefore, the Leuven PKD research group is currently developing and validating a 2D ultrasound-based model as an alternative.

Paediatric-specific models like the LIC provide a more tailored approach. Nevertheless, integrating clinical factors such as hypertension, obesity, and family history remains essential for comprehensive risk assessment (25,26). As research progresses, LIC may serve as a foundation for future paediatric stratification and prediction models.

Screening of at risk children in families with ADPKD

The necessity of screening or diagnosing ADPKD in at-risk children remains a subject of ongoing debate, largely due to the perception of ADPKD as an adult-onset condition. However, as outlined in the preceding sections, the disease presents with a broad clinical

FIGURE 1: Incorporation of the validation cohort (blue dots) in the Leuven classification paediatric model (full lines), with the MIC model extrapolated to the paediatric age range as comparison (dashed lines). Adapted from Breysem L, et al (2023). Risk Severity Model for Paediatric Autosomal Dominant Polycystic Kidney Disease Using 3D Ultrasound Volumetry. Clinical Journal of the American Society of Nephrology (CJASN), 18(5), 581-591. https://journals.lww.com/cjasn/. Used with permission.

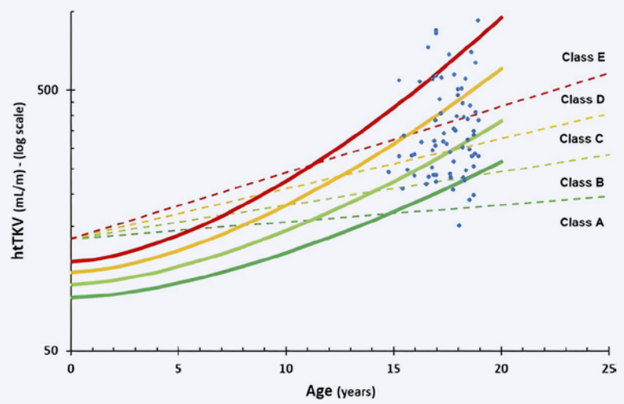
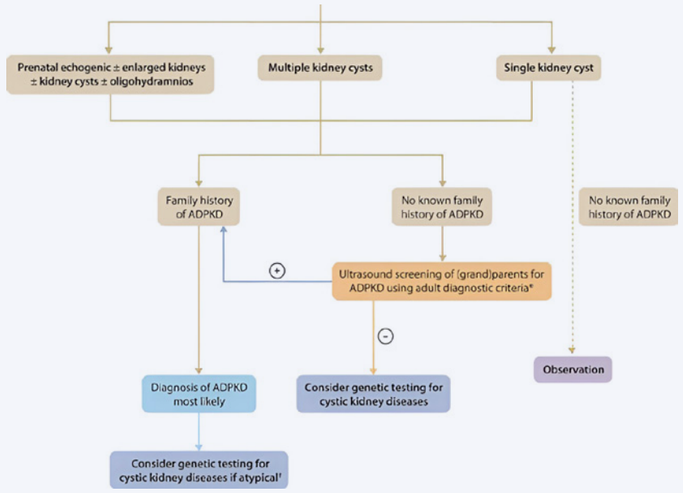


FIGURE 2: Diagnosis of children with clinical consideration of autosomal dominant polycystic kidney disease (ADPKD). Dash lines denote other pathway for consideration. *Consider screening grandparents if parent screening is negative or parents are aged<40 years. †For example, very early onset ADPKD; severe kidney involvement relative to age. From Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD). Kidney Int. February 2025;107(2S):S1-239. Used with permission.



spectrum in childhood. Hypertension and proteinuria can occur in children even in the absence of overt symptoms. So early screening provides an opportunity to identify and address modifiable risk factors and timely intervention may confer significant long-term benefits, as previously discussed (9).

One of the main arguments against screening or diagnosing ADPKD during childhood is the absence of a definitive cure (7). However, despite the lack of curative treatment, early lifestyle interventions and the management of modifiable risk factors can yield significant long-term benefits for affected individuals. Another frequently cited concern is the potential impact on insurance and future employment opportunities (1,5). While presymptomatic genetic testing may be legally protected from disclosure to insurance companies, no such protections currently apply to radiological findings (9).

The psychological burden of diagnosis and follow-up on both children and their families is also acknowledged (4). However, current guidelines recommend monitoring for hypertension, proteinuria, and other early manifestations in at-risk children, regardless of a confirmed diagnosis. On the other hand, since each child of an affected parent has only a 50% chance of inheriting the disease, children without the mutation could potentially be spared from unnecessary testing and repeated hospital visits.

A final argument often raised is the concern that screening during childhood removes the individual's autonomy to make an informed decision about knowing their disease status later in life (2). While this perspective is valid in conditions without therapeutic consequences during childhood, in the case of ADPKD, early intervention targeting modifiable risk factors may positively influence disease progression.

A family-centred approach is essential when guiding families in the decision-making process regarding testing. Open and balanced discussions should address the potential benefits and harms of both pursuing and deferring testing in children at risk for ADPKD. Therefore these families would benefit from counselling in an expert centre.

Ultrasound is the recommended imaging modality for testing or diagnosing ADPKD in children (2,4,5). The presence of a single kidney cyst in a child under the age of 15 with a positive family history of ADPKD is considered highly suggestive of the disease (4). However, the absence of kidney cysts does not exclude the diagnosis. In cases where kidney cysts are detected in a child without a known family history, the KDIGO guidelines recommend performing kidney ultrasound in the parents or in the grandparents if the parents are younger than 40 years of age to investigate a possible familial origin (Figure 2).

Genetic testing is recommended in children with VEO-ADPKD or those presenting with atypical clinical features (4). In children with a positive family history who do not meet these specific criteria, genetic testing may still be considered and discussed with the family, taking into account the potential benefits and harms. Additionally, genetic screening is recommended in children with cystic kidneys and no known family history, in order to confirm the diagnosis and guide further management. Expert counselling is needed for these complex cases.

Management

Even in the absence of a definitive cure for ADPKD, identifying at-risk children remains essential. Early screening and timely management of modifiable risk factors can significantly influence disease progression. Moreover, even when modifiable risk factors are not present, recognizing children at risk allows for early lifestyle counselling, which may positively impact long-term outcomes.

According to the KDIGO guidelines, counselling on lifestyle factors is essential in the management of patients with or at risk for ADPKD. Maintaining a healthy body weight is emphasized. Therefore, adherence to general dietary recommendations and engagement in regular physical activity are recommended (3,4). In children and adolescents with ADPKD who present with overweight or obesity, implementing these lifestyle modifications is crucial, with the goal of achieving and maintaining a healthy weight. A multidisciplinary approach is often necessary to effectively support these interventions. Additional lifestyle factors, particularly relevant during adolescence, include avoiding alcohol consumption and tobacco products, recreational drugs, and anabolic steroids (3,4). Avoidance of tobacco use is especially critical, as smoking represents a significant modifiable risk factor for kidney cysts growth and the development and rupture of intracranial aneurysms (4).

Recent KDIGO guidelines recommend annual office blood pressure measurements in all children with and at risk for ADPKD. In children aged ≥ 5 years with very early-onset or early-onset ADPKD, as well as in those with a family history of ADPKD and office blood pressure readings ≥ the 75th percentile, annual 24-hour ABPM is advised (3). Additionally, echocardiographic evaluation is recommended in children with ADPKD and confirmed hypertension, due to their increased risk of early-onset cardiovascular complications (4,14).

If hypertension (defined as BP above 75^{the} percentile for age) is present, referral to an expert centre is necessary. The KDIGO guidelines recommend angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) as first-line treatment (3,4). The target blood pressure is below the 50th percentile or below 110/70 mmHg in adolescents. The importance of identifying and treating arterial hypertension lies in its significant impact on both kidney function and long-term cardiovascular risk, as outlined in the section on modifiable risk factors. In addition, ACEi and ARB are also recommended for the treatment of proteinuria in children with chronic kidney disease (4). The initiation of treatment need to be discussed and the side effects need to be considered with education of the patient.

When adolescent girls with ADPKD consider starting contraception, it is important to avoid oestrogen-containing contraceptives. In patients with polycystic liver disease associated with ADPKD, oestrogen exposure has been linked to greater liver volume and a higher annual increase in liver volume (4).

The only available drug to this day is the vasopressin type 2 antagonist tolvaptan, which slows down disease progression but has only been approved in rapidly progressing adult patients and is associated with severe adverse effects of polyuria and polydipsia. Although a single RCT has indicated tolerability and suggests potential effect of tolvaptan on annual TKV expansion in children with ADPKD (27). There is insufficient evidence for the use of any targeted or disease-modifying treatments for ADPKD in affected children at this time.

Conclusion

While ADPKD is classically regarded as an adult disease, a growing body of evidence confirms that clinical manifestations and kidney damage can begin in early childhood. Paediatric ADPKD encompasses a wide spectrum - from asymptomatic to severe early-onset disease - and requires careful clinical judgement to guide follow-up and intervention. Identifying modifiable risk factors such as hypertension, proteinuria, and excess weight is essential, as their timely management may positively influence the disease trajectory. The development of the LIC marks an important advance in paediatric-specific risk stratification and provides a practical tool for clinicians. Though routine screening remains debated, an individualised, family-centred approach is key to counselling and decision-making and best coordinated in an expert centre. With increasing availability of genetic testing and improved imaging modalities, early recognition and multidisciplinary management can optimize outcomes for children at risk of ADPKD. The ADPedKD initiative (www.ADPedKD.org) lays the foundation for a more personalized and evidence-based approach to paediatric ADPKD. Its findings are expected to inform future clinical guidelines and improve long-term care for affected children worldwide.

The authors have no conflict of interest to declare.

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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.

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GSK

Diagnostic Value of Brain MRI in Newborns with Congenital Cytomegalovirus Infection

PhD Thesis Presented on 27/05/2025 at Ghent University, Ghent, Belgium

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Keywords

Congenital infection ; cytomegalovirus infection ; magnetic resonance imaging ; newborn.

Background

The association between brain abnormalities and congenital cytomegalovirus (cCMV) infection has been well known for decades, however the prevalence of these lesions remains unknown. While some abnormalities, like cortical malformations, seem strong predictors of poor neurological outcome, the prognostic role of others, such as white matter lesions is not well known. Neonatal MRI has shown a lot of potential in addition to ultrasound for detecting cCMV-related lesions, however, at present, there still is no consensus for its role in screening infected newborns, especially in the absence of clinical symptoms.

Aim

The aim of this thesis was to investigate the value of brain MRI in newborns with cCMV, with an emphasis on white matter lesions.

Results

The aim of the thesis was subdivided into 4 four research questions, which were presented in four publications:

1. Spectrum and frequency of abnormalities detected on neonatal brain MRI

First, we investigated the spectrum and frequency of abnormalities detected on brain MRI in a large cohort of 196 infected newborns. The overall frequency of brain abnormalities was 39%. Although brain abnormalities were significantly more frequent in clinically symptomatic patients (77 versus 33% , P<0.01), they were still detected in over 30% of otherwise asymptomatic patients (Figure 1). White matter lesions were the most commonly detected abnormality, followed by subependymal cysts and ventricular dilatation. Many patients showed multiple concomitant lesions. White matter lesions frequently occurred in association with other types of abnormalities (such as cortical malformations), however in 45%, they were noted as an isolated abnormality (1) .

2. Qualitative scoring of the white matter and correlation with clinical outcome

In the second, prospective study, we developed a qualitative scoring system for visually assessing the white matter on neonatal brain MRI. The white matter was subdivided into normal, abnormal and doubtful white matter. The clinical implications of isolated white matter lesions were investigated in terms of hearing, motor and cognitive development.

Qualitative grading of the white matter was feasible, with good interobserver agreement (Cohen's weighted kappa value 0.79). Isolated white matter abnormalities were associated with neonatal hearing loss (odds ratio (OR) 20, P <0.05) and mildly lower motor scores (OR 8, P < 0.05) at clinical follow-up. A tendency towards impaired cognitive development was seen (OR 5, P = 0.07). Patients with discrete or doubtful white matter did not show worse outcome, compared to children with a normal MRI (2).

3. Quantitative scoring of the white matter and correlation with clinical outcome

The third, retrospective study, investigated if quantitative measurement of the white matter on neonatal brain MRI, by means of apparent diffusion coefficient (ADC) values, could be used to predict clinical outcome. ADC was measured in 255 newborns. White matter ADC was significantly higher in patients with neonatal hearing loss and with cognitive and motor impairments during follow-up (P <0.05) . White matter ADC, in combination with other qualitative imaging variables, allowed a fairly good distinction between children with and without clinical impairments, with receiver operating characteristics area under the curve (ROC AUC) ranging between 0.73 and 0.89 (Figure 2) (3).

4. Systematic review of current literature on the value of MRI in congenital cytomegalovirus

Finally, we performed a systematic review of the current literature on the value of MRI in children with cCMV. Twenty articles were included in the review. MRI can detect a wide range of brain abnormalities, both in pre- and postnatal setting, both in clinically

symptomatic and asymptomatic patients. MRI can be a helpful tool in the prediction of clinical impairments and seems complementary to ultrasound (4).

Conclusion

MRI can detect a wide range of brain abnormalities, both in clinically symptomatic and asymptomatic patients. MRI, with qualitative and quantitative interpretation of the white matter, can be a helpful tool in predicting clinical impairments and guiding therapy. Although further research is necessary, MRI should be considered in all cCMV-infected newborns.

FIGURE 1: Bar chart displaying the rate of abnormal brain MRI, in cilincally symptomatic and asymptomatic newborns with cCMV.

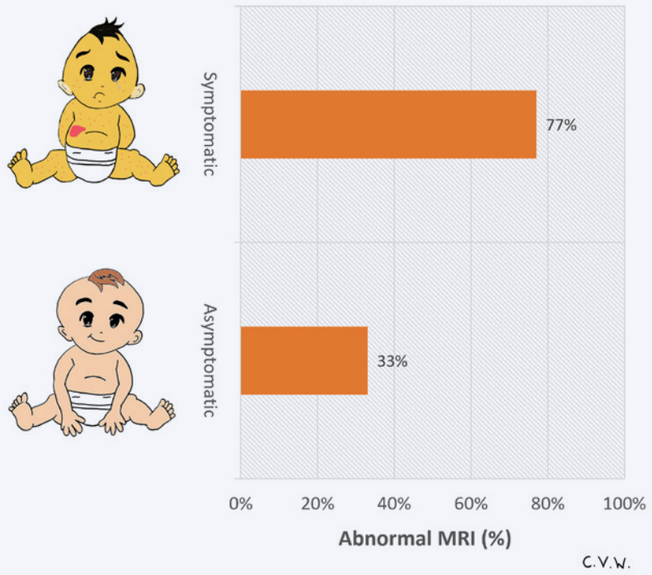
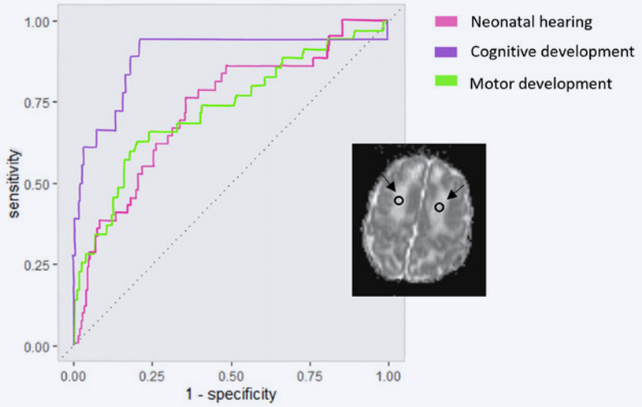


FIGURE 2: Receiver Operating Characteristics curves of the final models using white matter ADC for predicting clinical outcome.



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Speciaal ontwikkeld om het **immuunsysteem van baby's te ondersteunen**, dankzij *Bifidobacterium breve* M-16V en immuno-voedingsstoffen*[1-4]. Nutrilon® Profutura Care is ook geschikt bij **dysbiose van de darmmicrobiota door keizersnede en/of antibioticagebruik.**[5]

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→

- Herbalanceert de darmmicrobiota[5***]
- Ondersteunt het immuunsysteem[1-4(4*)]
- Vermindert het risico op infecties[1-4,6(5*)]

NUTRICIA

Belangrijk: Borstvoeding is de beste voeding. Informatie uitsluitend bestemd voor het (para)medisch korps. **Referenties: 1.** Bruzzese E et al. Clinical Nutrition, 2009;28:156–61. **2.** Arslanoglu S et al. Journal of Nutrition, 2007;137:2420–4. **3.** Chatchatee P et al. J Pediatr Gastroenterol Nutr, 2014;58(4):428–37. **4.** Arslanoglu S et al. J Nutr, 2008;138:1091–5. **5.** Chua M et al. JPGN, 2017;65:102–6. **6.** Reverri EJ et al. Nutrients, 2018;10,1346. *Vitamine C & D, ondersteunen de ontwikkeling van het immuunsysteem **structuuridentieke Human Milk Oligosacharides ***Meer lijkend op de darmmicrobiota samenstelling van vaginaal geboren baby's. Op basis van onderzoek naar de combinatie van prebiotische oligosachariden scGOS:lcFOS (9:1) en Bifidobacterium breve M16-V. ****Op basis van onderzoek naar prebiotische oligosachariden scGOS:lcFOS (9:1). *****Op basis van onderzoek naar prebiotische oligosachariden scGOS:lcFOS (9:1) of 2'-FL • **8/2025 V.U.: Danone Belux nv -Werkhuizenkaai 160 - 1000 Brussel**

Congenital Esophageal Myofibrotic Stenosis as a Rare Cause of Progressive Vomiting and Faltering Growth in a 5 Month-old: A Case Report and Review of the Literature

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Keywords
Congenital oesophageal stenosis ; myofibrotic stenosis ; faltering growth ; non-bilious vomiting ; infant.

Abstract
Congenital oesophageal stenosis is a rare congenital anomaly of the gastro-intestinal tract characterized by a fixed narrowing of the oesophagus. Onset of symptoms such as vomiting, dysphagia and faltering growth is variable, depending on the extent of the stenosis. There is often a significant delay between first symptoms and diagnosis We report on a five month-old infant presenting with symptoms of progressive nonbilious vomiting and weight loss. The diagnosis in this case was revealed by upper gastro-intestinal endoscopy after failed attempts to place a nasogastric feeding tube.

Introduction

Vomiting accompanied by faltering growth is relatively common in young children attending daycare centres, usually due to repeated viral infections. However, when vomiting persists, it may indicate underlying conditions such as congenital anomalies, pyloric stenosis, malrotation or metabolic disorders (1,2).

Congenital oesophageal stenosis (CES) is a rare cause of non-bilious vomiting in infants. CES is a congenital condition characterized by an intrinsic, fixed narrowing of the oesophagus, with an estimated incidence of 1 in 25.000-50.000 live births (3). It can appear in isolation or alongside other congenital anomalies, which has been reported in 17-42% of the cases across different series (1,4,5). It is most frequently associated with oesophageal atresia (0.4-14% of CES patients), The largest published case series to date is a multicentre study involving 61 CES patients from the French network of Oesophageal Malformations and Congenital disease, of whom 48% were also diagnosed with oesophageal atresia (6). Examples of other associated anomalies are congenital heart disease, trisomy 21, other gastrointestinal anomalies (such as anorectal malformations and duodenal atresia), tracheomalacia and hiatal hernia (1,2,6,7,8,9).

Case

Patient presentation

Informed consent for this case report was given by both parents of our patient. A 5-month-old boy was referred to the emergency department with a one-week history of upper respiratory symptoms and mild respiratory distress for the past 24 hours. The parents also reported a month-long history of vomiting and weight loss, with worsening symptoms over the past week. The vomiting, which occurred immediately after feeding, was non-bilious. His intake had decreased by 50% compared to a month ago and he had lost 500 grams in 14 days. Despite the parents' attempts to introduce solid foods two weeks before presentation, the boy consistently refused them. The patients medical history included two prior admissions at two weeks and two months of age due to non-bilious vomiting and faltering growth, both followed by a period of catch-up growth (see Figure 1). His weight-for-age percentile dropped from the 25th to below the 3rd centile, and his length-for-age centile decreased from the 50th to the 25th centile (Figure 1). Clinical examination revealed no abnormalities. During observation at the emergency department, the child experienced two short episodes of apnoea with desaturation, prompting admission for further observation.

Laboratory investigations revealed mildly elevated inflammatory markers but no hypoglycaemia or electrolyte imbalances. An abdominal ultrasound showed no anomalies, including a normal pyloric diameter. The initial diagnosis was persistent vomiting due to viral infection. During hospitalization, no additional episodes of desaturation or apnoea were observed, but the child continued projectile vomiting multiple times a day and failed to gain weight.

Nasogastric tube placement attempted by the nursing staff and otorhinolaryngology team remained unsuccessful. An upper endoscopy was performed and revealed an oesophageal pinpoint stenosis at the level of the lower oesophageal sphincter, located 17 cm from the dental arch (Figure 2). Prestenotic dilatation of the oesophagus was also noted. During the procedure a balloon dilation up to 6cm H2O (corresponding to ±7mm diameter) was performed resulting in a residual lumen of 2-3 mm, which allowed for the successful placement of a nasogastric feeding tube (ch 8). Histological examination of the stenotic area showed granulation tissue (Figure 3). Biopsies of the rest of the oesophagus did not show any changes compatible with reflux esophagitis or eosinophilic esophagitis. Imaging, including a contrast study of the upper gastro-intestinal tract, CT scan and MRI showed no evidence of tracheobronchial remnants.

Follow-up and outcomes

Following this diagnosis, a proton pomp inhibitor was started to facilitate healing of the tears after dilatation and feeding through the nasogastric tube was continued resulting in catch-up weight gain. In the eight first months after diagnosis, repetitive endoscopic balloon dilations were performed with intervals between dilatations varying from one to four weeks. Because of recurrent restenosis, intralesional injection with triamcinolone was performed the first time at four months after diagnosis. This treatment was repeated four times over a period of four months with less pronounced restenosis between dilatations. No more dilatations were needed in the four months since the last Triamcinolone injection with repeat endoscopies showing a persistent lumen allowing passage of an adult endoscope, corresponding with 9.9 mm diameter. Tube feeding could be stopped at 4 months after diagnosis.

Discussion

We report a rare case of CES as the underlying cause of non-bilious vomiting in a 5-month infant. This condition should be considered in the differential diagnosis of recurrent non-bilious vomiting, particularly when associated with faltering growth. Key diagnostic clues were the inability to tolerate solid feeds and the inability to insert a nasogastric tube.

The exact incidence of CES remains uncertain due to limited data, primarily derived from case reports and small case series, as it is often excluded from rare disease registries or categorized under broader groups of oesophageal or gastroesophageal anomalies (10). Estimates suggest an incidence of 1 in 25.000-50.000 live births (3). This data stems from a 1969 retrospective study at the Children's Hospital of Pittsburgh, which identified CES in approximately 10% of patients with tracheoesophageal fistula (24/200) over a period of 15 years. The true incidence of CES may be underreported, as its diagnosis is frequently delayed (3).

Based on histological findings, CES can be divided into three subtypes:

1) Tracheobronchial remnants (TBR): CES caused by TBR is characterised by the presence of ectopic cartilage within the stenotic segment. The cartilaginous tissue may form a ring, or may only be present in a part of the stenosis. Respiratory epithelium with seromucous glands and ciliated columnar epithelium, as well as lymphoid tissue may also be present. This subtype is predominantly found in the lower third of the oesophagus (1,11).
2) Fibromuscular thickening or stenosis (FMS): This form of CES is characterized by circumferential hypertrophy of smooth muscle tissue and submucosal fibrosis. There may also be an abnormal

FIGURE 1: growth curves.

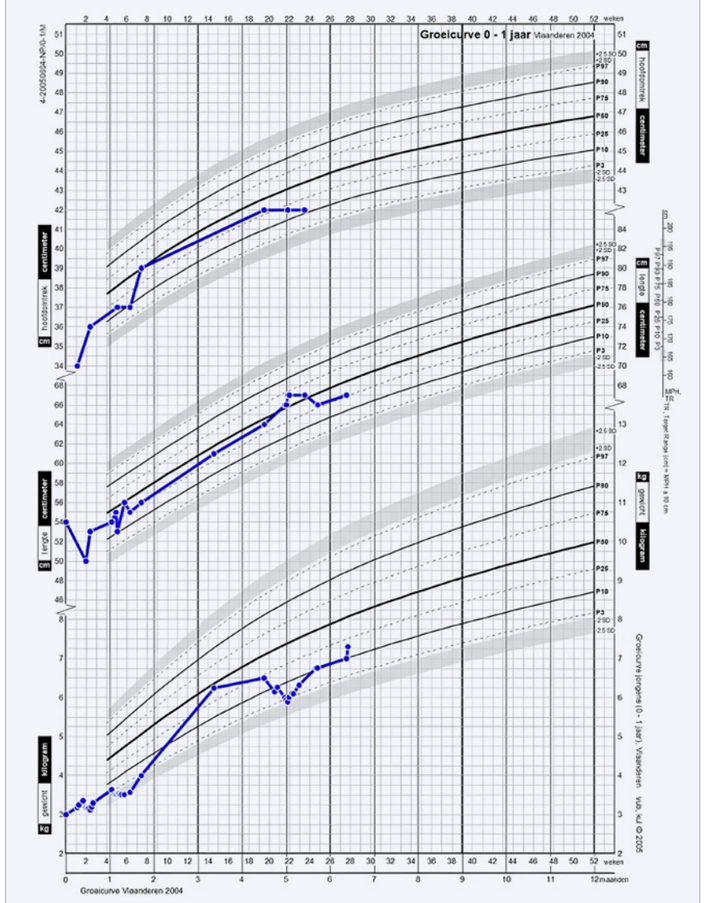


FIGURE 2:

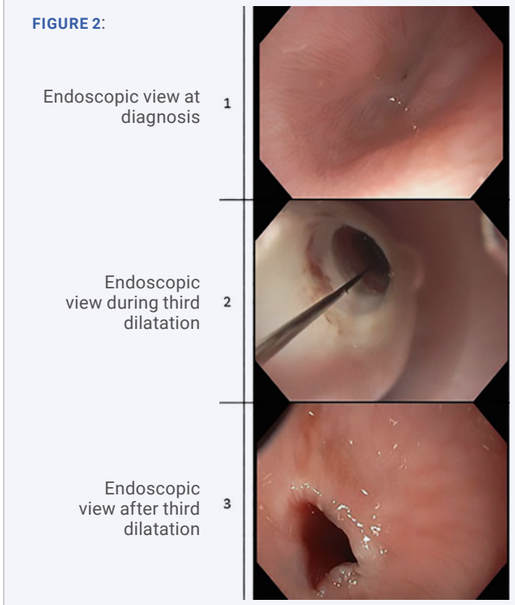
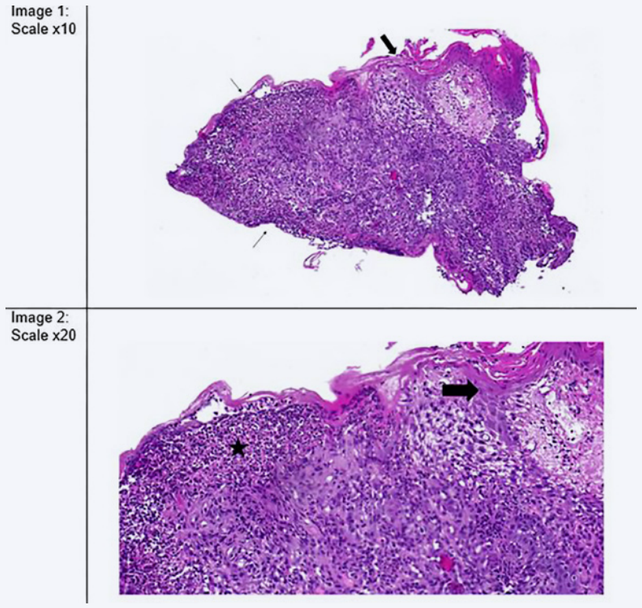


FIGURE 3:

- **Image 1 and 2** show histological images with hematoxylin and eosin stain at 10 and 20 times enlarged scale respectively
- **Image 1**: large arrow indicates reactively changed squamous epithelium. Small arrow shows ulcerative zones with fibrinopurulent material and granulation tissue.
- **Image 2**: large arrow indicated reactively changed squamous epithelium. Asterisk shows ulcerative zone with fibrinopurulent material (abundant granulocytes and some lymfocytes) and underlying granulation tissue



organisation of the muscular layer. This subtype is most commonly found in the middle of lower third of the oesophagus (1,11).

3) Membranous webbing or oesophageal membrane (EM): In this type of CES there is a normal submucosal and muscular organisation of the oesophagus. It mainly is found in the upper and middle third of the oesophagus (1,11).

Histological analysis in our case showed granulation tissue and signs of ulceration (Figure 3), which are non-specific findings. Oesophageal biopsies showed no signs of esophagitis. Due to absence of submucosal of muscular tissue in the biopsies, the subtype of CES could not be confirmed histologically.

Timing and nature of symptoms are determined by the severity of CES. Non-bilious vomiting is a hallmark clinical manifestation, with symptoms often worsening after the introduction of complementary feeding. Other symptoms include faltering growth, dysphagia and food bolus impaction. In cases of severe stenosis, the child may present with hypersalivation, chronic cough, respiratory distress, stridor during feeding, aspiration pneumonia and developmental delay (1,11). In a retrospective multicentre study conducted in France, reporting on 61 patients, 34% were asymptomatic at diagnosis, of the other 40 patients the following symptoms were present at diagnosis: dysphagia in 50%, food impaction in 50%, respiratory symptoms in 42%, and a history of repeated vomiting in 40% (6). Age of diagnosis is variable and delay between first symptoms and diagnosis may be long. (6,8). In less severe cases, symptoms may be more subtle, and diagnosis may only be confirmed later in childhood or even in adulthood (6,12). In the same French multicentre study, age at diagnosis ranged from one day up to 14 years of age, with seven patients who were diagnosed after the age of five years (6). While in another retrospective cohort study, reporting on 20 CES patients (four children with TEF), age of diagnosis ranged between one month and 4.5 years (5). In patients with associated anomalies, diagnosis is often made earlier (6,8).

The diagnosis of CES typically involves imaging techniques such as contrast studies of the upper gastro-intestinal tract, endoscopic ultrasound (EUS), magnetic resonance imaging (MRI) or computed tomography (CT) scan (1,13). EUS is particularly useful to differentiate between CES subtypes. It is especially useful in the identification of TBR, as cartilage is often not identified in biopsies. In FMS it shows hypertrophy of the muscular layer (13,14,15,16). However, successful application of EUS requires a sufficient calibre of the upper oesophageal sphincter and oesophagus to accommodate the passage of the probe. For this reason this investigation was not performed in our case. CT or MRI may also reveal ectopic cartilage in cases of TBR. Upper gastrointestinal endoscopy with biopsies remains the gold standard for diagnosis but may be challenging to distinguish CES from acquired oesophageal stenosis caused by other conditions like reflux esophagitis, eosinophilic esophagitis, caustic ingestion, mediastinal radiation, bullous skin disorders, extrinsic compression and long-term use of nasogastric feeding tubes (1,5,13). Based on the endoscopic, histological, and radiological findings, our case was most compatible with the FMS subtype, as both CT and MRI revealed no evidence of TBR, although we were unable to confirm this histologically.

Treatment of CES varies depending on the subtype and severity of the stenosis. Dilations performed with fluoroscopic or endoscopic guidance or bougienage (based on local expertise and availability of different techniques), are often the first-line treatment (9,13,15,17,18). Surgical repair is reserved as second line treatment, for cases resistant to dilation or complicated by perforation or mediastinitis (12,19). Patients with TBR are more likely to require surgical intervention, as dilations have lower success rates and higher complication rates in this subtype (1,8,11,13,15,20). However, diagnosis of TBR is often challenging, and in several cases, diagnosis is only confirmed in histological investigation after resection.

In a retrospective study reporting on 14 CES patients, 11 patients underwent surgical repair, eight of these patients had prior treatment with dilatations (11). In the French multicentre study, reporting on 61 patients, 16% underwent surgery as primary treatment while 30% underwent surgical repair as secondary treatment after failing dilatations (6). Interestingly, the authors reported that regardless of the type of treatment, 64% of patients continued to experience dysphagia symptoms during follow-up, possibly due to persistent oesophageal dysmotility (6). This advocates a long-term follow-up for these children. A retrospective Italian study involving 47 CES patients, all treated with dilations, reported a perforation rate of 10.6%. Despite this complication, only two patients required surgical intervention due to persistent dysphagia symptoms (17).

Adjuvant therapies, such as local or systemic corticosteroids, local mitomycin C, or proton pump inhibitors, have been used for oesophageal stenosis caused by other aetiologies such as after oesophageal atresia repair or stenosis due to caustic ingestion, but lack evidence in children with CES (13). In the guidelines for paediatric gastrointestinal endoscopy guidelines by the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) stenting and topical mitomycin C are suggested for the treatment of refractory stenosis in benign oesophageal strictures. They do not suggest routine use of intralesional steroids (23). The UK guidelines on oesophageal dilatation in clinical practices advocates for the use of PPI after oesophageal dilatation to decrease of the risk of symptomatic gastro-oesophageal reflux disease or ulcerative esophagitis after this procedure and to avoid recurrence of the stenosis. In this guideline intralesional corticosteroids are mentioned as a possible treatment modality in combination with dilatations in refractory strictures when there is evidence of inflammation and in postoperative strictures however this guideline offers no advice specific for CES (24). Mitomycin C is not advocated in this guideline due to insufficient evidence (24).

Oesophageal stenting may be considered for refractory cases, though its use in CES is rare. A systematic review from 2010 reported no cases of oesophageal stenting in CES, only in case of caustic strictures or strictures following oesophageal atresia repair (21). In an American study reporting on 36 patients, stents were utilized in conjunction with endoscopic incisional therapy (EIT) in 17 patients, and in four patients to address postoperative restenosis. The same study also showed success with the use of EIT in avoiding surgical intervention with an OR of 0.1 (p=0.007) compared to patients who received non-EIT endoscopic therapy. In this case series all patients who went for surgical repair had prior intralesional corticosteroid injections. However, the odds of complications after EIT were significantly greater than in those without EIT (odds ratio 6.39; p< 0.001) (22).

Conclusion

This infant with CES emphasizes the importance of considering this rare entity in cases of recurrent non-bilious vomiting and faltering growth. Invasive diagnostics, including endoscopy, may be required for definitive diagnosis, particularly when symptoms are progressive. Key diagnostic clues in our case included the inability to tolerate solid feeds and failed attempts at nasogastric tube placement.

The authors of this paper have no conflicts of interest to declare.

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▼ Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Les professionnels de 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. Excipients à effet notoire : Ce médicament contient 0,1 mg de polysorbate 80 (E433) pour chaque dose de 50 mg (0,5 ml) et 0,2 mg pour chaque dose de 100 mg (1 ml). 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. – Les enfants jusqu'à l'âge de 24 mois qui demeurent vulnérables à une infection sévère due au VRS au cours de leur deuxième saison de circulation du VRS (voir rubrique 5.1). Beyfortus doit être utilisé conformément aux recommandations officielles en vigueur. POSOLOGIE ET MODE D'ADMINISTRATION Posologie Nourrissons au cours de leur première saison de circulation du VRS La dose recommandée est une dose unique de 50 mg administrée par voie intramusculaire pour les nourrissons dont le poids est <5 kg et une dose unique de 100 mg administrée par voie intramusculaire pour les nourrissons dont le poids est ≥5 kg. Beyfortus doit être administré dès la naissance chez les nourrissons nés au cours de la saison d'épidémie à VRS. Pour les nourrissons nés en dehors de la saison, Beyfortus doit être administré idéalement avant 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 nirsévimab 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). Enfants qui demeurent vulnérables à une infection sévère due au VRS au cours de leur deuxième saison de circulation du VRS. La dose recommandée est une dose unique de 200 mg administrée en deux injections intramusculaires (2 x 100 mg). Beyfortus doit être administré idéalement avant le début de la deuxième saison d'épidémie à VRS. Chez les individus devant subir une chirurgie cardiaque avec circulation extracorporelle, une dose supplémentaire peut être administrée dès que l'individu 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 au cours de la première saison d'épidémie à VRS doit être de 50 mg ou de 100 mg selon le poids, ou de 200 mg au cours de deuxième saison d'épidémie à VRS. Au-delà de 90 jours, la dose supplémentaire peut être une dose unique de 50 mg indépendamment du poids au cours de la première saison d'épidémie à VRS, ou de 100 mg au cours de la deuxième saison d'épidémie à VRS, afin de couvrir le reste de la saison de circulation du VRS. 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. Si deux injections sont nécessaires, des sites d'injection différents doivent être utilisés. Pour les instructions concernant les précautions particulières de manipulation du médicament, voir la rubrique 6.6. 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 fièvre 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 Ci-dessous sont présentés les effets indésirables rapportés chez 2 966 nourrissons nés à terme et prématurés (AG ≥29 semaines) ayant reçu du nirsévimab dans le cadre d'études cliniques et dans le cadre de la surveillance après commercialisation (vor rubrique 4.4). Les effets indésirables rapportés au cours des études cliniques contrôlées 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 du système immunitaire · Indéterminé – Hypersensibilité1 Effet indésirabe rapporté dans le cadre de notification spontanée Affections de la peau et du tissu sous-cutané · Peu fréquent - Eruptions cutanées2 2 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'injection3 ; Fièvre 3 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 au cours de leur première saison de circulation du VRS La sécurité d'emploi a été évaluée dans l'étude 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 (n=614) ou du palivizumab (n=304). Le profil de sécurité du nirsévimab chez les nourrissons l'ayant reçu au cours de leur première saison d'épidémie du VRS était comparable à celui du comparateur palivizumab et cohérent avec celui observé chez les nourrissons nés à terme et prématurés d'AG ≥29 semaines (études D5290C00003 et MELODY). La sécurité d'emploi a également été évaluée au cours de l'étude MUSIC, étude ouverte, non contrôlée, à dose unique, menée chez 100 nourrissons et enfants immunodéprimés d'âge ≤ 24 mois, qui ont reçu du nirsévimab lors de leur première ou deuxième saison d'épidémie à VRS. Les sujets présentaient au moins l'une des conditions suivantes : immunodéficience (combinée, en anticorps ou autre étiologie) (n = 33) ; corticothérapie systémique à forte dose (n = 29) ; greffe d'organe ou de moelle osseuse (n = 16) ; chimiothérapie immunosuppressive (n = 20) ; autre traitement immunosuppresseur (n = 15) et infection par le VIH (n = 8). Le profil de sécurité du nirsévimab était cohérent avec celui attendu pour une population d'enfants immunodéprimés et avec celui observé chez les nourrissons nés à terme et prématurés d'AG ≥ 29 semaines (études D5290C00003 et MELODY). Le profil de sécurité du nirsévimab chez les enfants pendant leur deuxième saison d'épidémie à VRS était cohérent avec celui observé pendant leur première saison d'épidémie à VRS. Nourrissons nés à terme et prématurés entrant dans leur première saison à VRS La sécurité d'emploi du nirsévimab a également été évaluée au cours de l'étude HARMONIE, étude multicentrique randomisée, en ouvert, menée chez 8 034 nourrissons nés à terme et prématurés (AG ≥29 semaines) entrant dans leur première saison de VRS (non éligibles au palivizumab), qui ont reçu soit du nirsévimab (n=4 016) soit aucune intervention (n=4 018) pour la prévention des hospitalisations liées aux infections des voies respiratoires inférieures à VRS. Le profil de sécurité du nirsévimab administré lors de la première saison de VRS était cohérent avec le profil de sécurité du nirsévimab observé au cours des études contrôlées contre placebo (études D5290C00003 et MELODY). 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 : www.afmps.be – Division Vigilance : Site internet : www.notifieruneffetindesirable.be – e-mail: adr@fagg-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 : 04/2025. Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu

* Beyfortus® est remboursé les bébés nés depuis le 19/02/2025 (date de fin de la saison VRS 2024-2025) pour leur première saison de VRS.
** Beyfortus® est remboursé pour les jeunes enfants (<2 ans) qui subissent une chirurgie cardiaque avec circulation extracorporelle pendant leur première ou deuxième saison de VRS, ou les jeunes enfants (<2 ans) qui restent vulnérables à une maladie grave due au VRS pendant leur deuxième saison de VRS (comme décrit dans les recommandations du CSS (avis 9760)).

Référence:
1. Beyfortus® RCP, Avril 2025

Sanofi Belgium MAT-BE-2501425-V1.0-01/2026

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