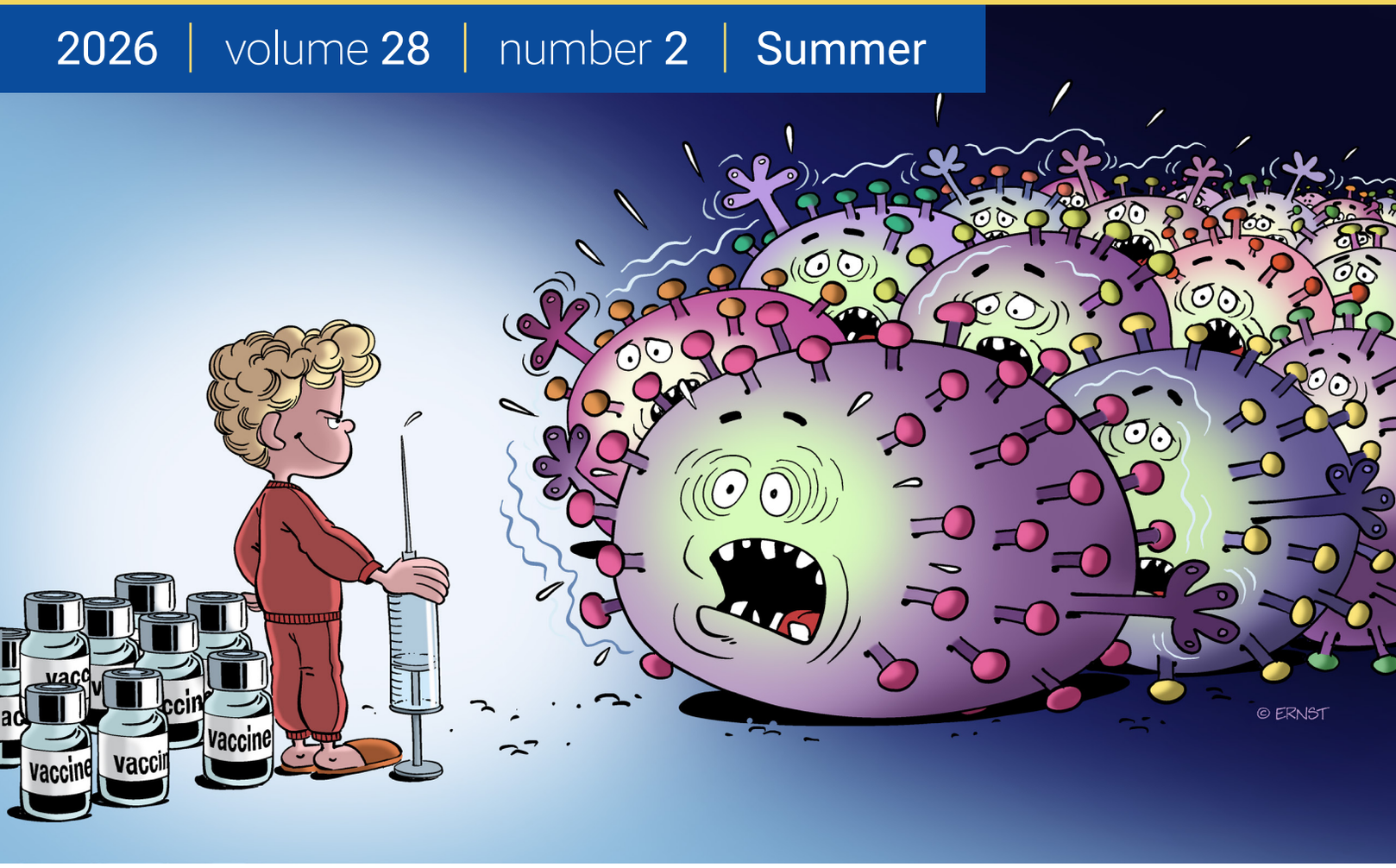
Belg J Paediatr. 2026;28(2): p.95-202

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2026 | volume 28 | number 2 | Summer



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Real-world Evidence from Diabetes Technology in Type 1 Diabetes: Towards Clinically Meaningful, Person-centered and Healthcare-informing Insights

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9h Plantons le décor
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- Zéro stress, zéro douleur.
- FLASH : La médecine d'urgence dans la poche.

11h10 Top 5 des urgences
- Douleurs thoraciques et malaises : ces plaintes qui nous embêtent.
- Les boutons d'urgence ?!
- Gare à la bosse !
- Trop petit, trop chaud.
- FLASH : La médecine d'urgence dans la poche (gauche !).

13h Pause lunch – visite des stands

14h → 18h Après-midi

14h • *« Pediavox : les actualités pédiatriques belges ».*

14h20 Vague à l'âme
- Quand le vase déborde.
- Place aux accompagnants..
- La communication thérapeutique, ça se soigne

16h20 Quand la clinique ne suffit pas
- To scan or not to scan ?
- Hocus POCUS.
- Examens complémentaires : alliés ou ennemis ?

18h • Fin de la réunion scientifique.

Renseignements :
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Belg J Paediatr. 2026;28(2): p.97

Prevention: a shared responsibility?!

The cover of the summer edition, 2026 of our Belgian Journal of Paediatrics speaks for itself and illustrates the editorial of this issue. The switch to a new editor led to a certain publication delay, but gave us the opportunity to further boost the quality of our journal.

In his Theory of Humours, Hippocrates (460-377 BC), the father of Western medicine, already focuses on prevention by maintaining internal harmony based on a healthy lifestyle (diaita) to stave off disease. “Praestat cautela quam medela”, translated as: “Prevention is better than cure”, is one of the most famous quotes mentioned in Adagia, the collection of proverbs by Desiderius Erasmus (1500 AD), not only applicable in healthcare, but also in many other domains, aspects and situations of life. A “healthy” life, is much more than the absence of disease; it concerns a state of total physical, mental, intellectual, social and emotional well-being for every human being, without any inequality or inequity. For infants, children and adolescents this means opportunities to be born and grow up in a protected community, a safe society and clean environment, to create the right circumstances to reach their fullest developmental potential, to provide adequate education. Globally, we need to protect children and adolescents from the direct and indirect, long-term harmful consequences due to any kind of environmental pollution, unsafe situations, threats and challenges of modern society, climate change. We must prevent children, adolescents and their families from starving or dying in wars. This is unbearable and immoral! As paediatricians, we have the privilege to be the advocates of these young people, to defend their rights, with special attention to the most vulnerable ones amongst them. We are their advocates fighting for their rights to optimal physical and mental health, safety and an adequate education. Prevention, from womb to adolescence and in many domains, is one of the core businesses and an inherent part of our daily paediatric practices, influencing and shaping individuals’ development and health across the entire life course. In Belgium, only 0,23 % relative to the gross domestic budget (GDP) is spent on preventive care, well below the European average (0,37%). This is just 2 % of the entire Belgian healthcare budget (OECD average: 3,4%; EU average: 4%). This low budget allocation in contrast to the investment in the curative-oriented healthcare, combined with the country’s complex division of authority between federal and regional governments (Belgium counts 9 ministers of Health), drives intense debates for many years. Although negotiations occur within the so-called Interministerial Conference (IMC), the fragmented distribution of responsibilities can still result in different decisions in different regions of the country, about the access to preventive services, the organization of programmes, the financial investment, without fully aligned policies or a national shared vision. Effective prevention requires cooperation between different stakeholders and strengthening of cross-sector collaboration, being convinced that this is a long-term strategy and a long-term investment.

In this issue, two articles focus on vaccination and immunization in infants and children. Globally, vaccination is one of the greatest achievements and clearest examples of successful preventive medicine, with a substantial return of investment on the short and the long-term for the individual and the community, in low-, middle- and high-income countries. Belgium has historically achieved high childhood vaccination coverage through well-organized programmes and strong collaboration between healthcare providers and the public health authorities. However, this success cannot be taken for granted and even can be further optimized. Decisions about the national immunization program (NIP) should be based on evidence, epidemiology and the overall individual and population disease burden, a coordinated strategy is needed and regional differences should be avoided as much as possible, vaccine confidence must be maintained, hesitancy must be monitored and minimized, equal access to childhood vaccination must be guaranteed, excluding inequality and inequity. Reflection on safe and effective vaccines not (yet) universally included in the Belgian NIP must continue. Decisions must be based not only on the incidence of the infection, but also on the individual disease severity, case fatality, long-term disabling complications with a significant negative long-life impact on quality of life, practical, psychological, employment burden on the family and societal economic consequences. The nature of current economic models to evaluate cost-effectiveness of vaccines differs from the methodology for curative treatments and is still somewhat speculative. They are based on limited assumptions and don’t take into account some under-recognized, neglected patient, family and societal burden. It’s not always easy to assign an agreed monetary value to the possible gains, avoiding these and they mostly remain “invisible” for policymakers. We could argue that health economics should guide, rather than determine immunization policy. Preventive healthcare is a shared responsibility, involving various stakeholders including scientists, epidemiologists, health care workers, policymakers, industry and also patient advocate groups. A finite health budget is a reality and some health interventions need to be prioritized over others. But, can we afford us not to prevent some preventable devastating diseases, complications of an unhealthy lifestyle, limited development and safety of our children and adolescents? Shouldn’t we consider prevention as an investment rather than an expense?

Let’s join forces!

The editorial team,

Christophe Chantrain and Marc Raes

Editorial BJP: summer edition, 2026.

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1. ESPGHAN 2023. Abstract 281. Supplementation with 5-hmos from birth to 15 months shifts the gut microbiome developmental trajectory of caesarean-section born infants towards a reference of breastfed, vaginally-delivered infants.

Ce document est exclusivement réservé à l'information des professionnels de la santé.
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 la 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 qui est exclusivement nourri au biberon nécessite environ 450g 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 une dilution incorrecte peuvent rendre le bébé malade. **Avec les compliments de Nestlé.** ER: K. Desmedt, Nestlé Belgilux SA/NV, Rue de Birminghamstraat 221 - 1070 Bruxelles/Brussel, BCE/KBO 0402.231.383. PID3952 – Mars 2026.

RESEARCH ARTICLE

Belg J Paediatr. 2026;28(2): p.99-106

Incidence of and Risk Factors for Postoperative Paediatric Cerebellar Mutism Syndrome in Children with Posterior Fossa Tumours: A Retrospective Study

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Keywords

Cerebellar mutism; Medulloblastoma; Pilocytic astrocytoma; Posterior fossa

Abstract

Objective

Postoperative paediatric cerebellar mutism syndrome (pCMS) can occur in children after resection of a posterior fossa brain tumour. It is characterised by mutism or reduced speech and emotional lability, often with disturbances in motor and cognitive functions. This study aimed to analyse the clinical features and risk factors for pCMS in the Ghent University Hospital.

Methods

Retrospective data of children treated for posterior fossa tumours in the Ghent University Hospital between 2008 and 2022 were reviewed, using the 2016 Delphi consensus definition of pCMS.

Results

Twenty-two out of 69 patients (32%) developed pCMS. Motor deficits were most frequent. Dysarthria was the leading speech impairment, mutism was the primary language disorder. The most prevalent affective disorder was anxiety. Univariate analysis showed significant associations with medulloblastoma (OR 3.41; 95%CI 1.19-9.78), brain stem invasion (OR 4.76; 95%CI 1.24-18.31) and midline tumour location (OR 1.58; 95%CI 1.30-1.91). Conversely, pCMS was less frequent in pilocytic astrocytomas (OR 0.21; 95%CI 0.06-0.73) and in tumours larger than 5 cm (OR 0.08; 95%CI 0.02-0.39).

Conclusion

This study highlights the clinical features and risk factors of pCMS in children treated for posterior fossa tumours. While motor deficits were most commonly reported, disorders in speech, language, and affective and cognitive function may have been underrecognised. Risk factors such as tumour type, brain stem invasion and midline location, are consistent with existing literature, whereas a "protective" effect of larger tumours might be attributed to the predominance of large pilocytic astrocytomas in this cohort.

Introduction

Brain tumours are the second most common type of malignancy in children, and represent the most prevalent form of solid tumours in this age group (1). Among all paediatric brain tumours, 45-60% are located in the posterior fossa, more specifically cerebellar tumours and tumours in the fourth ventricle (2). Postoperative paediatric cerebellar mutism syndrome (pCMS) can develop in children following the resection of a posterior fossa tumour and is characterised by delayed onset mutism or reduced speech, and emotional lability (3). The incidence of pCMS ranges from 11% to 29% in retrospective studies, but is higher in prospective studies, ranging from 24% to 30% (4-8). However, comparing studies and incidence rates is challenging, as a consensus on the definition was not established until 2016 (3). Mutism, defined as the (partial) absence of speech despite preserved physical speech ability, is the most characteristic symptom of pCMS, although it is not a diagnostic requirement (5). It typically manifests within hours to days after surgery, with vocalisations often limited to high-pitched crying (4). The mutism is always transient, lasting from

days to months with an average duration of five weeks. Some children continue to experience speech and language difficulties after the mutism resolves (8, 9). During the postoperative period, children with pCMS often develop additional symptoms related to motor and cognitive functions (3). The additional symptoms persist longer than the mutism, particularly ataxia, dysarthria and other impairments (10). The underlying mechanisms of pCMS remain incompletely understood. The current hypothesis attributes pCMS to diaschisis, a phenomenon in which damage to one brain region disrupts function in a distant but connected area due to reduced input (11, 12). In pCMS, injury to the dentato-thalamo-cortical (DTC) tract during posterior fossa tumour resection can lead to decreased cerebellar input, resulting in temporary hypoactivity in the cerebral hemispheres and affecting motor coordination, cognition, and emotional regulation (11, 13). Neural plasticity and compensatory mechanisms contribute to recovery, but persistent symptoms following the resolution of mutism are most likely attributable to direct injury to the cerebellum (9, 10, 12). Treatment is primarily supportive, involving multidisciplinary rehabilitation with physical, speech, and cognitive therapies (10, 14). It enables children to develop alternative strategies to compensate for functional deficits, supports the promotion of independence, and facilitates reintegration into activities with peers. However, rehabilitation alone is insufficient to prevent further decline in motor and cognitive functions, partly due to the impact of chemotherapy or radiotherapy in the postoperative period (8, 14). A limited number of studies and case reports have suggested a potential benefit of various pharmacological agents in the management of pCMS, including benzodiazepines and selective serotonin reuptake inhibitors (15-17). However, no large-scale studies have demonstrated consistent efficacy. Multiple risk factors for the development of pCMS have been identified in various studies, with three consistently confirmed: tumour type (medulloblastoma), midline tumour location, and brainstem involvement. This research aimed to evaluate the incidence of pCMS, identify its clinical features, and determine the associated risk factors at the Ghent University Hospital over the last 15 years.

Materials and Methods

This retrospective study included children up to 18 years of age who were diagnosed with a posterior fossa tumour at the Ghent University Hospital in Belgium over a fifteen-year period, between January 1st, 2008, and December 31st, 2022. The study was approved by the Ethics Committee affiliated with the Ghent University Hospital. The analysis focused on the first surgical intervention, data regarding surgery for recurrent tumours were not analysed. Patients whose initial surgery was performed at a different hospital before referral, were excluded. Patients under one year of age, in whom assessment of language and speech is challenging, were also excluded. Demographic data, patient characteristics, tumour characteristics on imaging and histopathology, and surgical details were collected. The selection of possible risk factors was based on those most frequently reported in the literature and included tumour type, midline location, brainstem involvement, tumour size, left-handedness, and surgical technique. Postoperative clinical information was analysed to determine the occurrence of pCMS. All children were evaluated postoperatively within a multidisciplinary rehabilitation program, including assessments by a speech therapist, physiotherapist, occupational therapist, and rehabilitation physician. Reports from all specialists were reviewed and consulted. These findings were subsequently compared with those reported in literature. This study adopts the 2016 Delphi consensus definition of pCMS, which is characterised by mutism or reduced speech and emotional lability following surgery for a cerebellar or fourth ventricle tumour in children (3). All patients were evaluated for development of symptoms related to language, speech, or emotional affect during the postoperative period. Additional symptoms, as delineated in the 2016 consensus article, were systematically evaluated. All possible symptoms were categorised into five distinct domains:

- Motor deficits; including hypotonia, dysmetria, dysphagia, ataxia, hemiparesis, oculomotor problems, oropharyngeal dysfunction, urinary retention or incontinence, and cranial neuropathies
- Speech impairments; including dysarthria, disturbed prosody, and reduced speech production such as speaking in short sentences or single words
- Language disorders; including mutism, word-finding difficulties, and reduced verbal fluency
- Affective disorders; including emotional lability, personality changes with apathy or inappropriate behaviour
- Cognitive impairments; defined as intellectual impairments, including reduced executive functions, attentional problems, visuospatial disorganisation, and impaired visuospatial memory

Statistical analyses were performed using SPSS Statistics 28. Statistical significance was set at $P < 0.05$. Univariate analyses were conducted using the Mann-Whitney U test for continuous variables and the Pearson's chi-square test for categorical variables. The Fisher's exact test was used when the expected values were less than five. For survival analysis, the Kaplan-Meier method and the Mantel-Cox log-rank test were used.

Results

Demographic Data, Patient and Tumour Characteristics

Table 1 presents the demographic and clinical data of the cohort. During the observational period, 76 paediatric patients were admitted to the Ghent University Hospital with a tumour in the posterior fossa. Seven patients were excluded from the analysis: three patients whose surgery was performed at the referring hospital, one patient with an inoperable tumour, and three patients younger than 1 year at time of diagnosis (11 months, 9 months, and 5 months of age). Data from 69 patients were analysed. The median duration of follow-up was 66 months, or 5.5 years. Within the cohort, 58% of patients were male, resulting in a male-to-female ratio of 1.38. The median age at diagnosis was 7 years. The three main tumour types were medulloblastoma, pilocytic astrocytoma and (anaplastic) ependymoma. Other diagnoses on histopathology, including atypical teratoid rhabdoid tumour (ATRT, 1 case), choroid plexus papilloma (1 case), diffuse low-grade astrocytoma (3 cases), hemangioblastoma (1 case), and grade 2 low-grade glioma (1 case), are categorised as "other" due to their low incidence. In the majority of tumours (88%), imaging revealed brainstem involvement due to invasion, external compression, or a combination of both. Most tumours (87%) were located at the midline. The tumours had a median size of 4.8 cm (largest diameter on imaging), and 44% of the tumours exceeded 5 cm in size. When fundoscopy was performed at diagnosis, papilledema was present in 42% of patients. Imaging revealed hydrocephalus in 78% of cases, for which surgical intervention—most commonly the placement of an external ventricular drain—was required prior to tumour resection. Detailed information on the surgical procedure was available for 41 patients, of whom 15 (37%) underwent splitting of the vermis. Postoperative imaging demonstrated complete resection in 58% of cases. During the 15-year follow-up period, 14 out of 69 children died. The 5-year overall survival rate reached 90% in this cohort, and the 10-year overall survival rate was 77%. Among patients with medulloblastoma, 10 patients died (37%). No deaths occurred in the group with pilocytic astrocytoma. In each of the groups with (anaplastic) ependymoma and combined other tumours, there were two deaths (29%). The

log-rank test (Mantel-Cox) confirmed a statistically significant difference in survival between all groups (p = 0.012).

Postoperative paediatric Cerebellar Mutism Syndrome

pCMS was retrospectively diagnosed in 22 children (32%), all of whom exhibited symptoms across multiple domains. Motor deficits were present in the majority of these patients (19/22), with hypotonia being the most prevalent (N=9), followed by hemiparesis, oculomotor dysfunction, and ataxia, each observed in 4 children. Speech impairments were identified in 13/22 children, most commonly dysarthria (N=9), and language disorders were present in 9/22 children, with mutism being the most frequent (N=7). Affective disorders were reported in 8/22 children, including anxiety (N=3) and autistic behaviour (N=2). Cognitive impairments were the least common, with only one child demonstrating diminished executive skills. Further information regarding the clinical features is presented in Figure 1. The demographic and clinical data of patients with and without pCMS are compared in Table 2. A statistically significant difference in the incidence of pCMS was observed based on tumour type, as determined by histopathological analysis. Patients with medulloblastoma had a higher probability of developing pCMS (odds ratio [OR] 3.41; 95% confidence interval [CI] 1.19–9.78). The molecular subgroups of medulloblastomas were also analysed. Only having been systematically examined since 2016, this could only be ascertained in 11 patients. Of these patients, three exhibited the wingless (WNT) type (one developed pCMS), two presented with the Group 3 type (one developed pCMS), and six manifested the Group 4 type (three developed pCMS). No patient with the sonic hedgehog (SHH) type was identified. The diagnosis of pilocytic astrocytoma was associated with a decreased likelihood of developing pCMS following surgical intervention (OR 0.21; 95%CI 0.06–0.73). Tumours with brainstem invasion (OR 4.76; 95%CI 1.24–18.31) or a midline tumour location (OR 1.58; 95%CI 1.30–1.91) were associated with a significant increased likelihood of developing pCMS. There was also a significant correlation for tumour size: children with tumours larger than 5 cm exhibited a significantly lower risk of developing pCMS (OR 0.08; 95%CI 0.02–0.39). To further elucidate this finding, the tumour size was evaluated per tumourtype. The median tumour size of the medulloblastomas associated with pCMS was 4.3 cm (maximum 7.0 cm), whereas medulloblastomas that were not associated with pCMS had a smaller median tumour size of 4.1 cm (maximum 6.4 cm). This finding was not statistically significant (P = 0.895), suggesting only a minimal difference between groups. In contrast, the four children with pilocytic astrocytomas who developed pCMS had a median tumour size of 4.1 cm (maximum 4.9 cm), whereas the remaining 24 pilocytic astrocytomas had a larger median tumour size of 5.3 cm (maximum 8.7 cm).

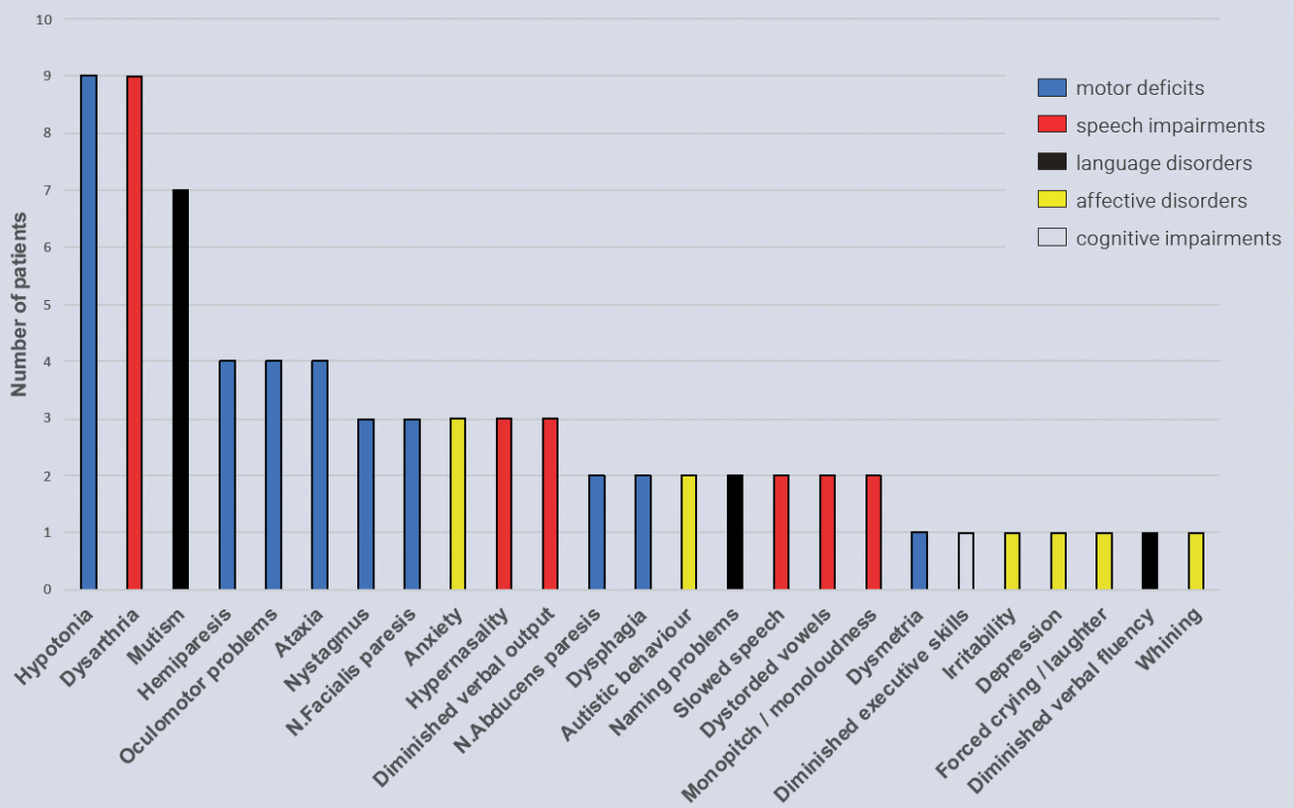
TABLE 1: Demographic and clinical data of the cohort.

	Total = 69 (range)	%
Sex		
Male	40	58
Female	29	42
Median age at diagnosis	7 years (13 months – 15 years)	
Brain stem involvement	**52**	**88**
External compression	47	**83**
Invasion	12	**21**
Tumour location		
Midline	60	**87**
Left cerebellar hemisphere	7	**10**
Right cerebellar hemisphere	2	**3**
Tumour size		
Median size	4.8 cm (2.0 cm – 8.3 cm)	
Larger than 5 cm	26	**44**
Smaller than 3 cm	7	**12**
Left-handedness	**10**	**28**
Papilledema	**14**	**42**
Hydrocephalus	**52**	**78**
Management of hydrocephalus		
None	11	**21**
External ventricular drain	40	**77**
Third ventriculostomy	1	**2**
Splitting of the vermis	**15**	**37**
Complete resection on radiology	**40**	**58**
Tumour type (as on histopathology)		
Medulloblastoma	27	**39**
Pilocytic astrocytoma	28	**41**
(anaplastic) ependymoma	7	**10**
Other	7	**10**
Development of pCMS	**22**	**32**
Deceased	**14**	**20**

Discussion

This retrospective single-centre study analysed data from 69 paediatric patients who presented with a tumour located in the posterior fossa. This study marks the first comprehensive analysis of data from Belgian children with posterior fossa tumours who are susceptible to developing pCMS. Tumour type was significantly associated with the development of pCMS. Medulloblastoma emerged as a strong predictor, consistent with the available literature (6, 18-21). These tumours often occur along the midline and invade the brainstem, increasing the risk of damaging the adjacent DTC-tract during surgery. In contrast, the diagnosis of pilocytic astrocytoma was significantly associated with a lower risk of developing pCMS—an association previously reported only once (21). This "protective effect" may be related to the typical lateral location of these tumours within the cerebellar hemispheres. Children with a tumour invading the brainstem had a significantly higher risk of developing pCMS, a result that matches several previous meta-analyses and retrospective studies (18, 19, 21, 22). A prospective study focusing exclusively on medulloblastomas also reported this risk factor (4). Patients with tumours situated on the midline had a higher probability of developing pCMS, which is also consistent with earlier research (6, 19-21, 23). This correlation can be attributed to the caudal structures of the DTC-tract being located medially (19). In this study, tumour size was significantly associated with pCMS, with larger tumours linked to a lower likelihood of developing pCMS. Overall, the pilocytic astrocytomas in this cohort were on average larger than medulloblastomas (Figure 2). In the subgroup of pilocytic astrocytomas, pCMS occurred in relatively smaller tumours, which may have contributed to the overall association between larger

FIGURE 1: Clinical features in children who developed pCMS.



tumour size and a lower likelihood of developing pCMS. In contrast, analysis of the medulloblastoma subgroup demonstrated a non-significant trend suggesting that larger medulloblastomas may be associated with the development of pCMS, with higher median and maximum tumour dimensions observed in the pCMS group. Although this finding did not reach statistical significance, it may suggest that increasing tumour size could play a role in medulloblastomas for causing pCMS. In a literature review, Ashida et al. reported an association between larger tumour size and pCMS (19). However, this conclusion was based on only three prior studies, the largest of which included exclusively medulloblastomas (24). This effect can be explained by the tendency of larger medulloblastomas to invade nearby anatomical structures, and thereby increasing the risk of damage to the DTC tract during surgery. The above-mentioned findings support the hypothesis that the development of pCMS is more strongly associated with the underlying histopathological tumour type, as each type has its distinct biological characteristics, with size or location reflecting the tumour type rather than acting as independent risk factors. In this cohort, medulloblastomas, which frequently invade adjacent tissues, were mostly located on the midline and smaller compared to pilocytic astrocytomas (Figures 2 and 3). In a large prospective cohort study it was observed that high-grade tumours, including medulloblastomas, were significantly linked to postoperative speech impairment, regardless of tumour location or surgical technique (20). In other studies, a significant correlation between increasing tumour size and pCMS was found only in medulloblastomas, likely due to larger medulloblastomas showing more invasion to adjacent tissues than other tumour types (18, 23). On the other hand, the "protective effect" of pilocytic astrocytomas against pCMS, as reported by Dhaenens et al., persisted even in midline pilocytic astrocytomas (21). More recently it was also observed that even the molecular subtype in medulloblastomas correlates with pCMS development. Jabarkheel et al. observed that children with SHH-type medulloblastomas were less likely to develop pCMS, partially because of the characteristic lateral positioning of this tumour subtype, although a protective effect was also noted in medial positioning (25). To further elucidate the effect of tumour type on the development of pCMS, larger prospective studies are required. No significant correlation was observed for other parameters, including left-handedness. Only one study had identified this feature as being significantly associated with pCMS, whereas others found no such association (26-28), aligning with the findings of this analysis. As pCMS is a postoperative complication, substantial research has focused on surgical techniques to reduce its risk. This study included both the traditional transvermian approach, which involves splitting the vermis, and the telovelar approach, in which splitting is not required. No significant association was observed between vermis splitting and the development of pCMS, as previously reported in multiple studies (7, 20, 22). However, two meta-analyses and one retrospective study did find a significant association between surgical technique and pCMS incidence, favouring the telovelar approach (18, 19, 29). Additionally, it was reported that gentle dynamic retraction can reduce the risk of pCMS compared to the use of static retracting spatulae, further supporting the benefit of the telovelar approach (29). Thanks to modern surgical techniques, such as neuronavigation and the use of ultrasonic surgical aspirator suction cannulas, it is possible to perform gross central tumour debulking before determining tumour margins. This enables smaller operative windows and minimises the need for brain tissue retraction, thereby facilitating

TABLE 2: Possible risk factors for pCMS (**Bold**: significant P-values).

	pCMS (N = 22)	%	No pCMS (N = 47)	%	P-value
Tumour type (as on histopathology)					
Medulloblastoma	13	59	14	30	**0.020**
Pilocytic astrocytoma	4	18	24	51	**0.010**
(anaplastic) ependymoma	2	9	5	11	1.000
Other	3	14	4	9	0.672
Tumour location					
Midline	22	100	38	81	**0.049**
Left cerebellar hemisphere	0	0	7	15	-
Right cerebellar hemisphere	0	0	2	4	-
Brain stem involvement	17	94	35	85	0.422
External compression	13	77	34	85	0.464
Invasion	7	41	5	13	**0.031**
Tumour size					
Median size	4.3 cm		5.2 cm		**0.042**
Larger than 5 cm	2	11	24	60	**<0.001**
Smaller than 3 cm	2	11	5	13	1.000
Splitting of the vermis	7	44	8	32	0.446
Left-handedness	5	42	5	21	0.247

the less invasive telovelar approach and permitting gentle, dynamic retraction (22). Although tumour-related factors likely play the major role in the development of pCMS, surgical technique remains the only modifiable factor that may influence its incidence. It therefore represents an important focus of preventive strategies, and surgeons should consistently aim to optimise their technique in order to minimise the incidence of pCMS. It was remarkable that postoperative reports primarily focused on motor deficits like hypotonia and hemiparesis, while speech impairments, language disorders and affective disturbances, essential for diagnosing pCMS, were reported less frequently. These symptoms were documented in subsequent reports by speech therapists and rehabilitation specialists. It is imperative for healthcare providers to consider these more subtle manifestations in the postoperative period, as they are sufficient to independently establish a diagnosis of pCMS. Early identification is essential for timely initiation of appropriate rehabilitation and follow-up. As previously mentioned, rehabilitation alone is not sufficient to prevent further decline in motor and cognitive functions in children with pCMS (14). The prognosis and symptom progression for individual patients are difficult to predict, as the course of recovery is highly variable. Speech impairments often persist for several months or even years, and mutism lasting longer than four weeks is associated with an increased risk of long-term speech and language deficits (8). Furthermore, pCMS appears to exert a substantial negative impact on cognitive function (30). The combination of these postoperative sequelae in children—who already contend with a brain tumour, the effects of chemotherapy and, in some cases, radiotherapy, and frequent school absenteeism—renders them particularly susceptible to learning difficulties and challenges in academic progression. Given that these impairments in speech, language, and cognition can persist throughout several years of childhood, it is therefore essential that paediatricians and other healthcare professionals involved in the long-term follow-up of these patients are familiar with pCMS and its clinical features. This study had several limitations, partly due to its retrospective single-centre design. A first limitation is the absence of correction for multiple testing. Although variables were selected a priori, multiple comparisons increase the risk of false-positive findings, and some associations may reflect chance. Given the small sample size and limited number of pCMS events, applying a strict correction would have reduced statistical power. Therefore, results should be interpreted cautiously and considered exploratory, requiring confirmation in larger cohorts. The limited sample size and missing values prevented a multivariate analysis. While imaging reports were reviewed, the images were not reanalysed by a (paediatric) radiologist, which could have reduced missing data regarding tumour characteristics on imaging. The diagnosis of pCMS was retrospectively established, based on the 2016 definition (3). A

FIGURE 2: Tumour size according to tumour typer.

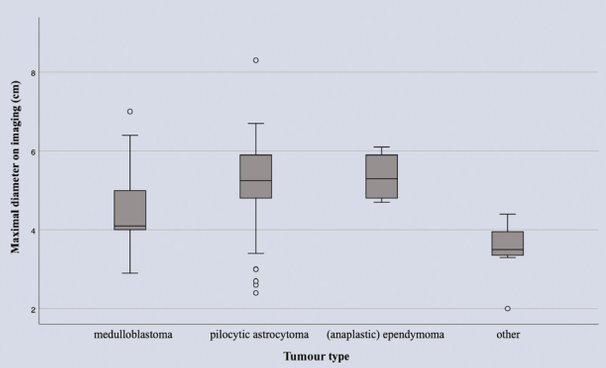
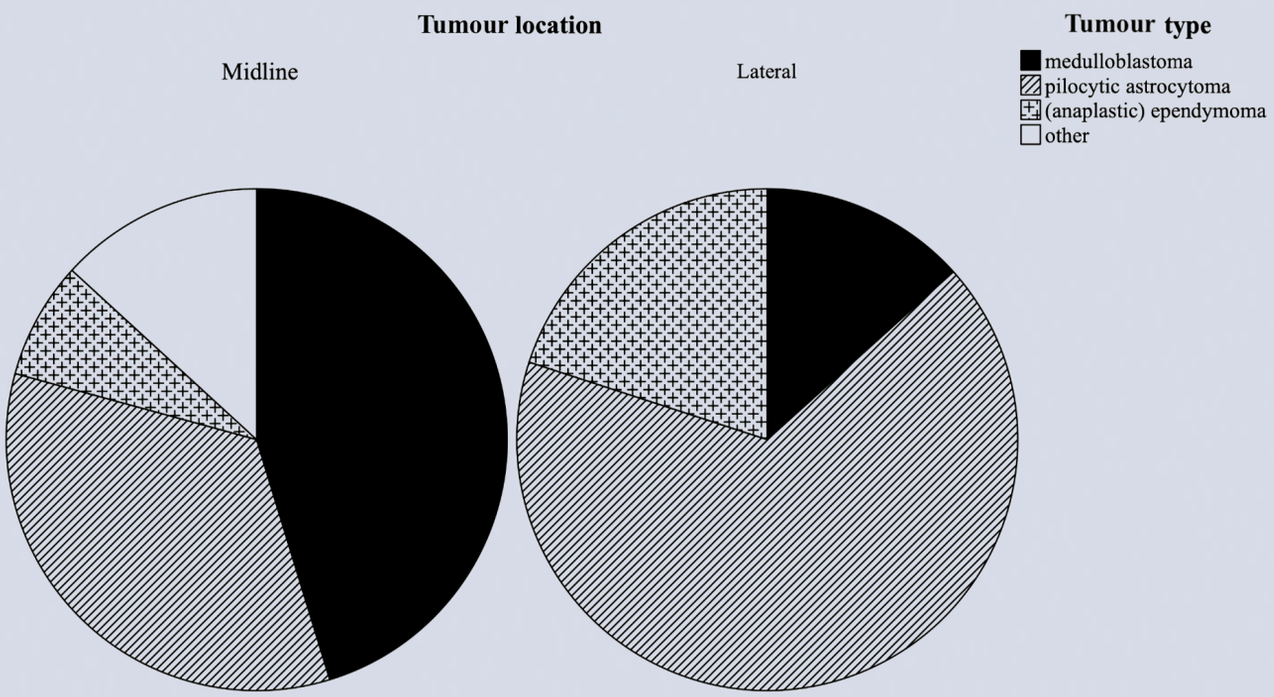


FIGURE 3: Tumour location according to tumour type.



standardized evaluation of language and speech was not conducted preoperatively, as this was not standard practice at our centre. Postoperative symptoms related to language, speech, or emotional affect can be more subtle than motor deficits, which may lead to missing data in retrospective studies due to inadequate recognition or reporting. The observed pCMS incidence of 32% is consistent with previous studies. Despite its retrospective nature, the current study appears to be representative of children with pCMS, as the incidence and the identified risk factors align with the findings reported in the literature. Prospective longitudinal studies employing multivariate analyses are the most effective tools for identifying risk factors and elucidating their underlying aetiology, which remains under investigation. Currently, a large prospective study, referred to as the Nordic Study of Cerebellar Mutism Syndrome in Children with Posterior Fossa Brain Tumours, is being conducted in Europe (31).

Conclusion

This study describes the clinical features and risk factors associated with pCMS in children treated for posterior fossa tumours at Ghent University Hospital. Motor deficits were reported most frequently, while disorders in speech, language, and affective and cognitive function may have been underrecognised. Several risk factors showed a significant association with the development of pCMS. The diagnosis of medulloblastoma, brain stem invasion, and midline tumour location were associated with an increased risk of pCMS, whereas the diagnosis of pilocytic astrocytoma and tumour size greater than 5 cm were associated with a reduced risk. The latter may be explained by the fact that pilocytic astrocytomas in this cohort were, on average, larger than medulloblastomas, and supports the hypothesis that certain tumour characteristics, such as location and size, may reflect the underlying tumour type rather than constitute independent risk factors for pCMS. Comprehensive postoperative monitoring of patients at risk for pCMS is crucial, with particular emphasis on language, speech, and affective and cognitive functions. This facilitates early detection of pCMS and initiation of rehabilitation, thereby enhancing patient outcomes and quality of life. Children with pCMS may experience lasting neurological deficits, which—combined with treatment effects and time away from school—can increase learning difficulties. Awareness of pCMS is therefore important for long-term follow-up by healthcare professionals.

Statements

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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**

RESEARCH ARTICLE

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Impact of RSV Prevention on Paediatric Patients Hospitalized for a Severe Acute Respiratory Infection (SARI): A Single Centre "Pre-Post" Cohort Study

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Keywords

Respiratory syncytial virus; RSV; Immunization; Prevention; Coinfection; Antibiotic treatment

Abstract

Objective

This study aims to evaluate the impact of the first year of respiratory syncytial virus (RSV) prevention on hospitalisations for severe acute respiratory infection (SARI) in a paediatric department.

Methods

During the 2023–24 and 2024–25 winter seasons, 215 and 191 patients were included, respectively, with 105 (49%) and 47 (25%) documented RSV infections, respectively. The proportion of nirsevimab-eligible patients testing positive decreased by 78% between the two seasons. Seven of the 48 (14.6%) patients who received prophylaxis and four of the five (80%) patients who did not received prophylaxis had an RSV infection. The median age of children testing positive for RSV increased from 7.2 months in the 2023–24 season to 20.2 months in the 2024–25 season, and the median length of stay decreased from three to two days, respectively.

Results

The currently licensed vaccines are highly effective in preventing varicella infection and the possible severe complications. They are safe with generally mild adverse effects. Cost-effectiveness studies show a benefit for the society. However, high vaccine coverage rates are needed to prevent the shift in varicella cases to older age groups. This can be achieved when administered in combination with the already established measles mumps rubella (MMR) vaccination at the age of 12 months.

Interpretation / Conclusion

The implementation and reimbursement of nirsevimab significantly affected RSV-related hospitalisations when comparing pre- and post-surveillance years. A significant increase of 13 months in the median age of RSV-positive hospitalized patients and a decrease in the median length of hospital stay were also observed.

Introduction

Respiratory syncytial virus (RSV) is a major cause of upper and lower respiratory tract infections (URTI-LRTI), particularly in infants. Preterm, patients under six months of age, and children with chronic conditions (cardiac, pulmonary, neuromuscular, …) are at highest risk. It is estimated that 5% of infected children develop LRTI, 0.4% require hospitalization, and 0.02% die from the infection (1). In Belgium, despite the absence of a national registry, epidemiological data reveal a substantial RSV burden. Between 5% and 10% of patients seen in primary care in Belgium are hospitalized, with approximately 5% requiring intensive care (2). Most hospitalized children have no identified risk factors except a very young age (67–80%) (2). From the literature, RSV is also known to be associated with an increased risk of bacterial pneumonia (particularly pneumococcus infection) and with the later development of bronchial hyperreactivity (3-6). A recent Belgian study quantified RSV's impact on paediatric departments: at the peak period, RSV-related hospitalizations accounted for up to 95% of paediatric bed occupancy in some hospitals (7). According to the Belgian Health Care Knowledge Centre (KCE), an estimated 116,000 RSV infections occur annually among each birth cohort of children aged 0–59 months, leading to over 8,600 hospitalizations and approximately 400 paediatric intensive care unit (PICU) admissions, half of which occur in infants under two months of age (8). From an economic perspective, the mean cost per RSV episode in Europe is evaluated to be €399.5 and €494.3 from the healthcare payer perspective and societal perspective, respectively (9). The development of nirsevimab (Beyfortus®) has dramatically transformed RSV prevention. Clinical trials have shown an efficacy of 70% in infections among preterm infants and an efficacy of 77% among full-term infants through at least 150 days (10-11). The HARMONIE trial confirmed an efficacy of 83% in hospitalizations (12). Real-world data support these findings, showing effectiveness between 80% and 90% (13-17). Another promising option is maternal vaccination (Abrysvo®). The MATISSE trial demonstrated 82% efficacy against LRTI in infants at 90 days of life, 70% at 180 days (18). Real-world data from the BERNI study confirmed a 71% effectiveness in hospitalizations and a 77% efffectiveness in severe infections in infants under six months in Argentina (19). The main aim of this study is to evaluate the impact of the first year of RSV prevention on severe acute respiratory tract infection (SARI) hospitalizations in a paediatric department. The secondary objectives of the study are the immunization coverage observed in eligible children and the effect of prevention on disease severity and viral co-infections.

Methods

All paediatric patients (0-15 years old) hospitalized at CHU UCL Namur (site Dinant) for SARI during winter epidemic seasons 2023-2024 and 2024-2025 (from October 1 to March 31), were prospectively enrolled, and clinical data were retrospectively analysed, focusing on the impact of RSV preventive measures (from 2024-25) on hospitalization rates, infection severity, and on the prevalence other viral (co-) infections. At the beginning of the immunization campaign in 2024, it was decided that the eligible children were those born from the end of the previous season, i.e. April 1-2024 to March 31-2025. It should be noted that the 2024-25 RSV season was officially declared over by Sciensano on February 18, leading to an early termination of the immunization campaign. For this reason, in order to compare the two seasons, we have defined eligible children born between April 1 and March 31 for both seasons. Patient inclusion continued until March 31, announced theoretical end date of RSV season, to assess any potential effect of this premature end. The SARI hospital network project is a surveillance program coordinated by the Belgian Scientific Institute for Public Health (Sciensano®) and involving nine acute care hospital settings, including CHU UCL Namur (site Godinne/adult population and site Dinant/paediatric population). Main objective is to monitor the impact of seasonal respiratory viruses on SARI paediatric and adult hospitalizations, using standardized enrolment criteria. The SARI paediatric case definition is defined as at least two of the following symptoms: fever > 38°C or history of fever; cough and/or dyspnoea and/or abnormal pulmonary auscultation, apnoea, cyanosis; and an acute onset of symptoms (<10 days prior to hospital admission); and a minimum 24-hour hospital stay. Apnoea and cyanosis only apply to children. The SARI surveillance uses a common clinical questionnaire and collects anonymized data on an electronic platform. Paediatric patients presenting to the emergency department (ED) with respiratory symptoms undergo a nasopharyngeal sampling (aspiration or swab) for viral analysis performed at the CHU UCL Namur laboratory using NeuMoDx™ Flu A-B/RSV/SARS-CoV-2 Vantage Test Strip (Qiagen®, Hilden, Germany) for (FLU-RSV-SARS-CoV-2 RT-PCR and Adeno Respi K-Set (Coris ®, Gembloux, Belgium) for, Adenovirus antigen detection). If the SARI case definition is confirmed (symptoms and hospitalization ≥ 24h), the patient is included in the national surveillance and an aliquot of the respiratory sample is sent to the National Influenza Reference Centre (Sciensano®) for subsequent molecular viral analysis (respiratory panels including FLU A/B, RSV A/B, SARS-CoV-2, picornavirus (PIV 1-2-3-4), human metapneumovirus (hMPV), enterovirus and human rhinovirus (EnV/HrV), human bocavirus (HBoV), seasonal coronaviruses HKU1-NL63-OC43-229E,…). The primary outcome of this study was the number of RSV positive hospitalizations in

TABLE 1: General results 2023-2024 et 2024-2025.

	2023-2024	2024-2025	
Number of SARI [a] patients	215 (44%)	191 (47%)	Reduction of 15%
RSV-positive patients	105/215 (49%)	47/191 (25%)	Reduction of 55% P-value: 0.0000004775 [b]
Co-infections	38/105 (36%)	21/47 (44%)	P-value: 0.3208 [c]
Nirsevimab eligible patients	86/215 (40%)	56/191 (30%)	Reduction of 35% P-value: 0.02662 [b]
RSV-positive patients nirsevimab eligible	50/86 (58.1%)	11/56 (19.6%)	Reduction of 78% P-value: 0.000005926 [b]
RSV-positive patients median age [Q1 – Q3] [d] (months)	7.2 [3 - 18]	20.2 [9.75 – 31.26]	+ 13 months P-value : 0.0005828 [e]
Hospitalizations during RSV season	487	403	Reduction of 18%
Emergency department visits	2269	2158	Reduction of 5%

[a] SARI: Severe Acute Respiratory Infection
[b] Fisher's exact test p-value
[c] Pearsons chi-squared test p-value
[d] interquartile range
[e] Mann-Whitney U test

TABLE 2: Comparison of risk factors and severity of RSV-positive patients between the two seasons.

	2023-2024 (n = 105)	2024-2025 (n = 47)	P-value
Risk factors	19 (18%)	11 (23.4%)	11 (23.4%)
Oxygen therapy	64 (60.9%)	24 (51%)	24 (51%)
High flow oxygen therapy	5 (4.7%)	3 (6.3%)	3 (6.3%)
PICU c admission	6 (5.7%)	3 (6.3%)	3 (6.3%)
Median length of stay [Q1 – Q3] d (days)	3 [2 – 5]	2 [1 – 3]	2 [1 – 3]
Chest X-ray	33 (31%)	11 (23%)	11 (23%)
Antibiotics prescription rate	36 (34%)	14 (29%)	14 (29%)
Patients with chest X-ray/patients having antibiotics f	22/36 (61.1%)	8/14 (57.1%)	8/14 (57.1%)

[a] Pearsons chi-squared test p-value
[b] Fisher's exact test p-value
[c] Paediatric Intensive Care unit
[d] Interquartile range
[e] Wilcoxon rank sum test with continuity correction
[f] Antibiotic prescription rate associated with chest X-ray

children eligible for RSV prevention. The severity outcomes (oxygen requirement, PICU transfer, length of hospital stay, antibiotic use) were compared between two seasons for RSV-positive patients. These severity outcomes were also compared between patients with a single RSV infections vs co-infection on the basis of all patients (both seasons). The nirsevimab eligibility criteria follow the National Institute for Health and Disability Insurance reimbursement conditions, based on the Belgian Superior Health Council recommendations: all infants born after April 1-2024, entering their first season of exposure, regardless of risk factors (20). The immunization campaign within our Paediatric Department was structured around following components:

- Communication: An information campaign was launched, albeit late, through media and posters distributed by the Belgian Academy of Paediatrics.
- Maternity administration: Newborns delivered in the maternity of CHU UCL Namur (site Dinant) between October 1-2024, and February 18-2025, were offered immunization with nirsevimab (Beyfortus®), provided their mother had not received Abrysvo® during pregnancy. Among the identified limitations were exclusion of children without regular health insurance (e.g. refugee children housed in Red Cross Centres because of non-reimbursement),
- Postnatal catch-up: A phone recall system was implemented for all eligible children born in our maternity unit after April 1-2024: parents were contacted and offered an appointment in consultation.

To compare the groups across the two seasons, as well as single infections and co-infections, several statistical approaches were employed. The percentage reduction between the values obtained in the two seasons was first calculated. Categorical variables were analysed using the chi-square test or Fisher's exact test for small samples. For continuous variables, including age and length of hospital stay, normality was first assessed using the Shapiro–Wilk test. Since these variables were not normally distributed, comparisons between groups were performed using the Mann–Whitney test (Wilcoxon rank-sum test with continuity correction). Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).
As part of the SARI surveillance, approval from a coordinating central ethical committee was obtained

Results

From October 1-2024 to March 31-2025, 191 SARI patients were enrolled compared to 215 in season 2023-24 (Table 1). The number of confirmed RSV cases decreased significantly, from 105 in 2023-24 to 47 in 2024-25, representing a global 55% reduction in RSV-related hospitalizations. Among patients eligible for nirsevimab prophylaxis, the proportion of RSV-positive cases dropped markedly, from 50 among 86 eligible patients (58.1%) in 2023-24 to 11 among 56 eligible patients (19.6%) in 2024-25, representing a 78% decrease. A high parental acceptance rate was observed at our maternity, with 92% of newborns immunized with nirsevimab and 3% through maternal vaccination. Overall, in the 2024/2025 season, 48/56 (86%) eligible patients received an RSV preventive measure (46 nirsevimab and 2 maternal immunization). Five eligible patients didn't receive prophylaxis treatment, and immunization status remained undetermined for three others. Among the five non-immunized children, the identified reasons were: organizational barrier (n=1), refugee status (n=2), and parental refusal (n=1) and one patient didn't receive prophylaxis as late birth after February (18). During the 2024-25 season, there were 11 cases of RSV in eligible patients. Of these 7 patients received prevention (6 antibodies, 1 pregnancy vaccine) and 4 didn't. After exclusion of 3 patients with undetermined status, an RSV infection occurred in 7/48 (15%) children who received prophylaxis (6 nirsevimab, 1 maternal immunization) , compared with 4/5 (80%) in the non-immunized children. From the seven patients

TABLE 3: Viral co-infections.

	2023-2024	2024-2025
Number of patients	38/105 (36%)	21/47 (44%)
COVID	11	2
AdV [a]	5	9
EnV/HrV [b]	14	6
FLU [c]	4	6
PIV [d]	4	1
hMPV [e]	1	2
HPeV [f]	1	1
HBoV [g]	4	0
CoNL63 [h]	1	0
CoOC43 [i]	2	0

[a] AdV: adenovirus
[b] EnV: enterovírus, HrV: human rhinovirus
[c] INF: Influenza Virus
[d] PIV: Parainfluenza Virus
[e] hMPV: Human Metapneumovirus
[f] HPeV: Human Parechovirus
[g] HBoV: Human Bocavirus
[h] CoNL63: Human Coronavirus NL63
[i] CoOC43: Human Coronavirus OC43

TABLE 4: Comparison of risk factors and severity between RSV single infections and co-infections (both seasons).

	RSV single infection N = 93	Co-infections N = 59	p-value
Risk factors	21 (22.5%)	9 (15.2%)	0.3032 [b]
Oxygen therapy	64 (68.8%)	24 (40.6%)	0.0006164 [a]
Chest X-ray	32 (34.4%)	18 (30.5%)	0.7236 [b]
Antibiotics	21 (22.5%)	19 (32.2%)	0.2566 [b]
High flow oxygen therapy	4 (4.3%)	4 (6.7%)	0.7117 [b]
PICU	4 (4.3%)	4 (6.7%)	0.7117 [b]
Median age [Q1 – Q3] [c] (months)	10.1 [3 – 23.91]	9.0 [3.6 – 24.78]	0.9652 [d]
Median length of stay [Q1 – Q3] [c] (days)	3 [2 – 4]	2 [2 – 4]	0,1078 [e]

[a] Pearsons chi-squared test p-value

[b] Fisher's exact test p-value

[c] Interquartile range

[d] Mann-Whitney U test

[e] Wilcoxon rank sum test with continuity correction

infected despite immunization, viral coinfection was detected in 4 and 2 patients with single RSV infection were transferred to PICU for severe respiratory deterioration and suspected bacterial pneumonia. These two patients had no specific risk factor. The effectiveness of prevention, based on the test-negative design, is 96%. Interestingly, median age increased, from 7.2 months to 20.2 months, respectively. In term of severity, patients hospitalized for an RSV-associated infections during both seasons, a significant decrease of the median length of hospital stay was found: 3 days in 2023-24 compared to 2 days in 2024-25. No significant difference was found regarding other variables as presence of risk factors, oxygen requirement, PICU transfer, antibiotic prescription rate (Table 2). Among the 7 eligible patients hospitalized with documented RSV infection despite receiving prophylaxis, two required a transfer to an external PICU due to severe pneumonia and four presented with a viral co-infection (adenovirus, influenza virus A, human metapneumovirus). The two patients transferred to the PICU had no specific risk factors. The antibiotic prescription rate for patients with a documented RSV infection ranged from 29 (2024-2025) to 34% (2023-2024). Antibiotic prescription was mainly associated with an abnormal chest X-ray (57 to 61%) (Table 2). Nevertheless because of the decrease of hospitalization due to RSV, important reduction in global antibiotics consumption could be seen. Regarding viral co-infections rates identified by respiratory PCR panels in the context of sentinel surveillance (Table 3), no significant difference was observed between the two seasons. During the 2023/2024 season, 38/105 (36%) RSV-positive patients had a documented viral co-infection mostly rhinovirus/enterovirus, followed by SARS-CoV-2). In 2024/2025, the co-infection rate was 44% (21/47), mostly adenovirus, rhinovirus/enterovirus, and influenza. In terms of severity (Table 4), we observed a significant difference (p-value < 0.05) between the co-infection group and the single-infection group regarding the need for oxygen therapy, with a higher O2 use in the single-infection group (both seasons). No difference was observed for other data analysed: mean/median age, length of hospital stay, high-flow oxygen therapy, PICU transfer, chest X-ray performed, and antibiotic prescription.

Discussion

The results observed at CHU UCL Namur (site Dinant) are consistent with published literature regarding the effectiveness of RSV immunization. A 78% reduction in RSV-related hospitalizations was observed among eligible patients, confirming the favourable impact of this strategy. These results are comparable to those reported by Dessers et al. in a Belgian multicentre study, which documented a 78.8% reduction in RSV hospitalizations among infants under six months of age (21). The effectiveness of prevention in our centre, based on the test negative design, is comparable to that reported in previously published studies (Table 5) (13-17). The Sciensano® report on the impact of nirsevimab during the 2024/2025 season, which includes data from 9 SARI surveillance hospitals, estimates the effectiveness of immunization at 85.6%. The reduction in RSV-related hospitalizations is estimated at 35-45% for children under 5 years of age, corresponding to approximately 4,000 cases (22). The advantage of our study is the rigour of real-life surveillance data, which offers greater precision and allows for a more accurate evaluation of the prevention impact at a local level. In line with international observations, RSV immunization campaign achieved a good acceptance rate among targeted population as 86% of eligible patients received an RSV preventive measure. Nevertheless, several limitations were identified in its implementation. The identified limitations of the catch-up strategy included: non-inclusion of children followed in our paediatric department but born outside our maternity unit, a limited time-window for catch-up administration (October 2024) and cumbersome administrative procedures (completion of Chapter IV Agreement Request System forms, transmission of proof of approval, and submission of the prescription to the pharmacy). The administrative burden associated with this campaign, largely assumed by paediatricians, also represented a barrier to its smooth implementation. This organizational complexity may have contributed to certain lapses in immunization pathways, with the hospitalization of non-immunized eligible patients in our cohort serving as a concrete example. Several aspects remain to be assessed during the next RSV season. Since January 2025, the maternal vaccine (Abrysvo®) is reimbursed for pregnant women whose expected delivery falls between September and January. This vaccine needs to be evaluated in real-world conditions in Belgium, even though literature data demonstrate very good vaccine efficacy (19). For the 2025-2026 season, prevention will also be reimbursed for children aged 12–24 months with high-risk comorbidities (congenital heart disease, chronic lung disease, immunodeficiencies, Down syndrome, etc.), entering their second RSV season. In terms of RSV clinical severity, several recent studies have shown a reduced case severity among immunized versus non-immunized children. This is particularly obvious in the Belgian study by Dessers et al., which reported a reduced use of oxygen therapy (both low- and high-flow O2) and less frequent PICU admission (21). These findings are corroborated by other publications, including Jeziorski et al. and Xu et al. (23,24). No statistically significant difference was observed in terms of severity criteria, except a decrease of length of hospital stay, between the RSV hospitalized children in our cohort. This absence of signal could be explained by the small sample size, which limits the statistical power of the analysis. RSV is a major cause of acute respiratory infection in infants and plays a central role in paediatric respiratory morbidity. Several recent studies have emphasized the role of RSV in bacterial complications, particularly pneumococcal pneumonia, and in antibiotic prescribing in viral contexts (1,3,25). The PROMISE-RESCEU cohort, which followed 9,154 children born between 2017 and 2020 in five European countries, prospectively documented RSV infection episodes and their management. Among children hospitalized for RSV-associated LRTI,

TABLE 5: Comparative table of observational studies on the real-world effectiveness of nirsevimab.

Study	Country	Type	Population	Effectiveness on hospitalizations	Effectiveness on severity	Reduction of emergency department visits
Ares-Gómez et al.	Spain (Galicia)	Prospective	13 000	82%	86,9%	69%
Coma et al.	Spain (Catalonia)	Retrospective	26 525	87,6 %	90,1 %	55%
Carbajal et al.	France (Paris)	Case-control	2786	83 %	91 %	
Moline et al.	USA	Case-control	700	90 %		
Wadia et al.	Australia	Case-control	24 000	88,2 %		

22.8% (33/145) received antibiotics, with a proportion reaching 62% in PICU admissions (5/8). Significant inter-country disparities were observed, with prescription rates ranging from 40% in Spain to 9% in the Netherlands (25). Even though RSV is a known risk factor for pneumococcal superinfection, one would expect the in-hospital rate to exceed 10%, especially outside the PICU (1,3). In our department, the antibiotic prescription rate for RSV-positive patients remains within the margins reported in the literature in other countries but well above the ideal recommended rate of 10% (3). Most of our antibiotic prescriptions were based on a pathological chest X-ray but there is a lack of reliable and reproducible criteria to diagnose a bacterial superinfection. This highlights the need to reassess our practices and that antibiotic prescription could benefit from the development of specific algorithm. The development of RSV prevention strategies, including vaccination and monoclonal antibodies, could represent a major opportunity to reduce viral morbidity and inappropriate antibiotic consumption in young children. The role of viral co-infection(s) in the severity of RSV respiratory infections remains a matter of debate. In our cohort, systematic use of PCR respiratory panels in the context of national sentinel surveillance made possible to identify occurrences of multiple respiratory viruses, in addition to standard analysis performed by our laboratory. Our observations align with variations described in the literature, where RSV viral co-infection rates range from 5% to 42%, most often involving rhinoviruses and adenoviruses. Nevertheless, available data remain heterogeneous and sometimes contradictory regarding the clinical impact of co-infections. Some studies suggest a milder clinical presentation in co-infected cases. For example, Milani et al. reported a shorter duration of oxygen therapy and reduced PICU admission rates among co-infected children (26). Similar findings were reported by Stobbelaar et al., with shorter hospital stays and fewer PICU admissions (27). Gil et al., in Portugal, also observed a reduction in hospitalization length of stay for children under two years of age, with no significant impact on oxygen therapy needs, ventilation, or PICU admission (28). However, co-infected patients more frequently received antibiotic therapy (28). Conversely, other studies have reported an association between viral co-infection and increased clinical severity. Richard et al. notably found a 2.7-fold higher risk of PICU admission among co-infected patients compared with those with isolated RSV infection (29). In contrast, Amarin et al. observed no significant impact of co-infections on clinical severity (30). These discrepancies highlight the complexity of interpreting viral co-infections and the need for further studies—including well-characterized cohorts and standardized diagnostic tools—to better assess their role in RSV-related morbidity. Several limitations should be acknowledged in this study, including its monocentric design, the relatively modest cohort size, and the very small non immunized patient subgroup. Those limitations may restrict the generalizations of the findings and reduce both the statical power and accuracy of the estimates.

Conclusion

The first season with an effective RSV prevention strategy implementation at CHU UCL Namur (site Dinant) demonstrated a clear reduction of RSV infections in our paediatric population, compared to previous winter season. The introduction of nirsevimab resulted in a 55% decrease in confirmed RSV cases and a 78% reduction in RSV infections among eligible patients, in line with national and international data, despite operational barriers affecting coverage. No major differences in disease severity were observed between seasons, except for length of hospital stay, likely due to the modest sample size. The role of viral co-infections remains uncertain and warrants further investigation to determine the potential impact on RSV-associated morbidity. RSV prevention also represents a key opportunity to reduce inappropriate antibiotic prescriptions. Expanding prevention strategies could further enhance impact on paediatric winter RSV-hospitalizations. Future seasons will require ongoing monitoring to confirm observed trends, assess overall impact on hospitalizations and frontline care, and tailor prevention strategies according to epidemiological and clinical data.

Statement

The authors have no conflicts of interest in relation to the subject matter of this manuscript.

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RESEARCH ARTICLE

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Parents' Risk Perception of Second-hand Smoke in Children Followed Up in Paediatric Consultations at H.U.B Erasme Hospital

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Keywords

Tobacco Smoke Pollution; Risk Assessment; Perception; Paediatrics; Parents

Abstract

Introduction

Exposure to second-hand smoke (SHS) is associated with numerous adverse health effects in children and remains a major public health concern. Analysing parents' risk perception of SHS can help improve interventions aimed at reducing children's SHS-related health risks

Methods

This study was conducted using an anonymous online questionnaire. Participants rated the children's health risk, on a scale from 1 (no risk) to 7 (high risk), in described situations or photographs depicting an adult smoking in the presence of a child. A risk perception score (RPS) was calculated, with higher scores indicating greater perceived risk. Linear and multivariate regression analyses were performed to identify factors associated with risk perception

Results

A total of 112 parents or legal guardians who attended paediatric consultations at the Brussels University Hospital (H.U.B) – Erasme Hospital, fully completed the questionnaire. On average, participants perceived a high risk (5/7) to the child's health (mean RPS = 86.18/119, SD = 19.67). Participants aged 50–65 years (p = 0.01), of Caucasian ethnicity (p = 0.045), smokers (p = 0.042), and those who smoke both indoors and outdoors (p = 0.022) had a significantly lower RPS.

Conclusion

Firstly, parents should be aware that exposure occurs even in the absence of visible or perceptible signs. Secondly, measures aimed at shielding children from the harmful effects of SHS should focus on factors associated with lower risk perception. Finally, paediatricians should be encouraged to take SHS exposure into account when assessing paediatric illnesses

Introduction

Second-hand smoke (SHS) is defined as: "A mixture of the smoke from the burning tip of a cigarette and the smoke exhaled by a smoker." Both smokers and non-smokers are exposed to the harmful pollutants, particularly in enclosed spaces (1). Exposure can occur even without visible or perceptible signs, as 85% of tobacco smoke is invisible and many particles are odourless. Moreover, tobacco smoke can linger in the air for hours, leading to exposure even after smoking has ceased (2). SHS is a major public health concern, causing 1.2 million deaths annually. According to the World Health Organization (WHO), approximately half of all children are exposed to air polluted by tobacco smoke, with 65,000 children dying each year from SHS-related diseases (3). In Belgium, the report « Roken in het gezin » by Kom op tegen Kanker indicates that despite a significant decline in exposure, 29,000 children from Flemish families - 2.2% of Flemish children – were still exposed daily to SHS in 2021 (4). Children's exposure to SHS is associated with numerous adverse health effects, including an increased risk of lower respiratory tract infections, acute otitis media, sudden infant death syndrome, and asthma (5). In addition to these well-known health risks, SHS is recognized as one of the main contributing factors to recurrent otitis media (6). Beyond postnatal exposure, tobacco exposure may already exert harmful effects during pregnancy, as numerous studies have established a link between maternal smoking and an increased risk of childhood obesity (7). In addition to physical harm, SHS also influences children's future smoking habits and addictive behaviours. Seeing others smoke encourages smoking. Children and adolescents often imitate adult behaviour, including tobacco use. Those exposed to smoking adults in their surroundings are therefore at greater risk of experimenting tobacco and becoming regular smokers (8). To reduce SHS exposure, Belgium enacted in 2009 a smoking ban in public places and, in 2020, a

TABLE 1: Participants inclusion and exclusion.

Participant's questionnaires after providing consent	Total N = 151	n (%)
Questionnaire not completed		8 (5%)
Questionnaire partially completed		31 (21%)
Questionnaire fully completed		112 (74%)
Type of consultation among fully completed questionnaires	**Total N =112**	**n (%)**
GPC		71 (63,4%)
PPAC		41 (36,6%)

ban on smoking in vehicles carrying minors under the age of 18 (9). However, these regulations do not extend to private settings, such as homes, where children spend a significant portion of their time - often near smoking parents or caregivers (10). To address SHS in private spaces, voluntary home smoking bans (HSB) can be implemented. A home with an HSB is defined as: "A home where the use of any tobacco product, as well as electronic cigarettes, is not permitted anywhere (including balconies and terraces)" (11). Parents' risk perception, regarding a specific threat to their children's health, influences their behaviours and their willingness to take measures to modify these behaviours - generally in a direction aimed at reducing health risks (12). Consequently, risk perception plays a key role in interventions designed to reduce SHS exposure. The objectives of this survey are fourfold: to assess parents' risk perception of SHS attending the paediatric consultation at Erasme Hospital; to identify risk factors associated with lower SHS risk perception; to compare parents attending general paediatric consultations (GPC) with those attending paediatric pulmonology-allergology consultations (PPAC); and to identify associations between risk perception and the implementation of measures reducing SHS exposure. A secondary objective of this survey is to improve interventions aimed at reducing SHS exposure, while raising parents' awareness and informing them about SHS and its harmful effects.

Materials and Methods

Study design

This is an epidemiological, observational, cross-sectional, single-centre study conducted using an anonymous online questionnaire. It was carried out from January 8, 2024, to March 12, 2024, at the Anderlecht site of the Brussels University Hospital (H.U.B) — Erasme Hospital. Eligible participants were recruited through posters displayed in waiting rooms as well as in nurses' and physicians' offices. In addition, physicians, postgraduate trainees, nurses, and medical students orally invited eligible participants to complete the questionnaire during paediatric consultations or through the distribution of flyers. This study was approved by the Ethics Committee of Erasme Hospital: P2023-351.

Study population

Parents or legal guardians of children attending the GPC or PPAC at H.U.B Erasme were eligible. Participants had to be more than 18 years old. A minimum of 40 participants, with at least 20 from each consultation type, was required by the Ethics Committee of Erasme Hospital.

Data collection instrument

Data were collected through an anonymous online questionnaire (Appendix 1) hosted on the secure REDCap platform, approved by the Ethics Committee (13). Access was provided via QR code displayed on posters and flyers. An information letter outlining participants' rights and study objectives was presented on the questionnaire homepage, and completion implied informed consent. The questionnaire comprised 62 questions, divided into six categories: Parental and family characteristics, Tobacco use, Children's exposure to SHS, Characteristics of the child attending the consultation, Knowledge of SHS, Risk perception of SHS. The first question identified whether the participant was attending the GPC or the PPAC, in order to allow comparison between the two parent populations. Parental and family characteristics, as well as tobacco use, were recognized predictors of children's exposure to SHS and were therefore examined (10). The section on children's exposure to SHS included questions assessing whether the child was exposed, as well as whether parents had implemented a HSB or a vehicle smoking ban as preventive measures to protect their children from SHS. A section of the questionnaire assessed parents' knowledge of SHS in order to identify gaps and areas requiring further awareness. The section on parents' risk perception of SHS is an adapted version of the questionnaire by Myers et al., which measured both the perception of SHS exposure and parents' risk perception of SHS (14). Section C of the questionnaire, which focused on risk perception, was used and translated into French. The questionnaire contained various situations of children's SHS exposure through photographs or descriptive situations (e.g., smoking indoors or outdoors, using barriers such as doors or windows, smoking in a car with the window open, and varying distances between the smoker and the child), thereby capturing both sensory perception (smelling and seeing) and the physical context (distance, location, time, movement) of exposure. For each situation, participants were asked to rate the health risk to the child using a 7-point Likert scale, ranging from 1 (no risk) to 7 (high risk). A 7-point scale has been recommended for questions assessing risk perception (15). Two additional questions were included to determine whether participants wished to receive further information on SHS and smoking cessation. The questionnaire was designed, approved and used in the study in French. It was later translated in English for the publication.

Statistical analyses

Statistical analyses were performed using Jamovi 2.3.28, Redcap, and RStudio 4.2.2. Participant characteristics were summarized using descriptive statistics. For the final section on parents' risk perception of SHS, each question was scored on a scale from 1 to 7. Each question was considered to represent an equal health risk from SHS exposure (7/7), based on the statement: "There is no safe level of SHS exposure; even brief exposure can be harmful to health" (16). The Risk perception score (RPS) was calculated as the sum of the 17 items, with a maximum possible score of 119. To identify factors associated with a significantly different RPS (p-value < 0.05), univariate linear regression was performed. Multivariate linear regression was then conducted to evaluate the overall relationship between significant variables (alpha threshold < 0.025) and the RPS. Group comparisons (GPC vs. PPAC) were conducted using Pearson's x^2, Wilcoxon rank-sum, and Fisher's exact tests. The Durbin-Watson (DW) test was performed, assuming no autocorrelation. No evidence of multicollinearity was observed, and residuals were normally distributed.

TABLE 2: Descriptive statistics and consultations comparison. (Continued in next table)

	N	Total n (%)	GPC, N = 71[1]	PPAC N = 41[1]	p-value[2]
Parental and Family Characteristics					
Gender	112				0.3
Female		80 (71,4%)	53 (75%)	27 (66%)	
Male		32 (28,6%)	18 (25%)	14 (34%)	
Other		0 (0%)	0 (0%)	0 (0%)	
Age	112				0.2
18–24		2 (1,8%)	2 (2.8%)	0 (0%)	
25–35		44 (39,3%)	25 (35%)	19 (46%)	
36–49		53 (47,3%)	33 (46%)	20 (49%)	
50–65		13 (11,6%)	11 (15%)	2 (4.9%)	
66+		0 (0%)	0 (0%)	0 (0%)	
Ethnicity	112				0.4
White/Caucasian		75 (67,0%)	49 (69%)	26 (63%)	
Black/African		17 (15,2%)	12 (17%)	5 (12%)	
Hispanic		7 (6,3%)	4 (5.6%)	3 (7.3%)	
Asian		1 (0,9%)	1 (1.4%)	0 (0%)	
Other		12 (10,7%)	5 (7.0%)	7 (17%)	
Education level	112				>0.9
No diploma		5 (4,5%)	4 (5.6%)	1 (2.4%)	
Primary school certificate		5 (4,5%)	0 (0%)	0 (0%)	
Secondary school certificate		20 (17,9%)	12 (17%)	8 (20%)	
Technical or vocational certificate		15 (13,4%)	10 (14%)	5 (12%)	
Higher education/university degree, PhD		67 (59,8%)	41 (58%)	26 (63%)	
Employment	112				0.7
Unemployed		25 (22,3%)	17 (24%)	8 (20%)	
Part-time employment		14 (12,5%)	7 (9.9%)	7 (17%)	
Full-time employment		66 (58,9%)	42 (59%)	24 (59%)	
Student		7 (6,3%)	5 (7.0%)	2 (4.9%)	
Marital status	112				0.14
Married		55 (49,1%)	29 (41%)	26 (63%)	
Divorced		9 (8,0%)	6 (8.5%)	3 (7.3%)	
Single		20 (17,9%)	15 (21%)	5 (12%)	
Widowed		0 (0,0%)	0 (0%)	0 (0%)	
Cohabiting		28 (25,0%)	21 (30%)	7 (17%)	
Number of children		2,2 (1, 6)3			
Parental composition	112				0.017
Single-parent		28,(25,0%)	24 (34%)	4 (9.8%)	
Two-parent		67 (59,8%)	38 (54%)	29 (71%)	
Blended family		17 (15,2%)	9 (13%)	8 (20%)	

TABLE 2: Descriptive statistics and consultations comparison. (Continued in next table)

	N	Total n (%)	GPC, N = 71[1]	PPAC N = 41[1]	p-value[2]
Tobacco use					
Smoking status	112				0.8
Current smoker		13 (11,6%)	9 (13%)	4 (9.8%)	
Non smoker		78 (69,6%)	50 (70%)	28 (68%)	
Former smoker		21 (18,8%)	12 (17%)	9 (22%)	
Other smokers in the household	112		12 (17%)	9 (22%)	
Yes		17 (15,2%)	8 (11%)	9 (22%)	
No		95 (84,8%)	63 (89%)	32 (78%)	
Other smokers in regular contact with your child	112				0.3
Yes		34 (30,4%)	19 (27%)	15 (37%)	
No		78 (69,6%)	52 (73%)	26 (63%)	

Results

A total of 151 responses were collected in the study, of which 8 were excluded because participants provided only consent without completing the questionnaire, and 31 were excluded due to incomplete responses. Consequently, the final sample comprised 112 participants, including 71 in general paediatrics (63.4%) and 41 in paediatric pulmonology–allergology (36.6%) (Table 1).

Parental and Family Characteristics (Table 2)

The majority of participants were women (71.4%), aged 36–49 years (47.3%), of Caucasian ethnicity (67%), holding a higher education degree, university diploma, or doctorate (59.8%), and employed full-time (58.9%). Families were primarily two-parent households (59.8%) with married parents (49.1%) and had an average of 2 children, with the maximum reported number being 6.

Tobacco use (Table 2)

Only 13 participants were current smokers (11.6%), while the majority were non-smokers (69.6%) or former smokers (18.8%). A small proportion of participants reported another smoker in the household (15.2%), yet one-third of children (30.4%) had regular contact with a smoker outside the home. No statistically significant association was found between consultation type and smoking status (p = 0.8).

Children's Exposure to SHS

Among smoking parents, only one reported smoking in the presence of children, with most smoking outdoors (84.6%), often on the balcony (69.2%). Half smoked inside a ventilated room (53.8%), and nearly half smoked in their vehicle (46.2%), though never with children present (Table 2). Most participants had implemented a HSB (87.5%). A higher proportion of smokers reported not having an HSB (23%) compared with non-smokers (14%) and former smokers (0%), although this difference was not statistically significant (p = 0.06). When established, the HSB was strictly enforced in 92% of households. Similarly, most participants who owned a vehicle had implemented a vehicle smoking ban (88%). Smokers were more likely not to establish this ban (27.3%) compared with non-smokers (11.8%) and former smokers (4.8%) (p = 0.2). No significant differences in the implementation of HSB or vehicle smoking ban were observed between consultation types or smoking status (Tables 2 and 3).

Characteristics of the child attending the consultation (Table 2)

Consultations concerned infants (25.9%), preschool-aged children (22.3%), and school-aged children (32.1%). Almost all participants in the GPC sought care for conditions other than lower respiratory tract infections, acute otitis media, or asthma (94%), in contrast to the Paediatric PPAC group (49%). A significant association was observed between consultation type and both the child's diagnosis (p < 0.001) and the identification of a link between the illness and tobacco smoke exposure by a paediatrician (p = 0.006). In five PPAC cases, paediatricians established such a link; none were reported in GPC. Notably, these five children were regularly exposed to a smoker despite their parents being non-smokers.

Knowledge of SHS (Table 2)

The majority of participants were familiar with SHS (83%), with comparable proportions in both PPAC and GPC groups. Prenatal smoking was most often associated with recurrent respiratory infections (83%) and preterm birth (83%), but rarely with childhood obesity (5.4%). Postnatal SHS exposure was strongly linked to asthma (88.4%) and respiratory infections (87.5%), while fewer participants associated it with infant regurgitation (16.1%), infant colic's (21.4%), Attention-Deficit/Hyperactivity Disorder (22.3%), or otitis media (25%). A majority considered their knowledge insufficient (63.4%). Significant differences were found between groups, with PPAC participants more frequently associating SHS with sudden infant death syndrome (prenatal p = 0.049; postnatal p = 0.004) and Attention-Deficit/Hyperactivity Disorder (p = 0.022).

Risk perception of SHS

The mean RPS was 86.18 (SD: 19.67) (Table 4), indicating a generally high perceived health risk (5/7). The highest RPS were assigned to a situation involving an adult smoking in the presence of a child in the kitchen (6.55/7; SD 0.97) (Table 5), followed by

TABLE 2: Descriptive statistics and consultations comparison. (Continued in next table)

	N	Total n (%)	GPC, N = 71[1]	PPAC N = 41[1]	p-value[2]
Children's exposure to SHS					
Smoking in the presence of children	13				>0.9
Yes		1 (7,7%)	1 (11%)	0 (0%)	
No		12 (92,3%)	8 (89%)	4 (100%)	
Where do you smoke	13				>0.9
Inside the home		0 (0%)	0 (0%)	0 (0%)	
Outside the home		11 (84,6%)	8 (89%)	3 (75%)	
Both inside and outside the home		2 (15,4%)	1 (11%)	1 (25%)	
Set a HSB	112				>0.9
Yes		98, (87,5%)	62 (87%)	36 (88%)	
No		14 (12,5%)	9 (13%)	5 (12%)	
Home ban enforced by all household members	112				0.5
Yes		103 (92,0%)	64 (90.1%)	39 (95.1%)	
No		9 (8,0%)	7 (9.9%)	2 (4.9 %)	
In which situations do you smoke	13				
Under the kitchen hood		0 (0,0%)	0 (0%)	0 (0%)	
With the window open		1 (7,7%)	1 (1.4%)	0 (0%)	>0.9
With the window closed		0 (0,0%)	0 (0%)	0 (0%)	
On the balcony		9 (69,2%)	6 (8.5%)	3 (7.3%)	>0.9
Other		4 (30,8%)	3 (4.2%)	1 (2.4%)	>0.9
Does the room where you smoke have ventilation	112				0.5
Yes		7 (6,3%),	3 (4.2%)	4 (9.8%)	
No		6 (5,4%),	4 (5.6%)	2 (4.9%)	
Does not apply to my situation		99 (88,4%)	64 (90%)	35 (85%)	
Do you smoke in the vehicle	13				>0.9
Yes		6 (46,2%)	4 (44%)	2 (50%)	
No		5 (38,5%)	4 (44%)	1 (25%)	
I do not have a vehicle		2 (15,4%)	1 (11%)	1 (25%)	
Do you smoke in the vehicle with children	13				
No		13 (100%)	9 (100%)	4 (100%)	
Set a vehicle smoking ban	112				>0.9
Yes		88 (88%)	55 (77%)	33 (80%)	
No		12 (12%)	8 (11%)	4 (9.8%)	
I do not have a vehicle		12	8 (11%)	4 (9.8%)	
Vehicle ban enforced by all household members	112				0.7
Yes		75 (67,0%)	49 (69%)	26 (63%)	
No		4 (3,6%)	3 (4.2%)	1 (2.4%)	
Does not apply to my situation		33 (29,5%)	19 (27%)	14 (34%)	

an adult smoking inside a car with the window open while a child sat in the back seat (6.13/7; SD 1.21) (Table 5), and the scenario described as: "The child is in a car where someone smoked 20 minutes ago" (6.06/7; SD 1.39) (Table 5). The situation perceived as the lowest risk to the child's health was: "The child is in the playground and sees their mother smoking but does not smell the smoke" (3.35/7; SD 2.13), followed by the scenario where a child plays in a yard while an adult smokes farther away on a bench (3.44/7; SD 1.9) (Table 5). Forty percent of participants wished to receive further information on SHS and 13% on smoking

TABLE 2: Descriptive statistics and consultations comparison. (Continued in next table)

	N	Total n (%)	GPC, N = 71[1]	PPAC N = 41[1]	p-value[2]
Characteristics of the child attending the consultation					
Child's age	112				0.10
Newborn (0–1 month)		5 (4,5%)	5 (7.0%)	0 (0%)	
Infant (1 month–2 years)		29 (25,9%)	17 (24%)	12 (29%)	
Young child (2–3 years)		6 (5,4%)	5 (7.0%)	1 (2.4%)	
Preschool-age child (3–5 years)		25 (22,3%)	11 (15%)	14 (34%)	
School-age child (6–12 years)		36 (32,1%)	26 (37%)	10 (24%)	
Adolescent (13–18 years)		11 (9,8%)	7 (9.9%)	4 (9.8%)	
Child's pathology	112				<0.001
Lower respiratory tract infections (pneumonia, acute bronchitis, bronchiolitis, ...)		9 (8,0%)	2 (2.8%)	7 (17%)	
Asthma		13 (11,6%)	0 (0%)	13 (32%)	
Acute otitis media		3 (2,7%)	2 (2.8%)	1 (2.4%)	
Other		87 (77,7%)	67 (94%)	20 (49%)	
Link made by a paediatrician between the child's illness and tobacco exposure	112				0.006
Yes		5 (4,5%)	0 (0%)	5 (12%)	
No		107(95,5%)	71 (100%)	36 (88%)	

cessation. Interest in smoking cessation information was significantly higher among PPAC participants compared with GPC (p = 0.009), regardless of their smoking status (Table 4).

Factors Associated with risk perception of SHS (Tables 6 and 7)

Significant lower RPS were observed among participants aged 50–65 (β = -14.82, p = 0.01), of Caucasian ethnicity (β = -7.89, p = 0.045), smokers (β = -11.78, p = 0.042), and those who smoked both indoors and outdoors (β = -39.32, p = 0.022). Higher RPS were associated with participants of "other" ethnicities (β = 12.77, p = 0.033), married participants (β = 7.44, p = 0.045), non-smokers (β = 8.15, p = 0.043), and those with a child suffering from lower respiratory tract infections (β = 15.39, p = 0.024). Multivariate analysis identified age 50–65 (β = -13.58, p = 0.017) and having a child with lower respiratory tract infections (β = 13.68, p = 0.041) as the strongest predictors of RPS. No significant associations were found between RPS and consultation type (p = 0.9), HSB (p = 0.559) or vehicle smoking ban (p = 0.119).

Discussion

Despite the relatively low proportion of participants who were active smokers, one third of the children was regularly in contact with smokers and therefore at risk of exposure to SHS. Having smoking parents or household members is among the primary risk factors for children's SHS exposure (17). Consequently, it is important during consultations to raise awareness among the child's accompanying parent or guardian about SHS and its harmful effects, even if they themselves are not smokers. Smokers - particularly those who reported smoking inside the home - demonstrated lower RPS, a finding consistent with previous studies (14,18–20). This may explain why children with smoking parents are at greater risk of SHS exposure at home (10). Furthermore, lower RPS were observed among participants aged 50 to 65 years, which may be attributable to limited public education on this issue in the past (21). Similarly, Caucasian participants exhibited lower RPS compared with participants from other ethnic groups. Previous research has shown that members of these other groups are less frequently exposed to SHS than Caucasians, a difference that could be linked to the stronger social unacceptability of smoking - particularly among women - in certain cultures (22, 23). It is therefore essential to raise awareness among groups with lower risk perception of SHS to prevent children's exposure. Moreover, an increase in SHS risk perception has been associated with the implementation of complete HSB (24). Prevention strategies should also be extended to the child's household members, including grandparents. In our study, situations perceived with the lowest risk involved those in which the child was outdoors, in an open space, in the presence of a smoking adult at a considerable distance, regardless of whether or not the smoke was smelled. These findings align with Junus et al. (19). Another study report that some parents do not perceive a risk of SHS exposure when there is no smell, no visible smoke, or no visible smoker, or if the situation occurs outdoors or in a ventilated room (2). It is therefore crucial to include, in SHS prevention strategies, actions aimed at eliminating these misconceptions and raising parental awareness that exposure to tobacco smoke can occur even without visible or perceptible signs. As reported in previous studies, non-smokers and former smokers were more likely than current smokers to implement home and car smoking bans, although the difference was not statistically significant (25, 26). Non-smokers also demonstrated a significantly higher risk perception compared to smokers, which may partly explain this trend. In contrast to some reports, but consistent with Junus et al., no significant association was observed between voluntary HSB and risk perception of SHS exposure (19, 26, 27). The prevalence of home (87.5%) and car bans (88%) in our study was

TABLE 2: Descriptive statistics and consultations comparison. (End of table 2)

	N	Total n (%)	GPC, N = 71[1]	PPAC N = 41[1]	p-value[2]
Knowledge of SHS					
Familiar with SHS	112				>0.9
Yes		93 (83%)	59 (83%)	34 (83%)	
No		19 (17,0%)	12 (17%)	7 (17%)	
Do you consider your knowledge sufficient	112				0.9
Yes		42 (37,5%)	44 (62%)	26 (63%)	
No		71 (63,4%)	27 (38%)	15 (37%)	
Tobacco exposure in utero increases the risk of	112				
Prematurity		93 (83,0%)	56 (79%)	37 (90%)	0.12
Low birth weight		79 (70,5%)	49 (69%)	30 (73%)	0.6
Small for gestational age		47 (42,0%)	27 (38%)	20 (49%)	0.3
Perinatal mortality		41 (36,6%)	24 (34%)	17 (41%)	0.4
Sudden infant death syndrome (SIDS)		44 (39,3%)	23 (32%)	21 (51%)	0.049
Obesity		6 (5,4%)	3 (4.2%)	3 (7.3%)	0.7
Recurrent respiratory infections (otitis, bronchiolitis, bronchitis)		93 (83,0%)	60 (85%)	33 (80%)	0.6
Effects of SHS on infants	112				
Sudden infant death syndrome (SIDS)		59 (52,7%)	30 (42%)	29 (71%)	0.004
Poor growth		60 (53,6%)	35 (49%)	25 (61%)	0.2
Infant colic		24 (21,4%)	15 (21%)	9 (22%)	>0.9
Physiological regurgitation		18 (16,1%)	11 (15%)	7 (17%)	0.8
Bronchiolitis		80 (71,4%)	51 (72%)	29 (71%)	>0.9
Respiratory infections		98 (87,5%)	61 (86%)	37 (90%)	0.5
Nicotine withdrawal syndrome		64 (57,1%)	38 (54%)	26 (63%)	0.3
Effects of SHS on children	112				
Asthma		99 (88,4%)	60 (85%)	39 (95%)	0.13
Acute otitis media		28 (25,0%)	17 (24%)	11 (27%)	0.7
Bronchiolitis		73 (65,2%)	46 (65%)	27 (66%)	>0.9
Bronchitis		86 (76,8%)	51 (72%)	35 (85%)	0.10
Pneumonia		74 (66,1%)	49 (69%)	25 (61%)	0.4
Cough		87 (77,7%)	56 (79%)	31 (76%)	0.7
Reduced lung function		77 (68,8%)	45 (63%)	32 (78%)	0.11
Attention-deficit/hyperactivity disorders (ADHD)		25 (22,3%)	11 (15%)	14 (34%)	0.022
Future tobacco addiction		54 (48,2%)	32 (45%)	22 (54%)	0.4

[1] n (%)

[2] Fisher's exact test; Pearson's Chi-squared test

[3] Médian, (minimum, maximum)

notably high, diverging from actual smoking practices such as smoking in vehicles (46.2%) or on balconies (69.2%). This discrepancy may reflect overreporting or misinterpretation of the definition of smoking bans by smokers. Overestimation and overreporting of health-protective behaviours has been documented in the literature. For instance, one study showed an overreporting of smoking bans among caregivers of children with asthma (28). Our results are also in line with a qualitative study suggesting that parents often do not consider a closed balcony to be an indoor space or part of the household environment (2). Awareness campaigns should highlight the health risks of SHS in private settings and clearly define which spaces are considered part of the household. The use of visual materials to illustrate SHS exposure, such as those used in our study questionnaire, may help parents better identify risk situations. Strengthening smokers' engagement to reduce SHS exposure is also crucial. Parents should be informed that such measures not only protect their children's health but also help preventing the normalization of smoking

TABLE 3: Comparison between smoking status and implementation of a smoking ban.

Smoking status					
		Current smoker	Non-smoker	Former smoker	p-value[1]
HSB					
Yes	N (%)	10 (76.9%)	67 (85.9%)	21 (100%)	0,06
No	N (%)	3 (23.1 %)	11 (14.1 %)	0 (0%)	
Vehicle smoking ban					
Yes	N (%)	8 (72.7 %)	60 (88.2 %)	20 (95.2 %)	0.2
No	N (%)	3 (27.3 %)	8 (11.8 %)	1 (4.8 %)	

[1] Pearson's Chi-squared test; Fisher's exact test.

and, ultimately, to reducing the likelihood of their children taking up smoking themselves. Smokers have an active role to play in awareness campaigns. In the project "tobacco-free generation", smokers were more willing to engage when the underlying motivation of the campaign was explained to them (29). Although participants generally perceived SHS as posing a high risk to children's health, the majority reported feeling insufficiently informed about the subject. Obesity was the condition least frequently associated with prenatal tobacco exposure, despite being a major public health concern. Physiological regurgitation, infant colic, attention-deficit/hyperactivity disorder, and otitis media were also among the conditions least associated with SHS exposure in infants and children. One study reported that between 1999 and 2006, risk perception of SHS in relation to otitis media even declined, unlike to other health outcomes (18). In contrast, respiratory conditions, including asthma and respiratory infections, were most commonly identified. These findings suggest that while awareness of respiratory risks is relatively high, knowledge gaps persist regarding non-respiratory consequences. This study therefore highlights the need for targeted parental and professional education, particularly regarding non-respiratory conditions and otitis media. We observed that the number of respondents from GPC was approximately twice that of PPAC. This difference may be explained by the substantially higher volume of GPC compared with PPAC at Erasme Hospital. Consequently, the greater exposure and patient flow in general paediatrics likely contributed to the higher response rate observed in this group. A significant association was observed between consultation type and whether paediatricians associated children's conditions with SHS. Paediatricians in PPAC occasionally made this connection, whereas none in the GPC did. Beyond parental education, these findings highlight the need to further raise paediatricians' awareness of the importance of considering SHS when evaluating children's conditions, even when the consultation is not for respiratory or allergic issues. Another difference between PPAC and GPC concerned the desire to receive additional information about smoking cessation. Parents attending PPAC were more likely to express interest in receiving information on smoking cessation after completing the questionnaire, reflecting a higher level of concern. Moreover, nearly half of all participants wished to receive further information about SHS. At the end of the questionnaire, participants were offered downloadable brochures on SHS and its impact on children, as well as two brochures on smoking cessation. These findings suggest that making SHS brochures available in the paediatric department at Erasme and providing smoking cessation materials in the PPAC could be beneficial.

Strengths and limitations

The primary strength of this study is the comparison between GPC and PPAC. In addition, the study provides data and proposes avenues for enhancing future interventions aimed at reducing SHS exposure. It also contributes to increasing parental awareness and knowledge about SHS and smoking cessation

TABLE 4: Descriptive and comparative analyses of consultations on RPS and additional information.

	Mean (SD) N = 112	GPC, N =71	PPAC, N =41	p-value[2]
RPS				0.9
Yes	86,18 (19.67)	89 (72, 102)[1]	85 (75, 98)[1]	
More information on SHS				0.2
Yes	45 (40%)[3]	25 (35%)[3]	20 (49%)[3]	
No	67 (60%)[3]	46 (65%)[3]	21 (51%)[3]	
More information on tobacco cessation				0.009
Yes	15 (13%) [3]	5 (7%) [3]	10 (24%) [3]	
No	97 (86%) [3]	66 (93%) [3]	31 (76%) [3]	

[1] Median (IQR)

[2] Wilcoxon rank sum test, Pearson's Chi-squared test; Fisher's exact test

[3] n (%)

TABLE 5: Analysis of the risk perception of SHS.

Risk perception of SHS	1 low risk[1]	21	31	41	51	61	7 high risk[1]	Mean score[2]
Picture 1 (See questionnaire)	6 (5,4%)	6 (5,4%)	22 (19,6%)	22 (19,6%)	25 (22,3%)	11 (9,8%)	20 (17,9%)	4.49 (1.70)
Picture 2 (See questionnaire)	5 (4,5%)	7 (6,3%)	21 (18,8%)	26 (23,2%)	26 (23,2%)	9 (8,0%)	18 (16,1%)	4.43 (1.64)
Picture 3 (See questionnaire)	0 (0,0%)	1 (0,9%)	2 (1,8%)	1 (0,9%)	13 (11,6%)	8 (7,1%)	87 (77,7%)	6.55 (0.97)
Picture 4 (See questionnaire)	24 (21,4%)	17 (15,2%)	18 (16,1%)	19 (17,0%)	17 (15,2%)	7 (6,3%)	10 (8,9%)	3.44 (1.9)
Picture 5 (See questionnaire)	0 (0,0%)	2 (1,8%)	5 (4,5%)	3 (2,7%)	16 (14,3%)	26 (23,2%)	60 (53,6%)	6.13 (1.21)
Picture 6 (See questionnaire)	0 (0,0%)	1 (0,9%)	9 (8,0%)	3 (2,7%)	23 (20,5%)	20 (17,9%)	56 (50,0%)	5.96 (1.3)
Picture 7 (See questionnaire)	7 (6,3%)	5 (4,5%)	13 (11,6%)	16 (14,3%)	30 (26,8%)	15 (13,4%)	26 (23,2%)	4.84 (1.57)
Picture 8 (See questionnaire)	2 (1,8%)	5 (4,5%)	3 (2,7%)	16 (14,3%)	22 (19,6%)	23 (20,5%)	41 (36,6%)	5.54 (1.53)
The child is in the kitchen, someone is smoking on the adjacent service balcony	8, 7,1%)	11 (9,8%)	16 (14,3%)	21 (18,8%)	21 (18,8%)	14 (12,5%),	21 (18,8%)	4.45 (1.84)
The child is in a room where someone smoked 12 hours ago	7 (6,3%)	20 (17,9%)	16 (14,3%)	24 (21,4%)	20 (17,9%)	10 (8,9%)	15 (13,4%)	4.07 (1.78)
The child is in a room where someone smoked 2 hours ago	3 (2,7%)	5 (4,5%)	9 (8,0%)	20 (17,9%)	21 (18,8%)	24 (21,4%)	30 (26,8%)	5.17 (1.62)
The child is in a car where someone smoked 1 hour ago	4 (3,6%)	4 (3,6%)	6 (5,4%)	16 (14,3%)	21 (18,8%)	17 (15,2%)	44 (39,3%)	5.44 (1.68)
The child is in a room where someone smoked 30 minutes ago	3 (2,7%)	4 (3,6%)	3 (2,7%)	9 (8,0%)	21 (18,8%)	21 (18,8%)	53 (47,3%)	5.82 (1.51)
The child is in a car where someone smoked 20 minutes ago	3 (2,7%)	2 (1,8%)	2 (1,8%)	5 (4,5%)	12 (10,7%)	30 (26,8%)	58 (51,8%)	6.06 (1.39)
The child is in the playground and sees his mother smoking but does not smell smoke	32 (28,6%)	14 (12,5%)	19 (17,0%)	17 (15,2%)	8 (7,1%)	4 (3,6%)	18 (16,1%)	3.35 (2.13)
The child is in the playground and smells cigarette smoke but does not see the smoker	2 (1,8%)	4 (3,6%)	17 (15,2%)	21 (18,8%)	20 (17,9%)	21 (18,8%)	27 (24,1%)	5.00 (1.61)
The child is in the playground and sees his mother smoking and can smell the smoke	1 (0,9%)	2 (1,8%)	10 (8,9%)	19 (17,0%)	21 (18,8%)	20 (17,9%)	39 (34,8%)	5.44 (1.49)

[1] n (%)

[2] ean score (SD)

by allowing participants to download supplementary educational materials. For future research, it is recommended to provide participants with the correct answers at the end of the questionnaire, allowing them to identify misconceptions and improve their understanding. The limitations of this study include its cross-sectional design, which permits the identification of associations but does not allow for causal inferences. A larger sample size would also be necessary to adequately incorporate variables with few observations into the statistical model. The used questionnaire was specifically developed for this study and was not previously validated, which may have introduced measurement bias. Although it was approved by the institutional ethics committee, its reliability and validity were not formally established. In addition, some questions may have been suggestive, potentially influencing participants' responses and leading to response bias. A selection bias toward individuals with a higher educational level and likely higher socioeconomic status must be clearly acknowledged. Most participants held a higher education, university, or doctoral degree (59.8%), substantially exceeding the prevalence in the Belgian population aged 20 and older (32%) (30). Previous studies indicate that smoking prevalence is inversely correlated with educational level (31). This overrepresentation of highly educated individuals likely contributed to the lower proportion of current smokers (11.6%) or former smokers (18.8%) observed in our sample, compared with the prevalence in Belgium in 2018 (15.4% daily smokers, 4.0% occasional smokers, and 23.1% former smokers). The lower prevalence of smokers in our sample may also be partly explained by the fact that 70.4% of participants were women, among whom smoking rates are generally lower (32). These findings highlight that our sample is not fully representative of the Belgian population. Furthermore, the questionnaire was provided exclusively in French. This represents an additional limitation, as it may have introduced a selection bias by restricting participation to French-speaking individuals. Future research should make the questionnaire available in multiple languages, particularly English and Dutch, to improve inclusivity and reduce language-related selection bias. Moreover, for future research, it is recommended to clearly specify the definition of a complete home or vehicle smoking ban, as well as to define which areas are considered inside the home (such as balconies), in order to avoid overestimation of HSB or VSR. Finally, it is recommended that future studies include age as a continuous variable rather than categorizing it, in order to avoid categorization bias.

TABLE 6: Results of the multivariate analysis.

Risk perception of SHS	N	R[2]	IC[3]	p-valeur[1]
Age 50-65		-13.58	-24.69 — -2.47	0.017
Child's pathology: lower respiratory tract infections		13.68	0.59 — 26.77	0.041

[1] Simple multivariable linear regression

[2] regression coefficient

[3] 95% confidence interval

Conclusions

This study highlights that one-third of children are regularly in contact with smokers and are therefore at risk of SHS exposure. Raising awareness among parents and the child's social environment about the risks of SHS is therefore essential. Smokers, particularly those who smoke indoors, participants over 50 years of age, and those of Caucasian ethnicity, showed lower risk perception regarding SHS. Consequently, these groups should be specifically targeted when designing educational programs aimed at raising awareness of the health risks of SHS in children. These interventions should emphasize the importance of smoking restrictions in private spaces, especially among smokers. It is also crucial to define high-risk SHS exposure scenarios for children and to educate parents that exposure can occur even in the absence of visible or perceptible signs. Furthermore, PPAC paediatricians occasionally recognized a link between SHS exposure and the child's illness, unlike GPC paediatricians. This underlines the need to sensitize all paediatricians to consider SHS and the child's environment when evaluating paediatric illnesses. Finally, the majority of participants reported insufficient knowledge about SHS and expressed a desire to receive more information on this topic, as well as on smoking cessation. These findings underscore the importance of implementing educational programs for parents to raise awareness about the harmful effects of SHS on children's health.

Statements

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TABLE 7: Factors associated with parents' risk perception of SHS.

	N	R^2	IC	p-valeur[1]
Parental and Family Characteristics				
Age	112			
18–24		21.200	13.952 — 1.519	0.132
25–35		1.652	3.820 0.433	0.666
36–49		3.028	3.728 0.812	0.418
50–65		-14.82	-26.03 — -3.62	0.010
66+		-	-	-
Ethnicity	112			
White/Caucasian		-7.89	-15.61 — -0.16	0.045
Black/African		2.70	-7.60 — 13.00	0.604
Hispanic		-0.04	-15.32 — 15.25	0.996
Asian		-	-	-
Other		12.77	1.06 — 24.49	0.033
Marital status	112			
Married		7.44	0.17 — 14.70	0.045
Divorced		-7.93	-21.45 — 5.60	0.248
Single		-0.40	-10.06 — 9.26	0.935
Widowed		-6.48	-14.93 — 1.98	0.132
Cohabiting		0.95	-1.90 — 3.81	0.509
Tobacco use				
Smoking status	112			
Current smoker		-11.78	-23.11 — -0.44	0.042
Non-smoker		8.15	0.26 — 16.05	0.043
Former smoker		-3.38	-12.84 — 6.07	0.480
Other smokers at home	112			
Yes		-	-	-
No		10.61	0.50 — 20.73	0.040
Characteristics of the child attending the consultation				
Child's pathology	112			
Lower respiratory tract infections (pneumonia, acute bronchitis, bronchiolitis, ...)		15.39	2.10 — 28.69	0.024
Asthma		-2.20	-13.75 — 9.34	0.706
Acute otitis media		10.78	-12.05 — 33.60	0.351
Other		-6.88	-15.67 — 1.91	0.124
Children's exposure to SHS				
Where do you smoke	13			
Outside the home		-	-	-
Both inside and outside the home		-39.32	-71.74 — -6.90	0.022
Set a HSB	112			
Yes		-	-	-
No		-3.31	-14.48 — 7.86	0.559
Set a vehicle smoking ban	112			
Yes		-	-	-
No		-9.48	-21.45 — 2.48	0.119

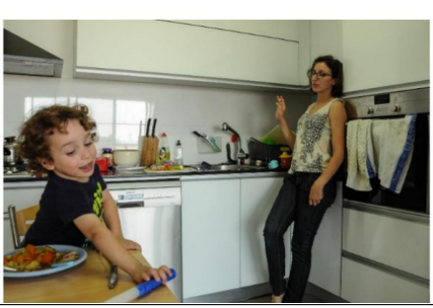
[1] Simple multivariable linear regression; [2] regression coefficient; [3] 95% confidence interval

Appendix 1: Questionnaire

Parental and family characteristics	
Which consultation did you attend?	- General paediatric consultations (GPC) - Paediatric pulmonology–allergology consultations
What's your gender?	- Female - Male - Other
How old are you?	- 18–24 - 25–35 - 36–49 - 50–65 - 66+
What's your ethnicity?	- White/Caucasian - Black/African - Hispanic - Asian - Other
What's your postal code?	
What's your education level?	- No diploma - Primary school certificate - Secondary school certificate - Technical or vocational certificate - Higher education/university degree, PhD
Do you have an employment?	- Unemployed - Part-time employment - Full-time employment - Student
What's your marital status?	- Married - Divorced - Single - Widowed - Cohabiting
How many children does your household count?	
What's the parental composition of your household?	- Single-parent - Two-parent - Blended family
Tobacco use	
What's your smoking status?	- Current smoker - Non smoker - Former smoker
Are there other people than you smoking in the household?	- Yes - No
Are there smokers, other than you, who are regularly in contact with your child (grandparents, nanny, …) ?	- Yes - No
What do you smoke?	- Cigarette - Electronic cigarette - Hookah/ shisha - Cannabis - Other
How often do you smoke?	- Daily - Several times per week - Once per week

	-	Less often
What is the mean number of cigarettes smoked each day?	-	Less than 5
	-	6–10
	-	11–20
	-	21–30
	-	More than 30
How soon after waking up do you smoke your first cigarette?	-	Less than 5 minutes
	-	6–30 minutes
	-	31–60 minutes
	-	More than 60 minutes
Have you ever tried to quit smoking?	-	Yes, successfully
	-	Yes, unsuccessfully
	-	Never tried
What is your attitude toward quitting?	-	I am not ready to quit
	-	I think I should consider quitting one day
	-	I think I should quit but I'm not ready yet
	-	I'm thinking about quitting
	-	I'm taking steps to quit
Are you ready to quit smoking?	-	I don't think I will quit in the next 6 months
	-	I am planning to quit within 6 months
	-	I am planning to quit within 30 days
Children's exposure to Secondhand smoke		
Do you smoke in the presence of children?	-	Yes
	-	No
Where do you smoke?	-	Inside the home
	-	Outside the home
	-	Both inside and outside the homeome
Have you introduced a smoking ban inside your home?	-	Yes
	-	No
Is this ban respected by all smokers in the home?	-	Yes
	-	No
In which situations do you smoke? (check all that applies)	-	Under the kitchen hood
	-	With the window open
	-	With the window closed
	-	On the balcony
	-	Other
Does the room where you smoke have ventilation?	-	Yes
	-	No
	-	Does not apply to my situation
Do you smoke in your vehicle?	-	Yes
	-	No
	-	I do not have a vehicle
Do you smoke in your vehicle in the presence of children?	-	Yes
	-	No
Have you introduced a smoking ban in your vehicle?	-	Yes
	-	No
	-	I do not have a vehicle
Is this ban respected by all smokers using the vehicle?	-	Yes
	-	No
	-	Does not apply to my situation
Have you ever been pregnant?	-	Yes
	-	No
What was your tobacco use during pregnancy?	-	Stopped smoking
	-	Reduced smoking
	-	No change

	- Not applicable
If you quit during pregnancy, when did you quit?	- Before pregnancy - First trimester - Second trimester - Third trimester - Not applicable
If you smoked during pregnancy, how much did you smoke?	- Less than 5 cigarettes - 6–10 cigarettes - 11–20 cigarettes - 21–30 cigarettes - More than 30 cigarettes - Not applicable
Did you think about quitting during pregnancy?	- Yes, successfully - Yes, unsuccessfully - No - Not applicable
Characteristics of the child attending the consultation	
What is your child's age? (For whom you're consulting)	- Newborn (0–1 month) - Infant (1 month–2 years) - Young child (2–3 years) - Preschool-age child (3–5 years) - School-age child (6–12 years) - Adolescent (13–18 years)
What pathology is your child being seen for?	- Lower respiratory tract infections (pneumonia, acute bronchitis, bronchiolitis, …) - Asthma - Acute otitis media - Infant (1 month–2 years)
Has a pediatrician linked your child's pathology to tobacco smoke exposure?	- Yes - No
Knowledge of Secondhand smoke	
Do you know what secondhand smoke is?	- Yes - No
Prenatal tobacco exposure increases the risk of: (more answers possible)	- Prematurity - Low birth weight - Small for gestational age - Perinatal mortality - Sudden infant death syndrome (SIDS) - Obesity - Recurrent respiratory infections (otitis, bronchiolitis, bronchitis)
Effects of secondhand smoke on infants: (more answers possible)	- Sudden infant death syndrome (SIDS) - Poor growth - Infant colic - Physiological regurgitation - Bronchiolitis - Respiratory infections - Nicotine withdrawal syndrome
Effects of secondhand smoke on children: (more answers possible)	- Asthma - Acute otitis media - Bronchiolitis - Bronchitis - Pneumonia - Cough - Reduced lung function

	- Attention-deficit/hyperactivity disorders (ADHD) - Future tobacco addiction
Do you think your knowledge about secondhand smoke is sufficient?	- Yes - No
Risk perception of secondhand smoke	
Would you like information about secondhand smoke and children?	- Yes - No
Would you like information about quitting smoking?	- Yes - No
Risk perception of secondhand smoke	
In the following questions you will be asked to rate the health risk to the child in various situations (depicted or described)	
Health risk to the child? 	1 2 3 4 5 6 7 no risk ○ ○ ○ ○ ○ ○ ○ high risk
Health risk to the child? 	1 2 3 4 5 6 7 no risk ○ ○ ○ ○ ○ ○ ○ high risk
Health risk to the child? 	1 2 3 4 5 6 7 no risk ○ ○ ○ ○ ○ ○ ○ high risk
Health risk to the child? 	1 2 3 4 5 6 7 no risk ○ ○ ○ ○ ○ ○ ○ high risk

Health risk to the child?



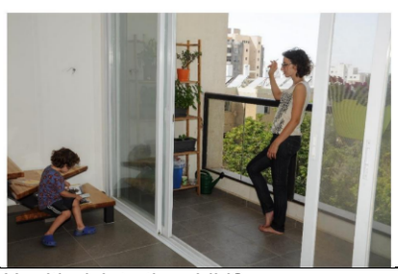
	1	2	3	4	5	6	7	
no risk	○	○	○	○	○	○	○	high risk

Health risk to the child?



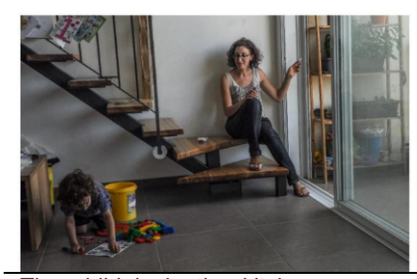
	1	2	3	4	5	6	7	
no risk	○	○	○	○	○	○	○	high risk

Health risk to the child?



	1	2	3	4	5	6	7	
no risk	○	○	○	○	○	○	○	high risk

Health risk to the child?



	1	2	3	4	5	6	7	
no risk	○	○	○	○	○	○	○	high risk

The child is in the kitchen, someone is smoking on the adjacent service balcony. Health risk to the child?

	1	2	3	4	5	6	7	
no risk	○	○	○	○	○	○	○	high risk

The child is in a room where someone smoked 12 hours ago.

Health risk to the child?

	1	2	3	4	5	6	7	
no risk	○	○	○	○	○	○	○	high risk

The child is in a room where someone smoked 2 hours ago.

Health risk to the child?

	1	2	3	4	5	6	7	
no risk	○	○	○	○	○	○	○	high risk

The child is in a car where someone smoked 1 hour ago.

Health risk to the child?

	1	2	3	4	5	6	7	
no risk	○	○	○	○	○	○	○	high risk

The child is in a car where someone smoked 30 minutes ago.

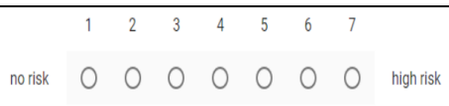
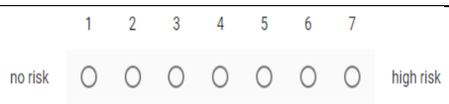
Health risk to the child?

	1	2	3	4	5	6	7	
no risk	○	○	○	○	○	○	○	high risk

The child is in a car where someone smoked 20 minutes ago.

Health risk to the child?

	1	2	3	4	5	6	7	
no risk	○	○	○	○	○	○	○	high risk

The child is in the playground and sees his mother smoking but does not smell smoke. Health risk to the child?	
The child is in the playground and smells cigarette smoke but does not see the smoker. Health risk to the child?	
The child is in the playground and sees his mother smoking and can smell the smoke. Health risk to the child?	

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Publishing in the Belgian Journal of Paediatrics: Insights from Authors and Paediatric Trainees

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Keywords

Paediatrics; Academic Training; Scientific Publication; Belgian Journal of Paediatrics Authors; Publication Motivation; Linguistic Differences; Paediatric Trainees

Abstract

Background
The Belgian Journal of Paediatrics serves as a national platform for paediatric research. However, recent data suggest an imbalance in contributions between French- and Dutch-speaking universities, raising questions about linguistic and institutional disparities in publishing practices.

Objective
To explore the motivations, barriers, and institutional support related to publishing among Belgian paediatric trainees and authors of the Belgian Journal of Paediatrics, with attention to linguistic differences.

Methods
A mixed-methods online survey was distributed to paediatric trainees (2016–2025) and first authors of the Belgian Journal of Paediatrics (2016–2024). Data on motivations, publishing experiences, perceived institutional support, and language barriers were collected and analyzed descriptively.

Results
Seventy-nine trainees and thirty Belgian Journal of Paediatrics authors completed the survey. Among trainees, publication was mainly motivated by diploma requirements (71.4%) and personal initiative (47.6%), with limited institutional encouragement (43%) or support (24.1%). Writing in English was not perceived as a barrier by most respondents (83.5%); however, those who did - predominantly affiliated with French-speaking universities - reported less institutional support for writing. Encouragement and guidance were significantly more common among Dutch-speaking universities. Training in scientific writing was limited (62% untrained), though most trainees had received critical reading instruction (73.4%).

Conclusion
The findings reveal persistent disparities between linguistic communities in institutional support and language-related confidence. Strengthening mentorship and integrating academic English and writing training across universities could promote more equal participation in national scientific publishing and enhance the inclusivity of the Belgian Journal of Paediatrics.

Introduction

Scientific publication plays a key role in the transmission of medical knowledge, the development of clinical practice, and the progression of academic careers. For medical trainees, engagement in research and scientific writing is both an opportunity and a challenge. In Belgium, paediatric trainees are required, as a condition for official recognition, to publish at least one first-authored article in a peer-reviewed journal to complete their specialization. While participating in research during training is intended as a formative learning experience, many trainees can face substantial obstacles such as limited time, lack of supervision and the

additional difficulty of writing in English (1). Despite this requirement, little is known about their actual publication practices, motivations, and the level of institutional support they receive. Beyond the context of training, the pressure to publish continues to grow among early-career doctors, for whom authorship often plays a decisive role in securing fellowship or advancing academically. Publishing may allow these authors to meet academic obligations, gain visibility, build a scientific reputation, or contribute to their field. However, they must navigate a complex publishing landscape influenced by numerous factors including a journal's academic standing, impact factor, scope of specialization, peer-review standards, time to publication, likelihood of acceptance, language, the geographical context of both the journal and the authors (which may affect audience relevance and institutional expectation), editorial policy, and ethical standards (2-8). Among the large panel of choices, the Belgian Journal of Paediatrics (BJP) stands as a potential national platform for disseminating paediatric research. The BJP traces its origins to the Acta Pediatrica Belgica, founded in 1946 by the Belgian Society of Paediatrics to promote paediatric research across linguistic communities. Initially dominated by French-speaking authors, the journal gradually became bilingual (French and Dutch) before being incorporated in the European Journal of Pediatrics in 1982. As many concerns were raised in Belgium due to exclusive use of English and a loss of a national platform, Mini Acta was created and evolved into a bilingual journal titled: Tijdschrift van de Belgische Kinderarts/Journal du Pédiatre Belge in 1999. In 2015, under the leadership of Marc Raes from Leuven and Samy Cadranel from the Hospital Universitaire des Enfants Reine Fabiola, the BJP was launched as the new official journal of the Belgian Society of Paediatrics. Over time, the language of publication gradually shifted to English, in line with worldwide academic standards, eventually becoming mandatory in 2020 (9). As a national platform, the BJP is intended to reflect the diversity of paediatric academic activity in the country and to provide an accessible publishing space for trainees, clinicians and researchers alike. A recent review of the journal's publications reveals that the majority (74%) of first authors over the past five years have been affiliated with Dutch-speaking universities or hospitals. This observation prompts reflection on the visibility and perceived accessibility of the BJP among French-speaking paediatricians and whether linguistic, institutional or cultural factors may influence submission patterns and engagement with the journal. To better understand these dynamics, we conducted a study aiming to explore the publishing practices, motivations and perceived barriers in paediatric trainees and recent first authors in Belgium and to examine whether these factors differ between French-speaking and Dutch-speaking communities. Particular attention was paid to their experience with scientific writing, the support they received from their institutions, linguistic barriers, the journal choosing process, and perceptions of the BJP.

Methods

A survey was designed to collect both qualitative and quantitative data. The survey was created using Google Forms, ensuring ease of distribution and accessibility for participants. The study sample consisted of two groups:

a) Current and past paediatric trainees: The survey was distributed to all Belgian universities with paediatric departments through their administrative offices. These offices confirmed the number of paediatric trainees who received the survey, for a total of 577 recipients. One reminder was sent. In total, 79 responses were received, corresponding to a response rate of 13.7%. The sample included both paediatric trainees currently

TABLE 1: Demographic Characteristics of Trainees (N = 79) and BJP Authors (N = 30)

Characteristic	Trainees (n=79)	BJP Authors (n=30)
Age (years)		
20–29	60 (75.9%)	4 (13.3%)
30–39	19 (24.1%)	9 (30.0%)
40–49	0 (0%)	8 (26.7%)
50–59	0 (0%)	6 (20.0%)
60+	0 (0%)	3 (10.0%)
Sex		
Female	63 (79.7%)	20 (66.7%)
Male	16 (20.3%)	10 (33.3%)
Nationality		
Belgian	71 (89.9%)	28 (93.3%)
French	3 (3.9%)	1 (3.3%)
Dutch	1 (1.3%)	1 (3.3%)
Spanish	1 (1.3%)	0 (0%)
Italian	1 (1.3%)	0 (0%)
Other	2 (2.5%)	0 (0%)
Medical school (multiple answers possible)		
KU Leuven	2 (2.6%)	7 (23.2%)
UAntwerp	5 (6.3%)	6 (20.0%)
ULB	28 (35.4%)	3 (10.0%)
UGent	24 (30.4%)	3 (10.0%)
UCL	11 (13.9%)	5 (16.7%)
ULiège	6 (7.6%)	1 (3.3%)
UNamur	5 (6.3%)	1 (3.3%)
UMons	4 (5.1%)	0 (0%)
VUB	2 (2.6%)	1 (3.3%)
Netherlands	2 (2.6%)	1 (3.3%)
UHasselt	1 (2.6%)	0 (0%)
Others	0 (0%)	4 (13.3%)
Paediatric training (multiple answers possible)		
ULB	29 (36.7%)	2 (7.1%)
UGent	23 (29.1%)	3 (10.7%)
UCL	9 (11.4%)	5 (17.9%)
UAntwerp	6 (7.6%)	6 (21.4%)
ULiège	6 (7.6%)	3 (10.7%)
VUB	4 (5.1%)	2 (7.1%)
KUL	3 (3.8%)	4 (14.3%)
Current place of employment (multiple answers possible)		
Academic hospital	56 (70.9%)	15 (50.0%)
Non-academic hospital	17 (21.5%)	10 (33.3%)
Rehabilitation centre	0 (0%)	1 (3.3%)
Private practice	1 (1.3%)	1 (3.3%)
University	11 (13.9%)	8 (26.6%)
Non-medical	0 (0%)	1 (3.3%)

in training and individuals who had been in training since 2016, with the exception of ULiège. This allowed the inclusion of both residents and recently trained early-career paediatricians.
b) First authors of articles in the BJP: To obtain perspectives from published authors, the survey was also sent to 627 first authors of articles published in the BJP between 2016 and 2024. These authors were identified using the journal's archives and were contacted via the email address they had provided at the time of manuscript submission. One reminder was sent. In total, 30 responses were received, corresponding to a response rate of 4.8%. The rationale for targeting first authors was to gather insights from those with direct experience of the publication process and who could reflect on their motivations for choosing this journal.

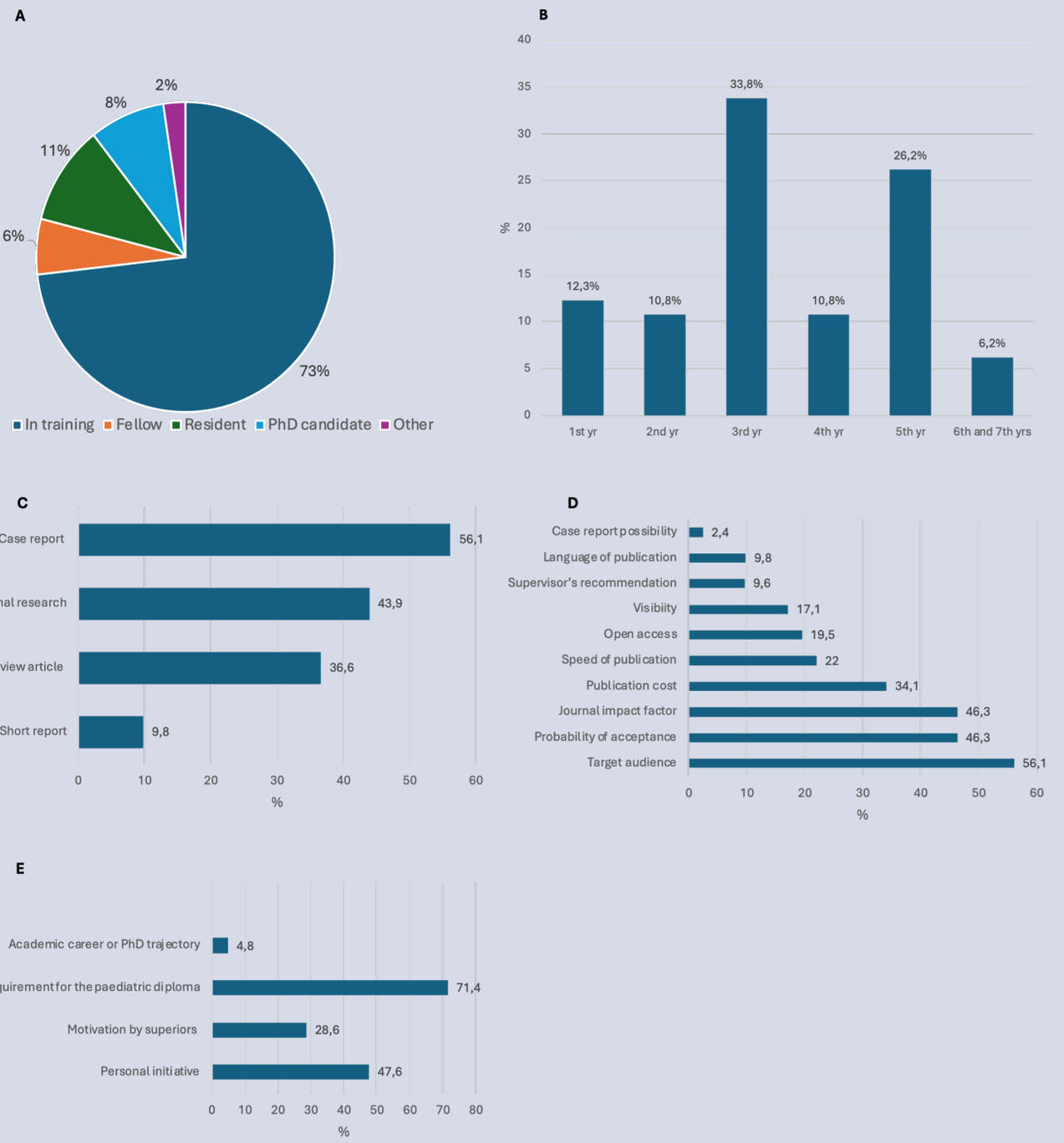
The survey was designed to collect anonymized data, including demographic characteristics, academic background of the trainees, and their previous experience with scientific publication. It also explored various factors influencing journal selection, such as perceived journal reputation, the importance of impact factor, visibility, relevance to the field, ease of the submission process, and overall publishing experience. Additionally, the survey investigated the level of perceived support from universities for publishing activities, the trainees' comfort with using English in scientific writing, and their reading habits of medical journals. A combination of multiple-choice questions was used to gather quantitative data, while open-ended questions aimed to capture the qualitative motivations underlying their choices. Data collection ran from February until June 2025. Data was extracted from Google Forms and analysed descriptively in July 2025. To prevent duplicate responses, each participant was required to use a unique email address to complete the questionnaire. For the analysis, only non-identifiable information was used. To explore whether the observed distribution of responses could be influenced by institutional overrepresentation, we conducted an exploratory post-hoc subgroup analysis stratifying respondents into four clusters: UGent, ULB, other Dutch-speaking universities, and other French-speaking universities. For single-response categorical variables, group differences were analysed using Chi-square tests, with Fisher's exact test applied when expected cell counts were below five. Continuous variables were compared using one-way ANOVA. Multi-response items were recoded into binary variables per response option and analysed separately using Chi-square tests. Given the large number of comparisons, p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) procedure. These analyses were exploratory and not pre-specified in the original study design. Ethics committee approval was judged not required, as the study consisted of a voluntary anonymized survey among professionals and did not involve collection of clinical or personal sensitive data.

Results

Profile and motivation of current and past paediatric trainees

The demographic characteristics of the respondents are summarized in Table 1. Respondents' professional status at the time of the survey is shown in Figure 1A. Figure 1B details the distribution of assistants by year of training. The distribution of respondents according to their workplace is detailed in Table 1. Nearly half of the respondents (49.4%) had authored an article as first author, of which 64.1% from Dutch-speaking universities and 35.9% from French-speaking universities. An overview of the published article types is presented in Figure 1C. At the time of publication, first authors were primarily trainees (87.5%), PhD students (22.5%), fellows (12.5%), or residents (5%). The factors influencing respondents' choice of journal are shown in Figure 1D and motivations to publish are presented in Figure 1E. Among trainees, 26.6% had conducted a research project during their paediatric training. Information on whether these projects were part of a PhD program was not collected. Regarding journal clubs, 49.4% of assistants had presented one, 68.4% had attended one, and 17.7% had never participated in one. As for reading paediatric journals, 19% never read them; 64.6% read them less than once a week, 15.2% more than once a week, and 1.3% fewer than four times per year. Awareness of the BJP was high (97.5%), but only 11.4% were active readers. Reading habits differed between French- and Dutch-speaking respondents. Among French-speaking trainees, only 29.5% reported reading any paediatric or medical journal, with most indicating that they did not read journals regularly and instead consulted individual articles when a specific topic of interest arose or when faced with a clinical question. Those who did cite journals most often mentioned Pédiatrie Pratique, Réalités Pédiatriques, Pediatrics, or Pediatrics in Review, while some also referred to general medical journals such as the New England Journal of Medicine or JAMA.In contrast, among Dutch-speaking respondents, 58.3% reported reading at least one journal. They more frequently described regular or structured reading, particularly of Praktische Pediatrie, Percentiel, and the BJP. Several also referred to international journals such as Pediatrics, the Journal of Pediatrics, or Pediatric Nephrology, and general medical journals like The Lancet, JAMA, or the New England Journal of Medicine. A few respondents from this group also indicated reading within the framework of institutional journal clubs. Concerning academic and institutional support for publishing, responses indicated modest overall encouragement and limited guidance (Figure 2A). Most assistants had received training in critical reading but not in article writing. As shown in Figure 2B, encouragement and support were more often reported by trainees from Dutch-speaking universities than by those from French-speaking ones. Writing in English was not perceived as a barrier by most respondents (83.5%). Among them, 20.3% had studied English at school, and 10.1% reported speaking it fluently at home. As illustrated in Figure 2B, considering English as a barrier was more frequent among trainees from French-speaking universities. Interestingly, however, the journals in which French-speaking trainees reported publishing, apart from the BJP, were not predominantly francophone. Respondents cited a range of English-language international journals, including Clinical and Experimental Pediatrics, Pediatric Pulmonology, Rheumatology, European Journal of Transplantation Medicine, The American Journal of Tropical Medicine and Hygiene, and Cureus Journal of Medical Science, alongside francophone or Belgian journals such as Revue Médicale de Bruxelles, Louvain Médical, Revue Française d'Allergologie, Archives de Pédiatrie and Percentile. This suggests that while language may influence perceived difficulty, it does not strictly determine publication choices. Additionally, 64.5% of all respondents reported receiving little or no institutional support for writing in English. The post-hoc subgroup analysis revealed several statistically significant differences between university clusters after FDR correction. These differences mainly concerned perceived institutional support, research involvement, motivation to publish, training in scientific writing, and selected professional characteristics. Respondents from Flemish universities consistently reported higher levels of institutional support for publication, English-language support, motivation to publish, perceived training in scientific writing, and involvement in research activities. For multi-response items, significant differences were also observed for specific response options, including employment in academic settings, publication of review articles, and the importance attributed to probability of acceptance when selecting a journal. These differences did not appear to be driven by a single institution such as UGent or ULB. Instead, response patterns tended to cluster along linguistic lines, with Dutch-speaking

FIGURE 1: A) Distribution of Respondents by Current Professional Status (%) ; (B) Distribution of Respondents by Year of Paediatric Training (%); (C) Distribution of Article Types Published by Paediatric Trainees (%) ; (D) Proportion of Trainees Selecting Each Factor Influencing Journal Choice (%)* ; (E) Proportion of Trainees Reporting Each Motivation to Publish (%)*. *Multiples Answers Possible.

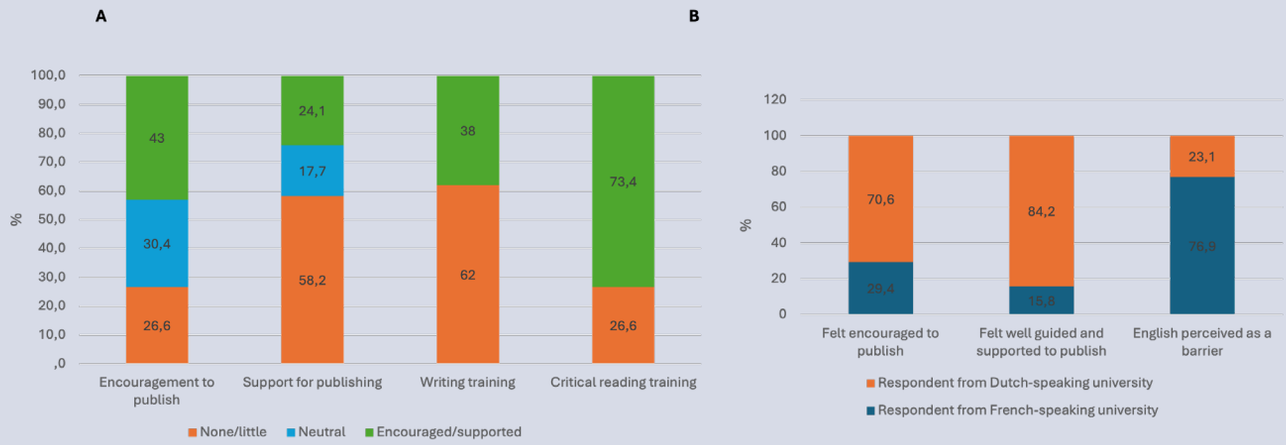


institutions showing similar distributions and French-speaking institutions displaying comparable patterns. The direction of these differences was consistent with the descriptive findings reported earlier, particularly regarding perceived institutional support and training-related factors.

Profile and motivation of first authors of the BJP

A total of 30 authors responded to the survey which was sent to 627 first authors of the BJP. This corresponds to a response rate of 4.8%. The demographic characteristics and details regarding the respondents' current workplace, medical school background, and location of paediatric specialization are summarized in Table 1. Figure 3 presents an overview of respondents' publication characteristics. Most publications occurred in recent years (Figure 3A) and most authors were staff members, followed by trainees and a smaller number of PhD students and others (Figure 3B). The main motivations for publishing were personal initiative and the requirement for the paediatric diploma, whereas other reasons such as encouragement from a supervisor, invitations, or editorial requests were less frequent (Figure 3C). The number of articles published by respondents varied widely, with the largest group reporting multiple publications and smaller groups having published only once or a few times (Figure 3D).

FIGURE 2: (A) Proportion of Trainees Reporting Institutional Encouragement, Guidance, and Training in Academic Publishing (%); (B) Proportion of Trainees Reporting Institutional Encouragement, Guidance, and Perceived Language Barriers, Stratified by University Language (French- vs Dutch speaking, %).

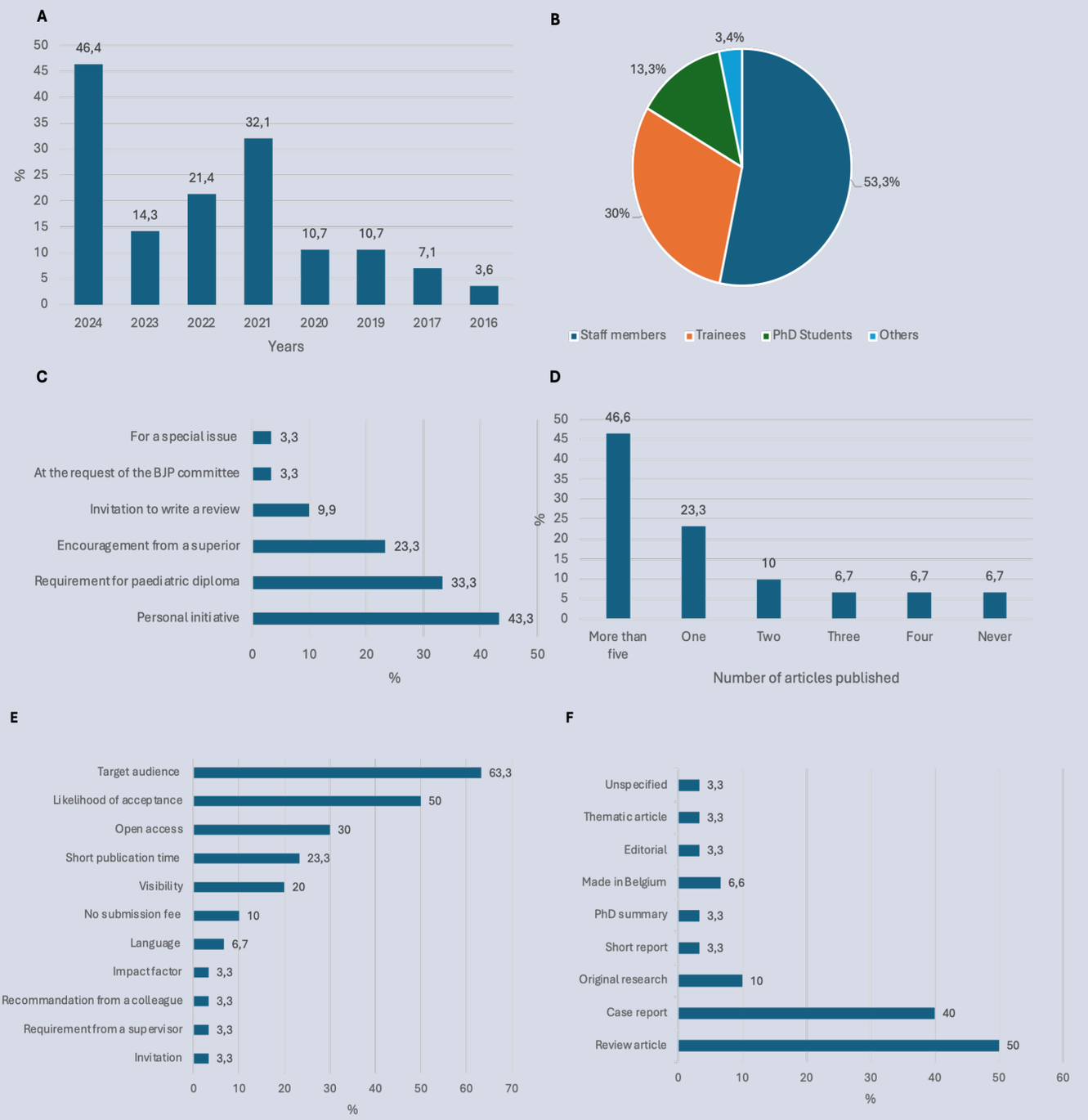


90% of respondents published as first authors; the others published as last authors. Only 4.3% of authors reported feeling very supported while writing their article, 26.1% felt supported, 21.7% felt neutral, 17.4% felt unsupported, and the largest group, 30.4%, felt not supported at all. Half of the authors (50%) had a background in scientific research; the other half did not. The reasons for choosing the BJP as the journal of publication are summarized in Figure 3E and type of articles published by BJP authors are presented in Figure 3F. 80% of authors stated that BJP was their first-choice journal. Another 16.7% chose it after being rejected by a European journal, and 3.3% after rejection from another Belgian journal. Authors who published in the BJP and in other journals did so in a wide variety of journals.

Discussion

This study aimed to examine the publication practices and motivations of two key author groups: paediatric trainees and authors who have published in the BJP. Our findings reveal that publication is often driven by institutional requirements especially among trainees, and that support for scientific writing remains suboptimal. The results provide insight into the publication practices of paediatric trainees in Belgium. While publication is largely perceived as a mandatory step for diploma completion, a significant proportion of assistants show genuine academic engagement. Part of this engagement may reflect differing career aspirations: trainees interested in academic or research-oriented careers are naturally more motivated to publish than those planning to work in private practice, where scientific output is less central. Although national data on paediatric career pathways in Belgium are limited, this variability should be acknowledged when interpreting motivation and publication activity. However, gaps in mentorship, training in scientific writing, and critical reading skills limit their full potential. Strengthening support systems—through structured training programs and enhanced supervisory guidance—may foster more active and confident participation in academic publishing (10). Addressing these needs will not only improve individual career development but also advance paediatric research and care nationally. In our study, 17.7% of paediatric trainees respondents have never presented nor participated in a journal club. This proportion is concerning, even if it may partly reflect differences in institutional organization, mandatory participation policies, clinical workload, or year of training. Journal clubs constitute a key component of postgraduate medical education. Encouraging participation in these activities helps cultivate a culture of evidence-based medicine and strengthens the connection between research and clinical practice (11–12). They contribute to the development of critical appraisal skills, enhance scientific literacy, and foster the analytical mindset required for professional growth. In addition, regular engagement in journal clubs may support a more individualized approach to patient care and sharpen professionals' critical scientific thinking. Limited exposure to such activities during training may therefore reduce opportunities to acquire competencies that are also essential for research involvement, scientific writing, and the publication process. A total of 26.6% of participants stated to have conducted a research project during paediatric training. This question was aimed to determine which portion of trainees were PhD trainees but given the high percentage of responders we believe this question has been interpreted differently and these results should be interpreted with caution. 19% of paediatric trainee respondents reported that they never read paediatric journals. Although engagement with the medical literature is an essential component of specialist training, we hypothesize that younger trainees may increasingly rely on secondary sources such as UpToDate, national and international society guidelines, or large language models (LLMs). The exploratory subgroup analyses suggest that observed differences in publication practices, institutional support, and perceived barriers are more likely to reflect broader linguistic and institutional contexts rather than being driven by overrepresentation of UGent or ULB alone. Nevertheless, these analyses must be interpreted with caution. Subgroup sample sizes were limited, the analyses were post-hoc, and the study was not powered for inter-institutional comparisons. As such, these findings should be considered hypothesis-generating rather than confirmatory. Future studies with larger and more balanced samples would be required to formally assess institutional versus community-level effects. Our findings are in line with previous studies highlighting the importance of structured support and mentorship in fostering scientific output. As shown by D'Arrietta et al. and Funston et al., early exposure to research and supervision positively influences motivation and engagement, while lack of support acts as a barrier (13, 16). In our study, over half of trainees and authors reported feeling unsupported, echoing these concerns. Moreover, Astaneh et al. and Raffing et al. emphasize that writing and publishing skills

FIGURE 3: Publication characteristics and journal selection factors among BJP authors : (A) Distribution of Publication Years* ; (B) Distribution of Professional Status at Publication ; (C) Proportion of Respondents Reporting Each Motivation to Publish* ; (D) Distribution of The Number of Articles Published (%) ; (E) Proportion of Authors Selecting Each Factor Influencing Journal Selection (%)* ; (F) Proportion of Article Types Published by BJP Authors (%)*. *Multiple Answers Possible



should be explicitly taught, preferably through dedicated courses (8, 17). The results provide new insight into the imbalance observed between Dutch- and French-speaking contributions to the BJP. While the majority of respondents did not perceive writing in English as a barrier, a closer look reveals that among those who did, a large majority were affiliated with French-speaking institutions. This suggests that language proficiency or confidence in academic English may remain a more significant obstacle for authors from the French-speaking community. Several factors might underlie this difference. Linguistically, English and Dutch both stem from the Germanic language family, sharing structural and lexical similarities, while French is a Romance language, which may make English acquisition more intuitive for Dutch speakers. Additionally, differences in English education curricula between the two communities may play a role, as well as variations in institutional support for scientific writing. These disparities could contribute to a lower submission rate from French-speaking authors to English-language journals such as the BJP. To address this imbalance, targeted measures could be considered, such as offering dedicated academic English courses for paediatric trainees or integrating tools like LLMs to assist with manuscript drafting. Such initiatives could help ensure more

equitable participation in academic publishing across linguistic communities. In line with all these observations, Wang et al. highlighted a psychological and practical gap among young physicians: although they exhibit strong intrinsic motivation and positive attitudes toward research, systemic barriers such as limited institutional support hinder their ability to translate this motivation into active research engagement (18). Among the 30 authors who responded and had published in the BJP, the majority were Belgian women aged between 30 and 49 years. While this may suggest a strong presence of female authors in this sample, it is unclear whether this reflects the overall gender distribution of first authors in the BJP, or whether it is influenced by a response bias. We did not analyse the evolution of gender representation among BJP authors over time, which limits our ability to draw conclusions about broader trends. However, this observation is interesting considering findings by Yao et al., who reported a significant global increase in female authorship in the biomedical sciences over the past two decades (19). Respondents came from diverse professional and academic backgrounds. Although half of them reported prior research experience, support during the writing process was generally low. Their main motivations for publishing in the BJP included the journal's targeted audience, high likelihood of acceptance, open access format, and fast publication timeline. These factors made the BJP the first choice for 80% of respondents. This aligns with findings by Bautista et al., who showed that authors often prioritize speed, visibility, and accessibility when selecting a journal (20). This study highlights that the BJP serves as an accessible journal, attractive to early-career clinicians. Despite many respondents having limited research backgrounds, they felt encouraged to publish in BJP, underlining the journal's inclusive and supportive role within the paediatric community. This study has several limitations related to both survey components, and the findings should be interpreted with appropriate caution. Among paediatric trainees, the response rate was low (13.7%), limiting the representativeness of the sample and introducing a risk of non-response and self-selection bias. However, this response rate should not be interpreted as a direct indicator of lack of engagement or interest among trainees. Survey participation may have been influenced by multiple factors, including workload, timing, survey fatigue, and dissemination procedures. In addition, it is possible that some of the email addresses used to distribute the survey were no longer actively consulted by former trainees, which may have further reduced participation. Furthermore, the survey was disseminated by the administrative offices of each university because of confidentiality; consequently, we had limited control over the distribution procedure. The response rate among first authors of the BJP was 4.8%, which is lower and requires even greater caution in interpretation. These authors were contacted using the email addresses provided at the time of manuscript submission, sometimes several years earlier, and outdated contact information may therefore have substantially limited participation. Consequently, the perspectives collected likely reflect those of reachable and motivated respondents rather than the full population of BJP contributors. Although the questionnaires were distributed exclusively to first authors, 10% of respondents identified themselves as second authors, possibly due to miscommunication within author groups or forwarding the questionnaire to co-authors. The modest sample size, voluntary participation, and over-representation of certain universities further limit the generalizability of the findings to all paediatric trainees and to authors publishing in other paediatric journals. Most responses came from professionals trained at Ghent University and ULB, likely because the survey was disseminated by two paediatric trainees from these institutions, facilitating personal outreach and increasing respondent motivation. The possibility of non-response bias therefore cannot be excluded, and the findings should be interpreted as exploratory and reflective of the respondents' views rather than fully representative of the entire trainee population. Exploratory subgroup analyses suggested that some observed differences in publication practices, institutional support, and perceived barriers may reflect broader linguistic and institutional contexts rather than being driven solely by the overrepresentation of UGent or ULB. However, these analyses should be interpreted with caution. Subgroup sample sizes were limited, the analyses were conducted post hoc, and the study was not powered to formally assess inter-institutional differences. Accordingly, these findings should be considered hypothesis-generating rather than confirmatory. Future studies with larger and more balanced samples would be required to better assess potential institutional or community-level effects. Finally, the survey relied on subjective, self-reported perceptions, which may not fully reflect the actual support, resources, or training opportunities offered by universities. For example, institutions may provide adequate research supervision or English-language writing courses that were not consistently perceived or reported by respondents. This subjectivity further limits the ability to draw objective comparisons between institutions. Nonetheless, the results point toward concrete recommendations. Embedding structured scientific writing training into paediatric curricula, increasing mentorship opportunities, and fostering a more supportive research culture could enhance both the quality and quantity of publications. Targeted support for French-speaking institutions may help rebalance representation in the BJP. Additionally, encouraging continued investment in accessible publication platforms like the BJP remains essential. Future research should explore the longitudinal impact of these support structures and assess whether enhanced training and mentorship influence long-term publication productivity and academic career trajectories. Cross-institutional efforts and collaboration between academic centres and professional societies may play a pivotal role in achieving this.

Conclusion

This study highlights differences between French- and Dutch-speaking universities in institutional support and language-related confidence in publishing. Strengthening mentorship and integrating academic writing and English-language training could help reduce these gaps and promote more balanced participation in Belgian paediatric research.

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RESEARCH ARTICLE

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Patient and Disease Characteristics of ADHD in Clinical Practice: A Retrospective Study in a Population- based Cohort of Children and Adolescents

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Keywords

Attention Deficit Hyperactivity Disorder (ADHD); Children/Adolescents; Comorbidity; Neurodevelopmental disorders; Psychosocial factors

Abstract

Background
Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that frequently co-occurs with various developmental, medical and psychosocial conditions. This study profiled children assessed for ADHD in a tertiary care setting.

Methods
Records of 164 children (3–18 years) assessed in 2023, resulting in 55 children suspected of and 109 diagnosed with ADHD, were retrospectively reviewed. Developmental, medical and psychosocial characteristics were analysed descriptively.

Results
Developmental coordination disorder (19.5%), learning disorders (13.4%) and language impairments (12.2%) were commonly associated. Medical comorbidities included atopic (14.6%), neurological (13.4%) and respiratory disorders (12.2%). Prematurity (21.3%) was also a notable risk factor for ADHD. Parental separation (31.1%) and family history of neurodevelopmental disorders (38.4%) were prevalent.

Conclusions
The clinical profile of children referred for ADHD assessment largely reflects patterns described in literature, underscoring the complexity of ADHD as a neurodevelopmental condition and highlighting the need for increased awareness, context-sensitive assessment and multidisciplinary collaboration.

Introduction

Definition

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental childhood disorder characterized by persistent inattention and/or hyperactivity-impulsivity across multiple settings such as personal, social, academic or occupational environments. Symptoms emerge during the developmental period and impair functioning and/or development. Clinical presentation can be predominantly inattentive, predominantly hyperactive impulsive or combined, depending on symptom pattern. Diagnostic classification is primarily guided by the International Classification of Diseases and Related Health Problems 10th revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) which provide standardized criteria for assigning a diagnostic label and forming the basis for multidisciplinary care and support. (1-3).

TABLE 1: List of included and analysed variables

Variables
Medical history
Gender
Term
Birth weight
Maternal usus during pregnancy
Medical history
Family history
Psychosocial background
Education level of both parents
Household composition
Language spoken with parents
Type of education
Professional guidance involved at time of assessment
Functional status
Course of development perceived by parents
Age at moment of diagnosis/suspicion ADHD
Referrer and reason for referral to the Centre for Developmental Disorders
Diagnosis after assessment (past and present)
Total intelligent quotient
Neurologic examination

Prevalence

Over recent decades, substantial efforts have been made to accurately estimate ADHD prevalence. An umbrella review of systematic reviews and meta-analyses by Ayano et al. reported a pooled global prevalence of 8.0% in children and adolescents with higher rates in boys (10%) compared to girls (5%). The included studies represented diverse populations across developed and developing regions showing broadly consistent prevalence worldwide with only modest variations among Black, White and Asian American groups and in samples from India and the Middle East (4).

Causes

The exact mechanisms underlying ADHD remain unclear. Strong genetic influences are well established with twin studies estimating heritability at around 76% (5). Although no single gene for ADHD has been detected, large genome-wide association studies have identified several loci in constrained genomic regions, loss-of-function genes and brain-expressed regulatory regions (6). ADHD risk is also increased in several genetic syndromes including fragile X syndrome, tuberous sclerosis and other microdeletion syndromes such as Smith-Magenis and velocardiofacial (VCFS; 22q11 microdeletion) syndrome (3). Observational and epidemiological studies link various prenatal and perinatal factors (such as very low birth weight, prematurity and smoking) as well as environmental toxins, diet and psychosocial factors to increased ADHD prevalence (2, 3). However, because genetic and environmental influences interact in complex ways establishing clear causal pathways remains challenging.

Comorbidities

ADHD frequently co-occurs with a wide range of neurodevelopmental and psychiatric conditions including autism spectrum disorder (ASD), learning or intellectual disabilities, motor disorders and behavioural problems such as oppositional defiant disorder and conduct disorder (2, 3, 7). Less common, yet still more prevalent than in the general population, are anxiety disorders, major depressive disorder, obsessive–compulsive disorder and intermittent explosive disorder (2). Besides psychiatric and neurodevelopmental conditions individuals with ADHD exhibit increased prevalence of several medical conditions particularly allergies, autoimmune disorders, epilepsy and sleep-related difficulties (2, 8). Additional factors such as visual or hearing impairments, metabolic abnormalities and nutritional deficiencies may influence ADHD symptom expression or severity and warrant careful consideration in clinical assessment (2).

Diagnosis

Because no specific laboratory tests exist for ADHD and given its broad range of potential comorbidities and contributing factors assessment must be comprehensive and extend beyond evaluating core symptoms. A thorough diagnostic process includes interviews, observations, symptom rating scales and input from multiple informants to assess functioning across different settings (9). Missed diagnoses may compromise academic, social or occupational outcomes and may result in inappropriate or unnecessary pharmacological interventions. Therefore detailed clinical history covering developmental and medical background, as well as family dynamics and psychosocial context, is essential to ensure accurate diagnosis and appropriate treatment planning (3).

Aims

This article aims to elucidate how the diagnostic complexities of ADHD manifest in clinical practice. Using a cohort of children and adolescents from a tertiary care centre, we retrospectively analysed a broad range of patient and disease characteristics to evaluate the extent to which real-world observations align with existing literature. This investigation addresses key gaps in ADHD research: underrepresentation of children from ethnically diverse backgrounds, limited consideration of ADHD heterogeneity and multiple comorbidities and limited research conducted in real-world clinical settings. By incorporating a comprehensive set of patient and disease characteristics the study aims to provide a more complete and clinically relevant understanding of ADHD.

Materials and methods

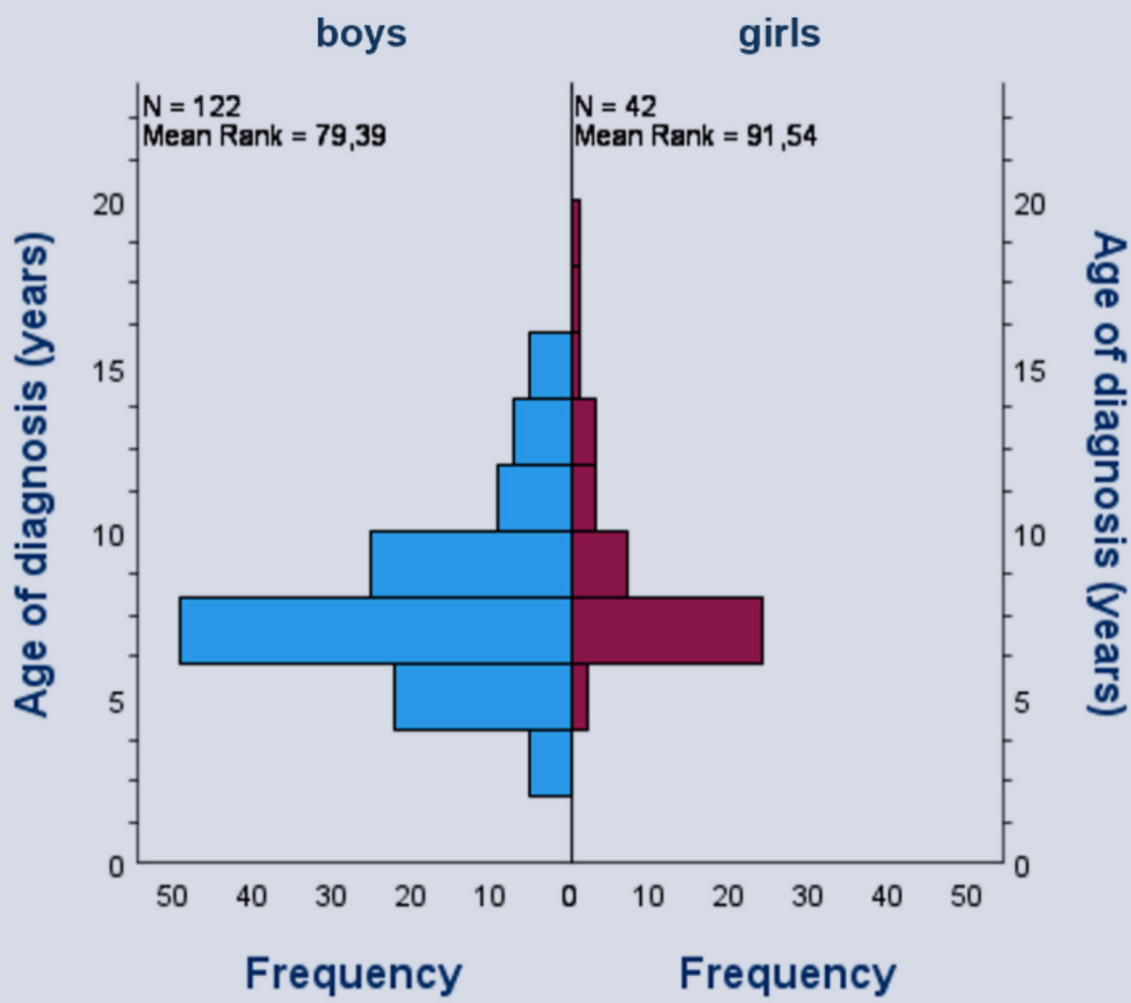
Literature search

We searched PubMed and Google Scholar using the MeSH terms: "Attention Deficit Disorder with Hyperactivity/epidemiology", "Risk Factors" and "Comorbidity". The search was restricted to systematic reviews and meta-analyses published in English within the last ten years focusing on children (6–12 years) and adolescents (13–18 years). After screening titles and abstracts, 81 articles were retained, of which 23 articles were included based on relevance.

Data collection

For this retrospective study we compiled a patient list from the database of the Centre for Developmental Disorders (CDD) at UZ Brussel. Inclusion required proficiency in Dutch, as evidenced by its use at home or in school. Patients assessed in 2023 who received

FIGURE 1: Distribution of the age at the time of ADHD diagnosis/suspicion in relation to sex.



a diagnosis or clinical suspicion of ADHD according to DSM-5-TR criteria were selected, yielding 204 records. After removing duplicates, 164 children remained. These were categorized into two groups: children younger than 6 years with suspected ADHD and children who reach 6 years of age or older during the year of assessment with either suspected or confirmed ADHD. The age threshold of 6 years is widely employed in ADHD research. This convention is supported by evidence indicating that in younger children behavioural symptoms are less readily distinguishable from typical developmental variation, psychometric reliability is reduced due to rapid developmental changes and the absence of a standardized school context may limit assessment validity and multi-informant information (2, 10). Despite these methodological considerations younger children were included in the present study to capture early developmental manifestations of the disorder. Medical records including the intake questionnaire, registration form, CDD assessment report and consultation notes from other healthcare disciplines were reviewed retrospectively. Table 1 summarizes the extracted variables.

Data analysis

Dichotomous variables were analysed and graphically represented using Microsoft Excel. Continuous and categorical variables were analysed using IBM SPSS Statistics 29.0 to generate descriptive statistics, no inferential statistical analyses were implemented. Missing data were not imputed as the primary aim of the study was descriptive. Instead, missing values were explicitly reported to ensure transparency. In the absence of inferential objectives no further adjustment for missing data were applied.

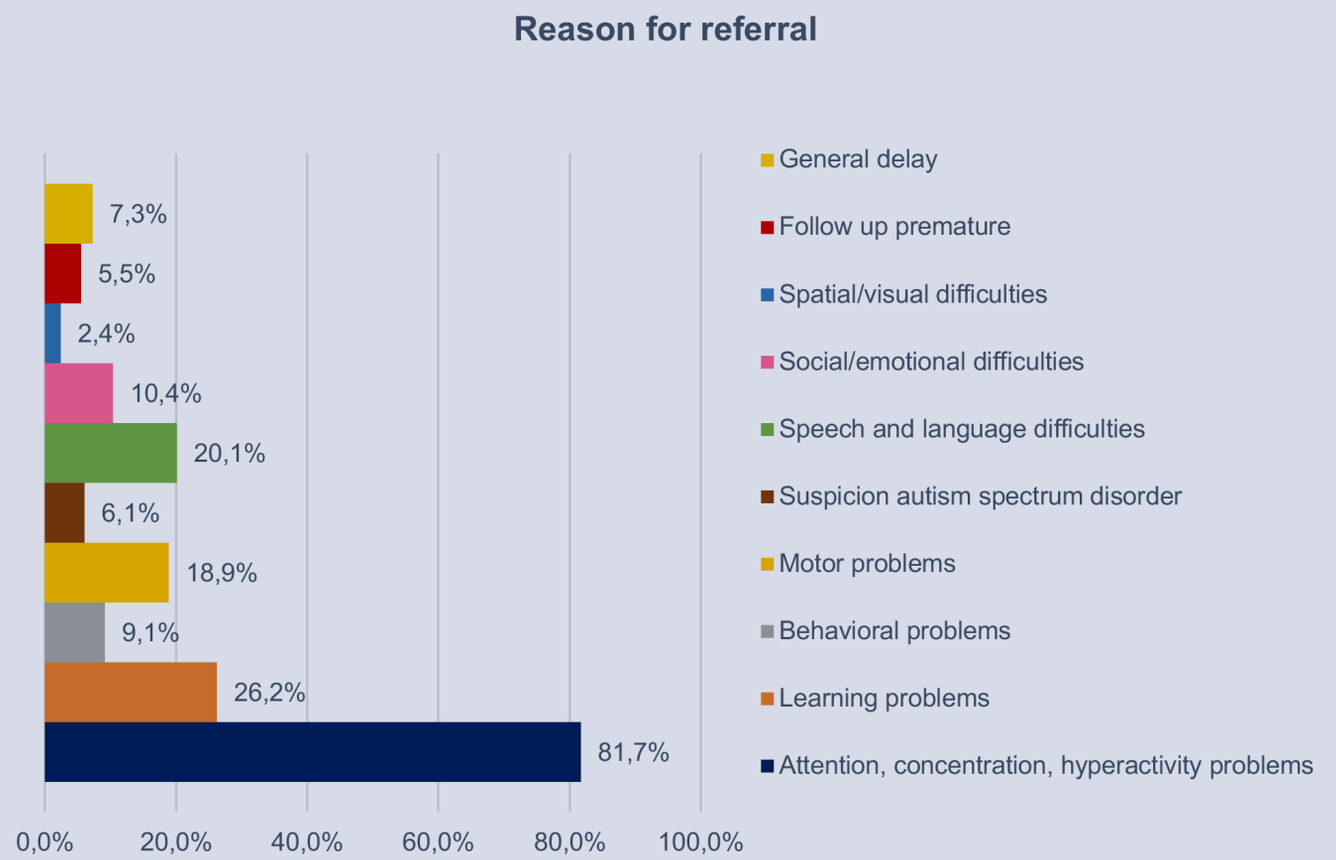
Ethical considerations

This study was reviewed and approved by the Medical Ethics Committee of UZ Brussel / VUB under protocol number EC-2024-205.

Results

The profiles of 164 children who underwent a diagnostic assessment in 2023 of whom 109 received a diagnosis of ADHD and 55 were suspected of having ADHD were analysed. The sample contained 122 boys (74.4%). Eight individuals had previously been diagnosed with ADHD and were reassessed in 2023 because of suspected comorbid developmental disorders. Most of the children (74.4%) were diagnosed between the age of 5 and 9 years, with a mean age of 7 years for boys and 8 years for girls. While girls were generally diagnosed at a later age than boys the peak age of diagnosis for both sexes was 7 years (Figure 1).

FIGURE 2: Overview of reasons for referral.



1. Referral patterns and functioning

A total of 145 children were referred of whom 24 indicated they were referred by a healthcare professional but also came on their own initiative. A total of 19 children presented solely on their own initiative, 12 of them were already receiving some form of professional support (as discussed further below) and 6 had a positive family history. An examination of language spoken at home within the cohort of children who self-referred (n = 43) revealed the following distribution: 6 were multilingual and did not speak Dutch at home, 19 were multilingual and Dutch-speaking, 17 were monolingual Dutch-speaking and 1 was monolingual and did not speak Dutch at home. Overall, 58.1% (25/43) of the self-referred cohort were multilingual compared to 41.9% (18/43) who were monolingual. Furthermore, 83.7% (36/43) of the cohort spoke Dutch at home whereas 16.3% (7/43) did not. Schools and pupil guidance centres (PGCs) accounted for 47.6 % of the referrals. Speech and physical therapists represented 10.4%. Psychologists and special education generalists accounted for 1.8% of the referrals. Surprisingly only 1.2% was referred by their general practitioner.

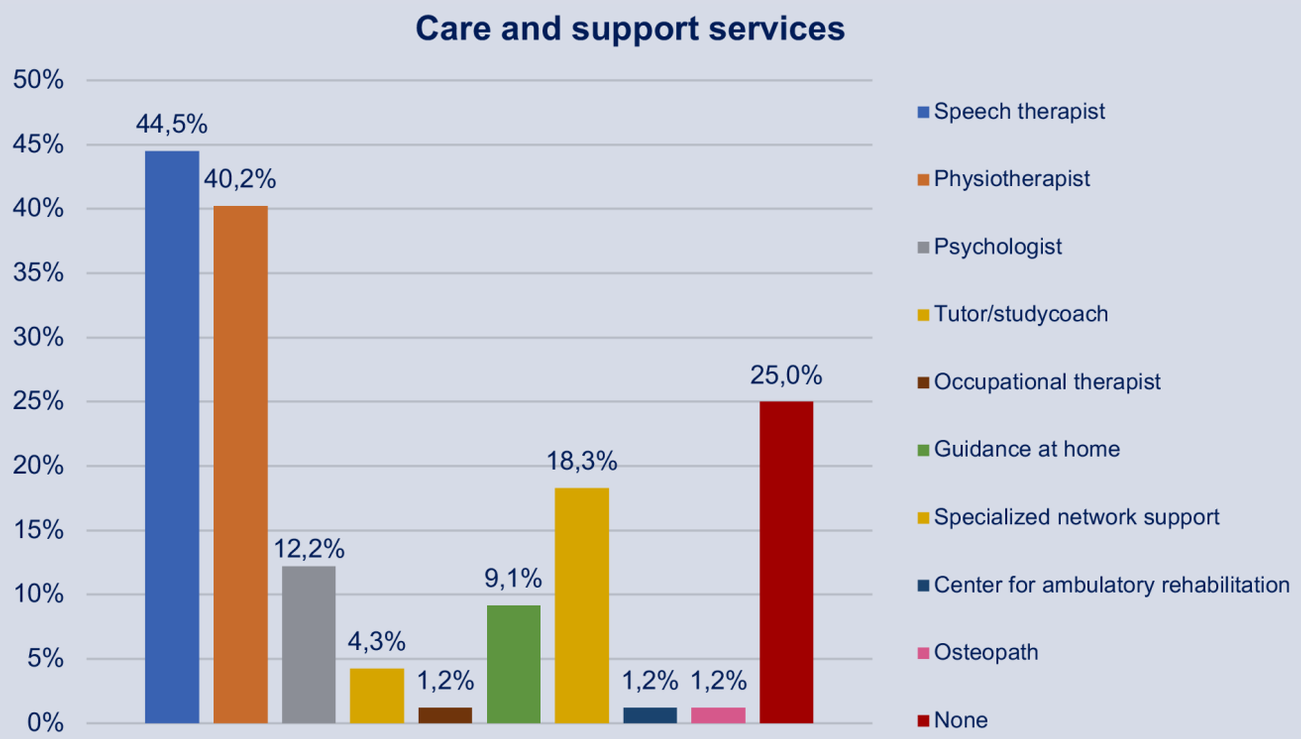
The primary reason for referral for a diagnostic evaluation was related to attention, concentration and hyperactivity difficulties consistent with ADHD's core diagnostic features. According to anamnestic data nearly half of the referrals (48%) presented with comorbid problems. Interestingly, 18% of referrals were made for reasons not related to attention, concentration or hyperactivity difficulties highlighting that children suspected of ADHD may present with a broad spectrum of developmental and functional issues. Other most prominent referral reasons included learning difficulties (26.2%), speech and language problems (19.5%) and motor difficulties (18.9%) (Figure 2).

Data on academic functioning revealed that 15.2% (n = 25) of our population had repeated a school year and 3.7% (n = 6) were enrolled in special education. 25% (n = 41) of the children had not yet received any therapeutic support at the time of the assessment. Of the 123 children who were already receiving care and support 12 (9.8%) independently requested an assessment. Speech therapy (44.5%) and physical therapy (40.2%) were the most common interventions followed by specialized network support at school (18.3%) (Figure 3). In most of the cases previously existing involvement of multiple healthcare professionals was reported.

2. Co-occurrence of neurodevelopmental disorders

Our cohort reflects the well-documented high comorbidity in children with ADHD and other neurodevelopmental disorders. The neurodevelopmental disorders are a group of conditions with onset in the developmental period. In general, a delay is considered a temporary lag in development often influenced by external factors with the potential for catch-up given appropriate support and intervention. In contrast, a disorder is characterized by persistent impairments whereby abilities are substantially and quantifiably below those expected for the individual's chronological age and cannot be explained by another medical or neurological condition. For a more detailed description and diagnostic criteria reference is made to the DSM-5-TR (2). Most of the children (n = 136) received more than one diagnosis with 62.2% exhibiting at least one delay in the domain of language, learning

FIGURE 3: Involved care and support services before diagnostic assessment for ADHD.



or motor development. The most frequently observed comorbid conditions were developmental coordination disorder (19.5%), learning disorders (13.4%) and communication disorders (12.2%) (Figure 4). Although parents report normal early development in 69 cases (42.1%), clinical evaluation revealed that 81.7% of these 69 children have a developmental delay or disorder in the

FIGURE 4: Proportion of co-occurring neurodevelopmental disorders.

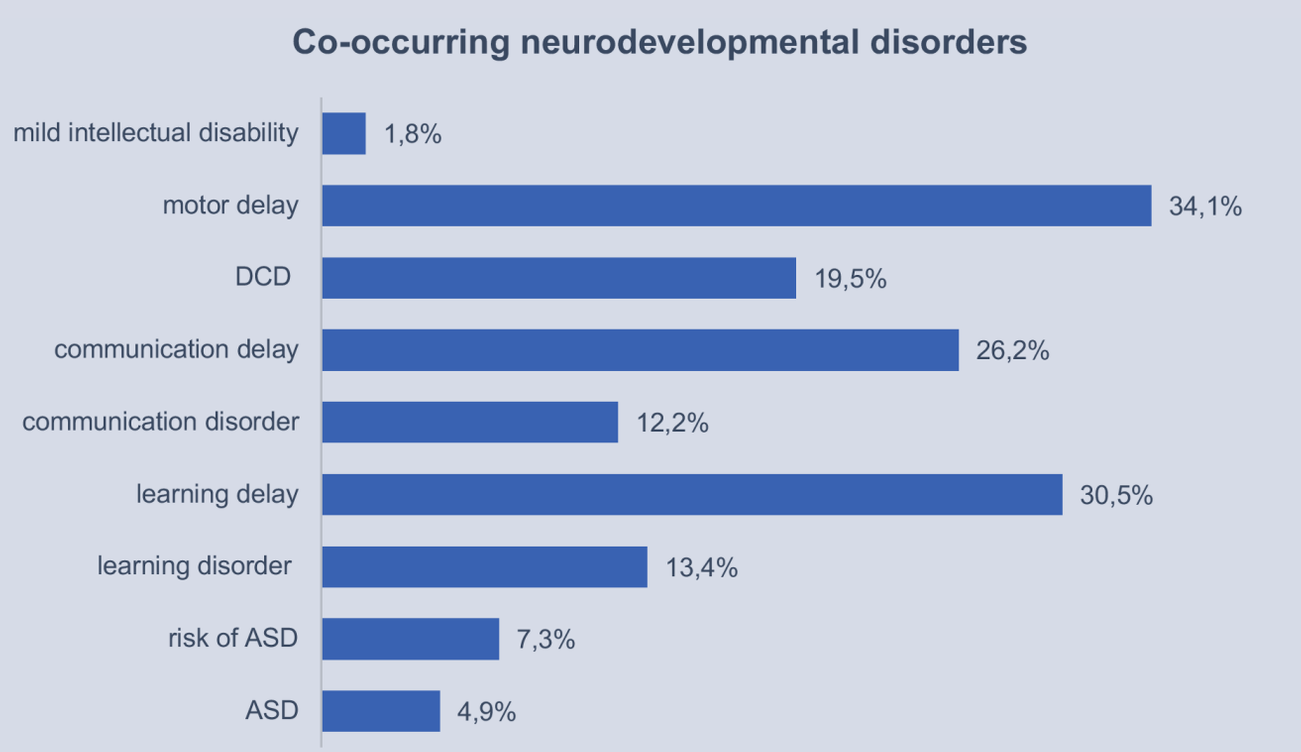


TABLE 2: Diagnosis within the referred group and distribution by home language.

Referral for communication problems (N=33)					
Diagnosis of disorder N=8		**Diagnosis of delay N=20**		**No diagnosis N=5**	
4 Dutch	4 non Dutch	8 Dutch	12 non Dutch	2 Dutch	3 non Dutch
3 multi	5 mono	13 multi	7 mono	1 multi	4 mono
Referral for learning problems (N=43)					
Diagnosis of disorder N=16		**Diagnosis of delay N=19**		**No diagnosis N=8**	
10 Dutch	6 non Dutch	13 Dutch	6 non Dutch	6 Dutch	2 non Dutch
8 multi	8 mono	10 multi	9 mono	6 multi	2 mono
Dutch = children that do speak Dutch at home (N=110) Non Dutch = children that don't speak Dutch at home (N=54) Multi = children that are raised in multilingual household (N = 79) of whom 56 also spoke Dutch Mono = children that are raised in monolingual household (N = 85) of whom 54 spoke Dutch					

domain of language, learning or motor development illustrating a significant discrepancy between parental perception and objective assessment. In 9 cases information on early development was not provided.

- a) Intellectual disability
  Cognitive functioning was assessed using the total intelligence quotient (TIQ). The TIQ was measured based on various intelligence tests depending on the child's age and functioning. TIQ scores were generally, in 63.4 % (n = 104), in the average to low-average range (80–100) and equal findings were observed across genders. To maintain uniformity this study reports only the total IQ (TIQ), even though 9.1% exhibited a disharmonic cognitive profile which is known to impact the interpretation. Within our study population 1.8% had a diagnosis of mild intellectual disability (IQ 50-69).
- b) Communication disorder
  Within the total study population of 164 children, 79 were raised in a multilingual context at home including 23 who grew up in households where Dutch was not spoken. In 54 of the 164 children, Dutch was not spoken at home implying that they were raised in a language different from the language of instruction. Our results indicate that children who did not speak Dutch at home were referred three times more frequently for speech and language difficulties. In contrast, the distinction between monolingual and multilingual background did not appear to affect the likelihood of referral (Table 2).
  A notably higher prevalence of language delay was observed among children who were not raised in Dutch at home, meaning in a language different from the language of instruction. Comparable proportions of language disorders were found between children raised in Dutch-speaking and non–Dutch-speaking households. However, children raised in multilingual environments showed a higher prevalence of both language disorders and language delays (Table 3). Despite being diagnosed with a communication disorder or delay, 55.6% of the children had no such concerns noted by their environment at the time of referral (Table 2 and 3).
- c) Specific learning disorder
  According to our findings, growing up in a non-Dutch-speaking family did not influence referral rates for learning difficulties. Children raised in multilingual environments, however, were referred more frequently due to learning problems (Table 2). The prevalence of diagnosed learning disorders was comparable between children who were exposed to Dutch at home and those who were not. In contrast, learning delays were 2.5 times more frequently diagnosed among children who spoke Dutch at home. Learning disorders were slightly more prevalent in the group raised in a multilingual environment compared to the monolingual group, whereas the prevalence of learning delays was similar across both groups (Table 3). In 51.4% of children diagnosed with a learning disorder or delay, no such concerns were reported by their environment at the time of referral (Table 2 and 3).
- d) Motor disorders
  Neurological examinations revealed motor abnormalities in 39.6% of cases with fine motor deficits being the most frequent finding (n = 47). Impairments in gross motor function were observed in 7.9% (n = 13) of the children while disturbances in gait and balance were noted in 6.7% (n = 11). Coordination difficulties were present in 4.9% of cases. Motor difficulties also appear to occur with a notably high prevalence. Of the 31 children referred with concerns regarding motor development, 58.1% were diagnosed with developmental coordination disorder (DCD) and 35.5% exhibiting delayed motor development.
- e) Autism spectrum disorder
  Within our cohort 4.9% were diagnosed with ASD. Of those referred for suspected ADHD and ASD (n=10), 30% did not receive a diagnosis while 40% were considered 'at risk' at the moment of assessment due to either the need for further assessment because of their young age, the limited cooperation or possible alternative explanations such as hearing impairments or genetic conditions.
- f) Other
  Referrals due to a general developmental delay including language acquisition, academic learning and motor skill development, were seen in 12 individuals of which 66.7% (n = 8) were diagnosed with a developmental delay and 16.7% (n = 2) were determined to exhibit a general developmental disorder. Meaning 2 were left without a diagnosis of developmental delay or disorder.

TABLE 3: Diagnosis according to language environment.

Communication disorder	Communication delay	Learning disorder	Learning delay
Group of children raised in Dutch-speaking household (N=110)			
13 (11.8%)	19 (17.2%)	14 (12.7%)	36 (32.7%)
Group of children raised in a non-Dutch-speaking household (N=54)			
7 (12.9%)	24 (44.4%)	8 (14.8%)	14 (12.7%)
Group of children raised in a multilingual household (N=79)			
12 (15.2%)	25 (31.6%)	12 (15.2%)	23 (29.1%)
Group of children raised in a monolingual household (N=85)			
8 (9.4%)	18 (21.2%)	10 (11.8%)	27 (31.8%)

3. Behavioural problems

Amongst the 14 individuals who were referred for behavioural problems, only 2 were diagnosed with a behavioural disorder. No specific behavioural disorders were identified because of the

young age of the children. Further diagnostic clarification will be pursued throughout the ongoing treatment and support process. However, given the very small sample size these observations should be interpreted with caution.

4. Medical conditions

Perinatal data indicated that 21.3% (n = 35) of children were born prematurely (<37 weeks of gestation). It should, however, be noted that in 6.7% of the cohort gestational age data were missing. Moreover, 11.0% was classified as small for gestational age (SGA, birth weight below the 10th percentile) and 10.4% as large for gestational age (LGA, above the 90th percentile) demonstrating a relatively balanced distribution across growth percentiles. Notably one-third (33.3%) of children who met the criteria for SGA were also born preterm. 14.6% (n = 25) of the children experienced neonatal complications, within this group 13.5% was born preterm. Three cases involved term births with admission for phototherapy, respiratory support, IV antibiotics and/or tube feeding. Medical history analysis revealed a wide spectrum of comorbid conditions within the cohort. Otolaryngologic issues were reported in 12.2% of the children consisting primarily of surgical interventions. Neurological conditions were present in 13.4% with cerebral haemorrhage and headaches being the most frequently documented. Cardiovascular disorders were identified in 2.4% of the sample while 12.8% presented with respiratory conditions, predominantly related to bronchial hyperreactivity. Urological or nephrological concerns were documented in 7.9% of the children, approximately half of whom were diagnosed with nocturnal enuresis. Atopic disorders were observed in 14.6% of the cohort mainly characterized by allergic manifestations. An additional 6.1% presented with other medical conditions (Table 4). Genetic abnormalities were identified in 12 children representing 7.3% of the cohort. Within our study population three distinct syndromic conditions (Turner syndrome, Jacob's syndrome and the 22q11.2 duplication syndrome) were identified along with a pathogenic variant in the SOX gene. All of these have previously been reported in association with ADHD. The remaining cases involved variants of uncertain significance.

5. Psychosocial factors

Analysis of prenatal exposures demonstrates that 12.2% of the mothers of the included children reported medication use during pregnancy predominantly for managing pregnancy-related complications. Tobacco use during pregnancy was reported by 4.9% of mothers and 1.2% reported alcohol use. It is important to note that prenatal exposure data were incomplete in 20.7%. Socioeconomic status (SES) was assessed indirectly through parental education level. In only 3.7% of families neither of the parents had received their high school diploma. In 89% of families one or both parents had finished high school and in 37.8% of the couples at least one parent had completed higher education (7.3% missing data). This pattern may reflect underlying sociodemographic characteristics of the ADHD population or indicate a referral bias within our sample. Family composition data indicated that 31.1% of children grow up with divorced parents with 12.8% experiencing limited or no contact with one of the parents. Within our cohort one child had been adopted and two lived in foster care. Review of the occurrence of neurodevelopmental disorders within the families showed that 67 out of 164 participants (40.1%) had other family members with a neurodevelopmental disorder. Among those, ADHD and attention and/or concentration problems were the most frequently reported (n = 34) followed by learning difficulties (n = 23) and ASD (n = 16). Additional reported conditions included communication problems (n = 9), motor problems (n = 4), intellectual disabilities (n = 3) and other developmental problems not otherwise specified (n = 4). Of the familial cases, 27 were reported in first-degree relatives, 32 in second-degree, 13 in third-degree and 17 in fourth-degree relatives. In four cases the degree of relatedness was not clearly specified by the parents.

Discussion

Most children in our cohort were referred for core ADHD symptoms and nearly half presented with ADHD and other developmental comorbidities. These findings are consistent with studies highlighting ADHD as a complex, multidimensional disorder associated with academic underachievement and increased support needs, as suggested by the elevated rates of grade retention observed in our sample (11). Furthermore, our data suggest a potential gap in access to care indicated by the substantial proportion of children who had not received prior therapeutic support. Based on these observations, several hypotheses can be proposed and might be recommended for further investigation. The higher retention rates among children with ADHD may be explained by core deficits in attention, executive functioning and self-regulation which are often exacerbated by comorbid learning disorders and reduced school engagement. In addition, these outcomes may be reinforced by structural limitations within the educational system. For instance, in practice, schools in Belgium frequently require a formal diagnosis before initiating support which's necessity is not supported by the guidelines, even though school-based intervention is the most common. Moreover, long waiting times and high private costs, as reported in literature, may further restrict access to care and delay timely intervention. Such delays have been associated with increased societal costs and elevated risks, including school dropout, substance abuse and worsening of existing comorbidities, outcomes that could potentially be mitigated by early and adequate support (12, 13).

In the context of healthcare accessibility, our study revealed an unexpectedly low proportion of referrals originating from primary care physicians. A plausible explanation is that general practitioners may initially refer children to general paediatricians or paediatric neurologists, who are subsequently recorded as the referring clinicians. This observation may also serve as a rationale for further evaluation and optimization of interdisciplinary collaboration with primary care providers to ensure timely identification, referral and management of children with ADHD. An additional finding in our study concerns differences in self-referral patterns between Dutch-speaking and non-Dutch-speaking families with Dutch-speaking families appearing more likely to initiate referral. This may suggest more limited access to diagnostic services among non-Dutch-speaking families. However, this interpretation should be made with caution as no comparison with the general population is available to determine whether this distribution reflects a true representation. Moreover, access to care is a multifactorial construct that extends beyond language proficiency alone. Factors such as cultural background, knowledge and confidence in the local healthcare system and overall health literacy are also likely to play a significant role in shaping referral behaviours and service utilization. These findings should furthermore be interpreted within the specific institutional and sociolinguistic context of the present cohort. The centre for developmental disorders in which this study was conducted operates within the Flemish healthcare system. Within this context, children raised in monolingual French-speaking environments are generally directed toward the French-speaking care circuit. In contrast, for multilingual and non-Dutch-speaking families with diverse cultural backgrounds referral pathways are less clearly defined. In such cases the choice between Dutch- and French-speaking services is frequently influenced by the language of the child's school. This

structural complexity may further contribute to variability in access to care and to the observed differences in referral patterns.

The high frequency of developmental delay in our cohort aligns with literature describing frequent comorbid neurodevelopmental conditions in ADHD (7, 14, 15). However, a key discrepancy emerged between parental reports and clinical findings. Although not well quantified in the literature, this gap may reflect limitations in parental recall or knowledge which may in turn be influenced by language barriers and low levels of health literacy. This may lead to an underestimation of developmental difficulties and underscores the value of professional, objective evaluation.

Consistent with prior research, cognitive functioning in our cohort was generally within the average to low average range supporting the view that ADHD is characterized by executive dysfunction and uneven cognitive performance rather than global intellectual disability (ID) (16). The low prevalence of mild intellectual disability in our sample was surprising as the literature suggests an overlap between ADHD and ID but also highlights the difficulties in assessing ADHD in individuals with ID (17). This discrepancy may reflect under-recognition as co-occurring difficulties are often attributed to the disability itself or referral bias as individuals with ID are more likely to be assessed in specialized settings.

The observed prevalence of learning and communication impairments is consistent with findings in the literature confirming that ADHD frequently co-occurs with learning and communication disorders (14, 18). Our findings extend the literature by highlighting language exposure and multilingualism as critical contextual factors. Children from non-Dutch-speaking households were more frequently referred for speech concerns but more often diagnosed with delays rather than disorders. These findings should be interpreted with caution as no inferential statical analyses were performed, however, they may suggest that limited exposure to the language of instruction can mimic or exacerbate communication difficulties raising the possibility of misclassification.
Although prior research supports the importance of considering language background in diagnostic evaluation, a factor particularly relevant in diverse urban settings such as Brussels, evidence focusing specifically on these subgroups remains limited (19). In contrast and warranting cautious interpretation, learning delays were more frequently observed among children who spoke Dutch at home. This finding suggests the possibility of underrepresentation of non-Dutch-speaking households as cultural differences and communication barriers may limit access to healthcare services as discussed above.

The prevalence of developmental coordination disorder (DCD) in our cohort was substantially lower than the 50% prevalence reported in the literature (20). This discrepancy may reflect underdiagnosis or differences in assessment practices as motor difficulties are often secondary concerns and may not be systematically evaluated. Nevertheless, the identification of such deficits remains important as existing evidence indicates that motor impairments can intensify academic difficulties, as fine motor skills support many cognitive and school-related tasks (20).

Despite the lower prevalence of autism spectrum disorder (ASD) in our cohort, the observed co-occurrence still supports literature identifying ADHD and ASD as frequently overlapping conditions (7, 14, 15). The difference likely reflects differences in diagnostic thresholds, referral patterns or population characteristics. The presence of a substantial at-risk group for ASD indicates the

TABLE 4: Detailed summary of the medical conditions observed among the study group

Neurological disorders (N = 22)	**13,4%**
migraine	3
tension headache	2
headache, not other specified	1
epilepsy	2
febrile convulsion	3
cerebral haemorrhage *	6
axial hypotonia	1
Erb's palsy	3
periventricular leukomalacia	1
Respiratory disorders (N = 20)	**12,2%**
bronchial hyperreactivity	9
asthma	9
bronchopulmonary dysplasia	4
Atopic diseases (N = 24)	**14,6%**
atopic eczema	9
allergic rhinitis	6
allergy not further defined	13
Uro/nephrological disorders (N = 13)	**7,9%**
hydronephrosis	1
vesicourethral reflux	2
nephrolithiasis	1
duplicated renal system	1
enuresis nocturnal	6
cryptorchidism	3
Cardiac disorders (N = 4)	**2,4%**
supraventricular extrasystoles	1
congenital heart disease	1
ASD II	1
VSD	1
Otolaryngological disorders (N = 20)	**12,2%**
adenectomy or adenotonsillectomy	14
eardrum tubes	9
thyroglossal cyst	1
tympanoplasty	1
obstructive sleep apnoea	2
vocal cord paresis	1
Genetic abnormalities (N = 12)	**7,3%**
Other (N = 10)	**6,1%**
dyssomnia	1
strabismus	3
herniotomy	2
oral aversion	2
Obesity	2

* Cerebral haemorrhage: pinpoint haemorrhage, subdural, cerebellar, subependymal, intraventricular haemorrhage

necessity of continued monitoring and follow-up and may reveal higher rates over time

A striking discrepancy was observed in the extremely low rate of behavioural disorder diagnosis which contrast sharply with literature reporting high comorbidity rates for conditions such as oppositional defiant disorder (20-60%) or anxiety disorders (1-44%) (11, 21). This difference may be explained by service organization rather than true prevalence as children with suspected behavioural disorders are more likely to be referred to specialized services. Additionally, such disorders may emerge later beyond the timeframe of assessment in developmental centres.

Overall, the pattern of somatic comorbidities in our cohort is largely consistent with existing literature particularly regarding respiratory, atopic, urological and cardiovascular conditions (8, 22-25). However, some differences emerged. Although epilepsy was not specifically observed in our cohort, literature reports a significantly higher prevalence of ADHD (30.7%) among children with epilepsy compared to the general population (7.2%) (26). The presence of neurological symptoms in our sample may reflect a broader neurodevelopmental vulnerability, though the absence of epilepsy limits direct comparison. Additionally, otolaryngologic issues were relatively frequent, a finding not widely discussed in literature and potentially indicative of underexplored developmental or anatomical associations. Prematurity and SGA births were consistent with known risk factors though literature suggests that genetic and familial influences may outweigh isolated prenatal factor underscoring the need to explore postnatal and epigenetic mechanisms (27). Genetic findings in our cohort further support ADHD's polygenic nature. Notably, none of the identified variants matched those described in the reviewed literature underscoring the heterogeneity of genetic contributions and the limitations of current knowledge (6). This observation may also reflect underrepresentation as genetic testing is not routinely performed in children with ADHD.

Our findings diverge from literature in several psychosocial domains. Most notably, prenatal tobacco exposure was reported at low rates contrasting with strong evidence identifying maternal smoking as a major risk for ADHD (28). This discrepancy likely reflects underreporting and recall bias as well as incomplete documentation. In contrast, family disruptions rates were consistent with prior studies supporting the association between parental separation and ADHD risk and may be of particular relevance as early family interactions can shape the developmental trajectory or lead to secondary behavioural issues (2, 29). Socioeconomic findings however differed substantially. Only 3.7% of parents had not completed secondary education which is lower than expected based on literature linking low parental education to increased ADHD risk (29, 30).

This finding may be indicative of selection and access bias as families with lower socioeconomic status may face greater obstacles to reaching specialized services including limited awareness, cultural or language barriers and practical or financial constraints. Differences in how "low education" is defined across studies, as well as the requirement for Dutch language schooling at our centre, may also contribute to the observed discrepancy. It is also important to note that socioeconomic adversity may be underestimated in our study as detailed indicators of socioeconomic status such as income and wealth, occupational status and housing conditions were not available. Finally, the high rate of family history aligns with literature emphasizing the strong heritability of ADHD and ASD, supporting the role of genetic predisposition (5).

Interpretation of our results requires caution due to several limitations. As this was a retrospective review data quality depended on the accuracy and consistency of clinical documentation. Some variables, particularly prenatal exposures and early milestones, were incomplete or inconsistently reported. Parent-reported information may be affected by recall bias and language barriers. The tertiary setting likely introduced selection bias, over-representing complex cases and limiting generalizability particularly across socioeconomic and linguistic groups. Absence of a neurotypical control group and small sample size further restricts comparisons and statistical power. These limitations highlight the need for large-scale, prospective studies with standardized data, control groups and systematic follow-up to clarify ADHD's interactions with comorbidities and contextual factors enabling earlier and more targeted interventions.

Conclusion

This retrospective study of a tertiary care cohort confirms that ADHD in children and adolescents is a complex, multidimensional disorder often accompanied by comorbid neurodevelopmental difficulties. While many findings align with existing literature, discrepancies regarding prenatal exposures, parental education and context-dependent factors, such as language exposure, suggest underexplored influences. Additionally, limited referrals from primary care and many children lacking prior therapeutic support may reflect systemic barriers affecting clinical presentation and outcomes. The results underscore the importance of multidimensional, interdisciplinary, context-sensitive assessment and targeted strategies to improve access to care and support early intervention.

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REVIEW ARTICLE

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Should Universal Chickenpox Vaccination Be Included in Routine Vaccination? A Critical Analysis of the Literature

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Keywords

Varicella ; Chickenpox ; Vaccination

Abstract

Background
Varicella is a well-known infectious disease caused by the varicella zoster virus. It usually is a self-limiting disease. However, severe complications requiring hospitalisation, and long-term sequelae can occur.

Methods
A critical analysis of the literature was performed to analyse arguments pro and contra universal vaccination.

Results
The currently licensed vaccines are highly effective in preventing varicella infection and the possible severe complications. They are safe with generally mild adverse effects. Cost-effectiveness studies show a benefit for the society. However, high vaccine coverage rates are needed to prevent the shift in varicella cases to older age groups. This can be achieved when administered in combination with the already established measles mumps rubella (MMR) vaccination at the age of 12 months.

Conclusion
Universal varicella vaccination is recommended if high coverage rates can be achieved.

Introduction

Varicella is caused by the varicella zoster virus (VZV), a member of the Alphaherpesvirinae subfamily (1, 2). VZV is characterised by its ability to settle in the dorsal root ganglia, causing lifelong latent infection (1, 2). Varicella is highly contagious, with a reproduction number (R0) of between 3.3 and 16.9, and is primarily transmitted via airborne infectious respiratory particles and by direct contact with the vesicular rash associated with varicella or herpes zoster (1, 2). The clinical picture is well known to paediatricians. The different clinical phases are summarised in Table 1. The diagnosis is clinical, but PCR can confirm acute cases. Serological tests are useful to identify seronegative individuals and can differentiate between primary infection and reactivation (1). Varicella primarily affects young children, with most having been infected by the age of 10 (1-3). Between 90 and 95% of individuals will have been infected by adulthood (2). The exact disease burden of varicella is difficult to assess as it is not a notifiable disease in many countries (3). However, it has been estimated that the number of cases annually is roughly proportional to the size of a country's birth cohort. Between 2021 and 2024, the average number of births in Belgium was 108,696 per year (4). Complications occur in 2-6% of the cases (3, 5). It is important to note that the majority of these occur in healthy children with no underlying conditions (6). The most common complication is a secondary bacterial infection (1-3). Necrotising fasciitis is a rare, but life-threatening complication (7). Other complications include laryngitis, pneumonitis, thrombocytopenia, hepatitis, deep vein thrombosis, stroke and neurological problems such as cerebellar ataxia, encephalitis, Guillain Barré syndrome, meningitis, and transverse myelitis (1, 5, 8-10). Complications often result in hospitalisation (8). Between 2010 and 2019, an average of 767 hospital admissions per year were recorded in Belgium (11). The highest hospitalisation rates were seen in children 0-12 months (3). Long-term sequelae such as severe scarring, ataxia and epilepsy are present in 0.4–10.1% of children hospitalised for varicella (3, 5). Varicella is responsible for around 4,200 deaths worldwide each year (12). The case fatality rate for varicella in high-income countries has been estimated at 2–4 per 100,000 cases (13). These figures challenge the common perception that varicella is always a mild disease and not a priority for policymakers. If a pregnant woman contracts varicella in the first or second trimester, her foetus may develop congenital varicella syndrome. Defects and scarring of the skin, abnormalities of the limbs, brain

TABLE 1: Results of chest x-ray: Calcifications in the upper left lobe and middle right lobe. Examination within normal limits.

Phase	Pathophysiology	Signs and symptoms
Incubation time (14-21d)	Replication in epithelial cells of tonsils	No
Prodromal phase	First viraemia	Fever, generalised malaise and loss of appetite
Second viraemic phase (14d after infection)	Spread to skin and mucous membranes	Vesicular rash - Face/trunk à extremities - Vesicles → pustules → crusts - +/- involvement of oral mucosa
Healing phase (1-2w)		All lesions scab

and eyes, and low birth weight, and even foetal death, occur in 0.4–2% of infants born to mothers who became infected with VZV during the first 20 weeks of pregnancy (1, 5, 14). If a woman contracts varicella from five days before to two days after giving birth, her newborn baby may develop severe varicella due to an insufficient transfer of maternal antibodies. The mortality rate in such cases can be as high as 30% (1, 5, 14).

Herpes zoster (shingles) is caused by the reactivation of a latent VZV infection, which typically results in a painful vesicular rash in a single dermatome (1). However, reactivations are most commonly subclinical (1). Pain is caused by acute neuritis (2). Postherpetic neuralgia develops in around 50% of adults and is often difficult to treat (2, 5). Herpes zoster occurs in 10-20% of people after primary infection with an increasing incidence with age (1).

Treatment for uncomplicated varicella is usually supportive only (1). Early treatment with antiherpetic agents may be considered for children at high risk of complications and is often started in adolescents and adults (1). Immunotherapy with anti-VZV antibodies is an effective alternative for specific patients such as immunocompromised individuals, pregnant women with no evidence of immunity against VZV, and newborns exposed postnatally (1).

Varicella vaccination

All available varicella vaccines are live, attenuated vaccines. With the exception of South Korea, where the MAS strain is used, all other licensed vaccines are based on the OKA strain. New vaccines are under development, for example in China (15). Takahashi developed the OKA strain in Japan, deriving it from a wild-type strain isolated from the vesicular fluid of a child with varicella (1). In 1974 the vaccine was given to 23 children in a Japanese clinic and successfully prevented varicella transmission from an infected child admitted to the same ward (1). The vaccine is available as a single-antigen vaccine or as a combined measles-mumps-rubella-varicella (MMRV) vaccine. The single antigen vaccine was licensed in several European countries in 1984, the combined antigen vaccine was approved by the US Food and Drug Administration (FDA) in 2005 and by the European Medicines Agency (EMA) in 2006 (16, 17). The vaccine's efficacy and effectiveness have been investigated in various studies.

Vaccine efficacy

Table 2 provides an overview of the cited efficacy studies.
A double-blind, placebo-controlled efficacy trial of a single dose of the single-antigen live-attenuated Oka varicella vaccine was conducted in the USA in 1984. A total of 914 children aged 1-14 who had not previously had varicella were included (18). The

TABLE 2: Overview of efficacy studies

Single dose studies					
Authors	**Study type**	**Vaccine**	**Numbers of children**	**Study period**	**Efficacy**
Weibel, RE et al., 1984 (15) Kuter B et al., 1991 (16)	Double blind placebo controlled	Single-antigen 1 dose	914	9 months 2 years 7 years	(100%) 98% 95 %
Prymula, R et al., 2014 (17) Povey, M et al., 2019 (18)	RCT	Single-antigen added to MMR (MMR+V) 2 doses	2263	3 years 10 years	64.5 67.2%
Two-dose studies					
Prymula, R et al.,2014 (17) Povey, M et al., 2019 (18)	RCT	Combined antigen (MMRV) 2 doses	2279	3 years 10 years	94.9% 95.4%

vaccine was well tolerated, with none of the vaccinated children contracting varicella during the 9-month follow-up period (18). However this short follow-up period did not allow definitive conclusions to be drawn. The same authors published the results of a 2-year efficacy and a 7-year follow-up study a few years later (19). They concluded that the overall vaccine efficacy was 98% after 2 years and 95% after 7 years (19). The breakthrough cases had considerably milder disease than natural varicella (19). In 2005, a randomised controlled trial involving healthy children aged between 12 and 22 months was conducted in 10 European countries. Of the children involved, 2,263 received one dose of the single-antigen varicella vaccine together with the second dose of MMR (MMR+V); 2,279 received two doses of the combined-antigen vaccine (MMRV); and 743 received two doses of MMR (20). After three years, an evaluation of efficacy showed that a single-antigen dose was 64.5% effective against all varicella and 90.7% effective against moderately severe to severe varicella. For the two-dose combined antigen vaccine, the efficacy rates were 94.9% and 99.5%, respectively. A re-evaluation after ten years showed an efficacy of 67.2% against all varicella and 89.5% against moderately severe to severe varicella for a single-antigen dose. For the two-dose combined antigen vaccine, the efficacy against all varicella was 95.4%, and against moderately severe to severe varicella, 99.1% (21). It is important to note that combining the varicella antigen with the MMR vaccine does not reduce the MMR efficacy (22, 23).

Vaccine real world effectiveness

Although varicella vaccination is licensed in many countries, it is included in immunisation programmes in only a some of them. The United States of America (USA) was the first country to implement a national varicella vaccination programme in 1995, initially with a single dose schedule and changing to a two-dose schedule in 2006 (12–15 months and 4–6 years), achieving high coverage (93.3% for the first dose in 2021–2023, 92.1% for the second in 2024–2025) (3, 24-26). A few years after implementation Vázquez et al. conducted a matched case-control study to evaluate the effectiveness of the varicella vaccine (27). They calculated the vaccine effectiveness to be 87% against all varicella and 97% against moderately severe and severe varicella. The number of varicella cases reported annually decreased from four million before 1995 to fewer than 15,000 in 2024 (25). The annual varicella-related hospitalisation rate in the USA decreased from 0.5 hospitalisations per 10,000 population from the pre-vaccination era to 0.26 per 10,000 population by 1999, and halved again to 0.13 per 10,000 by 2001 (28). It is currently estimated that 10,500 to 13,500 hospitalisations are prevented annually (25). Hospitalisation associated costs more than halved as well (28). Furthermore, an 88% decline in the annual average mortality rate for varicella was observed from 1990-1994 to 2005-2007 (29). It is estimated that 100 to 150 varicella-related death are prevented annually (25).

Germany introduced universal vaccination with a single dose of the varicella vaccine to its immunisation schedule in 2004. In 2009, this was changed to a two-dose schedule (30). The vaccine is administered together with the measles, mumps, rubella (MMR+V) vaccine or as a tetravalent vaccine (MMRV) (30, 31). The vaccine effectiveness was 86.6% after one dose and 97.3% after two doses. Hospitalisations decreased by 65%. Even herd immunity effects were noted in paediatric oncology patients, who are not eligible for vaccination (30). No evidence of a shift towards older age groups was observed (32). Nor was the incidence of herpes zoster affected (30).

Italy introduced universal varicella vaccination (UVV) in several regions between 2003 and 2011. For example, UVV was introduced in Tuscany in 2008. Over the 10-year period from 2010 to 2019, the vaccine effectiveness after one dose was 84.8%, and after two doses 95.7%. The effectiveness in preventing varicella-related hospitalisations reached 98.5% (33). Moreover, a decrease in varicella incidence was noted, from 164 cases per 100,000 in 2006 to 101 cases per 100,000 in 2009 ($p < 0.01$), across the whole country, following the introduction of a single dose of the vaccine in just a few regions (27). In 2017, Italy implemented a national, mandatory (and reimbursed) UVV programme with a two-dose schedule (30, 34). A coverage of 90% was achieved in 2019. The incidence rate of varicella decreased from 49.8 per 1,000 person-years in 2017 to 3.2 per 1,000 person-years in 2022 (34). A notable decrease in varicella-related complications was also observed (30).

A 2021 Cochrane review examined the effectiveness of the MMR+V or MMRV vaccine in children aged up to 15 years. The effectiveness against all forms of varicella was 95% in children

TABLE 3: Adverse effects of the varicella vaccine

Frequency	Adverse effect	Sources
Very Common ≥ 10%	Soreness Redness at injection site within 3 days	CDC (21); Product Monograph
Common ≥ 1% and < 10%	Fever ≥ 38°C Swelling at injection site Irritability Disturbed sleep	CDC (21); Product Monograph; Woodward et al. (35)
Uncommon ≥ 0.1% and < 1%	Upper respiratory infection Headache Nausea, vomiting Varicella like rash Myalgia	Leung et al (14).; Product Monograph
Very rare ≥ 0.01% and < 0.1%	Febrile convulsions Pneumonia Hepatitis Meningitis Disseminated vaccine strain infection Anaphylaxis	Woodward et al. (35); Casabona et al.(56); CDC (21); Committee to Review Adverse Effects of Vaccines (36)

aged 11 to 22 months after two doses, over a follow-up period of 10 years (22).

All studies and data confirm that a two-dose vaccine schedule is more efficacious and effective than a one-dose schedule. Although the manufacturers recommend a minimum interval of four weeks between doses, various countries use longer intervals (up to five or six years). This does not appear to have a significant impact on the increase in antibody titres (24, 30, 35, 36).

Post-exposure prophylaxis

Post-exposure vaccination reduces infection rates and the severity of cases in over 90% of susceptible individuals when administered within three days of exposure. The sooner the vaccine is administered, the more effective it is, with an effectiveness rate of up to 95% being achieved. In varicella outbreak settings, where exposure risk may persist for weeks, a second dose may be indicated (8, 37, 38).

Possible adverse effects of varicella vaccination

The live, attenuated OKA strain of varicella-zoster virus (VZV) is a safe vaccine. In a 22-year post-marketing safety review, only 0.8 reports of serious adverse events were recorded per 1 million doses (39). However, like any other vaccine, the varicella vaccine can have adverse effects. These are summarised in Table 3. According to the Committee to Review Adverse Effects of Vaccines, there was insufficient evidence to establish a causal relationship between vaccination and neurological symptoms such as encephalopathy, seizures, cerebellar ataxia, acute disseminated encephalomyelitis, transverse myelitis, and Guillain–Barré syndrome (40). In 2010, Klein et al. reported a higher incidence of febrile convulsions following the first dose of the MMRV vaccine compared to the MMR+V vaccine, respectively 7–9 cases per 10,000 children versus 3–4 cases per 10,000 children (41). This equates to one additional case of febrile convulsions per 2,300 doses of the MMRV vaccine administered (37). However, this only applies to the first dose, not the second (42).

Breakthrough varicella

Breakthrough varicella is defined as varicella caused by the wild-type VZV, occurring at least 42 days after receiving at least one dose of the varicella vaccine (15). Breakthrough varicella is most frequent after a single dose of the vaccine, due to either primary vaccine failure or waning immunity, and is generally much milder than natural varicella. However, severe breakthrough cases are rare. These include severe infections, such as pneumonia or sepsis, neurological complications, and any hospitalisation or death (15). Adding a second dose to the vaccination schedule reduces the incidence and severity of breakthrough cases by six to nine times (20, 30).

Possible concerns about introducing universal a varicella zoster vaccination programme

Notwithstanding the occurrence of severe cases of varicella, complications and fatalities, and despite the proven effectiveness and safety of the vaccine, universal vaccination against chickenpox has not yet been implemented in all countries (3). Reasons for not implementing include concerns about the duration of protection, the possibility that vaccination could cause varicella to shift to older age groups, mathematical models predicting possible increases in herpes zoster incidence due to the elimination of exogenous boosting, and questions about cost-effectiveness given that varicella is perceived as a mild disease (3).

Duration of protection

The duration of protection following varicella vaccination is currently unknown. Although studies had demonstrated no waning of antibodies over nine to 14 years, the most interesting study is from Italy and was published by Bianchi et al. in 2021 (43-45). A seroprevalence study was conducted among 182 adult medical students who had received two doses of the varicella vaccine in childhood. 34.1% of these students had no protective antibody titres. Antibodies wane over time. An antibody survival model was used to calculate that half of the fully vaccinated population will have lost circulating antibodies after nine years. However, a booster dose in the seronegative group was 100% effective. It should be noted that the cellular-mediated immunity was not examined directly.

Varicella shift to older people

A major concern is that by vaccinating young children, the occurrence of varicella will shift to older age groups (46). The risk of varicella-related complications and death is higher in adults (5, 47). Some authors fear that severe cases of varicella could offset the benefits of the vaccine in children (47). However, following the introduction of a universal varicella vaccination programme in Germany and Italy, no increase in incidence was observed in older age groups (30). In fact, an overall decrease in incidence was observed due to herd immunity (30). This can only be achieved if an immediate and sustained high vaccination coverage rate is achieved (46). The WHO recommends a two-dose schedule and a coverage rate of more than 80% (48). Compliance can be enhanced by concomitant administration with the MMR vaccine, either as an add-on or as the tetravalent vaccine, as the majority of European countries with available data achieve MMR vaccine rates of 85% or more (5, 46). Catch-up campaigns can help if initial coverage is low (47).

Increased herpes zoster incidence

In 1965, Hope-Simpson published his research on herpes zoster, proposing the hypothesis that it resulted from the reactivation of the VZV virus following a decline in immunity. This could be counterbalanced by boosting immunity, 'endogenously' through subclinical reactivation of latent VZV, or 'exogenously' through exposure to individuals with varicella (49, 50). By vaccinating large cohorts of people this boosting effect may disappear, potentially causing more herpes zoster infections in the elderly (51). Mathematical modelling based on the 'exogenous boosting hypothesis' predicted a major herpes zoster epidemic in adults following the introduction of varicella vaccination (52). This theoretical risk has been occupying the minds of many policymakers ever since. Many studies have been published on the 'exogenous boosting hypothesis', yielding a variety of results. A large self-controlled case series was conducted in the United Kingdom to assess the protective effect of household exposure to a child with varicella on the incidence rate of herpes zoster in adults (53). The results, published in early 2020, confirmed the protective effect of exposure to varicella, albeit only at 30% over 20 years (53). This was confirmed in a study by Ogunjimi et al. on boosting in grandparents exposed to varicella, which showed that boosting occurred in only 16-25% and lasted for less than one year (54). These data suggest that the role of exogenous boosting is more limited than previously thought and used in several mathematical models (53). A 2022 study by Leung et al. found that there had been no increase in the incidence of herpes zoster in the USA, the country with the longest-running UVV programme, during the period from 1998 to 2019 (55). Van Hoek et al. used mathematical models to look at the cost-effectiveness of introducing universal

varicella vaccination for children alongside the available zoster vaccine for the elderly. They concluded this approach could be cost-effective, provided that the zoster vaccination programme is terminated once the vaccinated childhood cohort has reached adulthood (51). An Italian analysis came to the same conclusion (52). In the United Kingdom Finn also proposes moving beyond theoretical discussions about the role of exogenous boosting and finding an explanation for the rise in herpes zoster incidence, and instead looking at the zoster vaccine as a solution to this possible problem (56).

Cost effectiveness

A recent study by Rodrigues et al. examined health-related quality of life (HRQoL) parameters, such as Quality Adjusted Life Years (QALYs), in both ambulatory and hospitalised children, as well as in carers of children with varicella in Portuguese public hospitals between 2019 and 2020 (3). This prospective study concluded that a single episode of varicella that does not require hospitalisation has a relatively small impact on HRQoL. However, admitted cases had a very high impact on HRQoL, on the patients and their families (3). The study demonstrates that varicella infection, with its possible complications has a significant impact on public health, resulting in healthcare costs and loss of work productivity (3). An Italian transmission model estimated that if a vaccine coverage of 90% was reached, a saving of €1.20 from health system perspective and of €3.50 from societal perspective would be gained for every €1 invested in vaccination (30). In both Germany and Italy, the costs of varicella-related hospitalisation declined by up to 90% within a few years of the implementation universal varicella vaccination programmes (30). In 2003, a Belgian team claimed the cost of implementing a universal varicella vaccination programme would exceed the cost of treating varicella (46). They argued that, from a societal viewpoint, universal infant vaccination is cost-effective because of averted unproductive days for parents, but not from the healthcare payer's viewpoint when considering the price of the vaccine and the costs of implementing the programme (46). From this perspective, vaccinating adolescents and adults is more cost-effective (5, 46). However, this would not reduce overall viral transmission (5). Nevertheless, in 2010, the Belgian Healthcare Knowledge Centre concluded that, if the exogenous boosting theory were not true, universal varicella vaccination with a two-dose schedule would probably be cost-effective at the vaccine price of that moment (57).

Factors to consider when implementing a UVV programme

The World Health Organization recommends varicella vaccination "for the prevention of varicella in populations where it is an important public health problem" (58). This vague and somewhat disappointing WHO recommendation is understandable because, for policymakers, the significance of concerns listed above in deciding about the implementation of a UVV, is influenced by socio-economic, demographic, cultural and ethnic factors. These include the organisation of the healthcare system, the capacity of UVV funding, the age distribution of the population, demographic disparities, immigration, vaccine hesitancy, and the decline of public trust in institutions and politicians. Currently, as described below, 16 of the 27 countries in the European Union have adopted a UVV programme.

Countries wishing to launch a UVV programme must first establish a robust surveillance system to monitor its effects. It is recommended that this surveillance is made mandatory (6, 59). The survey should include vaccine coverage, effectiveness, age specific incidence of varicella and herpes zoster cases, occurrence of adverse events and disease needing hospitalisation. This will require adapting the existing surveillance systems and the cooperation of all clinicians to report cases. The possibility of self-reporting varicella cases can be explored (55).

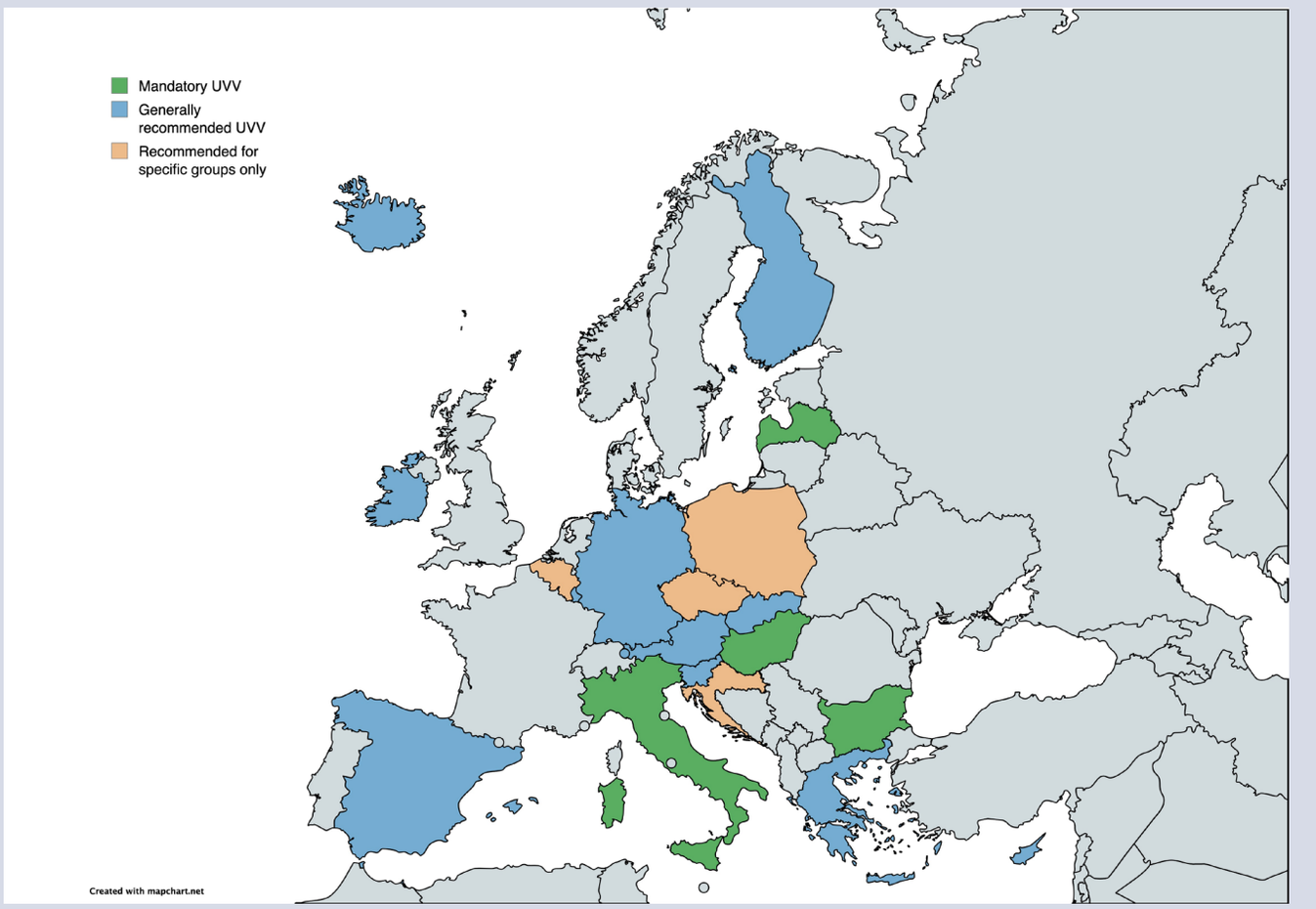
A review article published in Vaccine in 2016 identified five determinants of vaccine uptake, known as the 5A's. These are Access, Affordability, Awareness, Acceptance and Activation (60). These determinants are important for the successful implementation of a UVV programme, with the aim being to reach a coverage rate of ≥ 80%. Access is "the ability of individuals to be reached by recommended vaccines" (60). The varicella vaccine can be added to the existing MMR vaccination schedule. To avoid concerns about an additional injection, the combined MMRV vaccine can be used The slightly increased risk of febrile convulsions should be taken into account (30, 61). Affordability is "the ability of individuals to afford vaccination, in terms of both financial and non-financial costs (e.g. time)" (60). In order to achieve vaccine coverage of more than 80%, the vaccine must be accessible to all. Full government reimbursement is the ideal scenario (60). If the varicella vaccine is added to the existing MMR vaccination programme, time should not be an issue. Awareness is "the degree to which individuals have knowledge of the need for, and availability of, recommended vaccines and their objective benefits and risks" (60). Acceptance is "the degree to which individuals accept, question or refuse vaccination" (60). Examples of acceptance factors include safety concerns, the perceived severity of the disease and, individual health believes (60). A recently published review identified physician recommendation as the strongest factor influencing acceptance of the varicella vaccine (59). Often both parents and physicians view varicella as a mild disease. A 2016 study in the Netherlands proved this to be a major barrier to the implementation of UVV (62). Therefore, it is important to support both parents and physicians with appropriate information before and during the rollout of UVV (59). Activation "refers to the actions that nudge people who intend to get vaccinated towards vaccine uptake" (60). This includes extra reminders such as leaflets and parent meetings (60). Existing information platforms can be used for this purpose.

Status of varicella vaccination in the European Union countries

Currently, 20 of the 27 European Union countries recommend varicella vaccination as part of their national immunisation programmes (Figure 1). Sixteen countries recommend UVV. Mandatory UVV is in place in four of these countries: Bulgaria, Hungary, Italy and Latvia. It is not mandatory in Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Liechtenstein, Luxembourg, Slovakia, Slovenia and Spain. In four countries, vaccination is recommended for specific groups only: Belgium, Croatia, Chechia and Poland (where it is mandatory). All countries recommend a two-dose schedule, but at different ages. The ECDC's vaccine scheduler provides an overview (63).

The vaccines currently available in Belgium are two monovalent live-attenuated vaccines called Varilrix and Varivax, and a combined live-attenuated vaccine containing strains of measles, mumps, rubella and varicella called ProQuad. These vaccines are not routinely reimbursed. The Belgian Superior Health Council does not recommend universal vaccination, but only the vaccination of specific groups, including adolescents and young adults with no history of chickenpox; individuals working in the healthcare sector who are not immune; individuals in contact with immunocompromised patients or young children who are not immune; and women who are not immune and are planning to become pregnant (37). However, this approach only protects

FIGURE 1: Varicella vaccination recommendations in European Union countries in 2026 (map created with MapChart)



a few individuals and does not reduce viral transmission in the community (5).

Conclusion

Varicella is a highly contagious infectious disease caused by the varicella zoster virus. Although it is usually self-limiting, severe complications can occur, resulting in hospitalisation and long-term consequences. Reactivation of the latent virus can lead to zoster in adults and the elderly, causing significant morbidity in these age groups. Many studies over the years have shown that the currently available and licensed varicella vaccines are safe and highly effective in preventing infection, severe disease and death. A significant reduction in the number of cases and complications was observed in the countries where UVV has been implemented. The adverse effects are generally mild. Once high vaccine coverage rates have been achieved, herd immunity ensues, protecting those who are not eligible for vaccination. For this reason, we believe that UVV should be recommended.
While most cost-effectiveness studies demonstrate societal benefits due to averted unproductive days for parents, the benefits for healthcare payers can be limited depending on the vaccine's price and the cost of implementing the vaccination programme. If a country wishes to implement universal varicella vaccination, it is crucial that high coverage rates are achieved to prevent varicella cases shifting to older age groups. The combination with the already established MMR programme can increase vaccine uptake. Otherwise, catch-up programmes are recommended. Regarding the unproven theoretical concern of an increased incidence of zoster following the introduction of universal childhood vaccination, countries could consider introducing zoster vaccination at the same time.

Statements

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REVIEW ARTICLE

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Management of Facial Palsy in Children: A Narrative Review

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Keywords

Facial Palsy; Neuroborreliosis; Bell's Palsy; Cranial Nerve Dysfunction

Abstract

Background & Objective

Facial nerve palsy in children arises from diverse aetiologies, including Bell's palsy as well as infectious, neoplastic, and neurologic conditions. Differentiating peripheral from central causes is critical, as each entails distinct management and prognostic implications. This narrative review summarizes the diagnostic criteria and management strategies of paediatric facial palsy by comparing protocols from major reference centres and reviewing the recent literature. We present four clinical cases that underscore the importance of a multidisciplinary approach, provide practical clues for timely diagnosis, and offer key messages for the management of facial palsy. Finally, we propose a management algorithm derived from these findings.

Methods

We reviewed literature (2010–2025), reference centre protocols, and four Hôpital Universitaire de Bruxelles paediatric cases to summarize diagnosis, management, and outcomes of paediatric facial palsy, adapting adult guidelines where paediatric data were lacking.

Key Content and Findings

Paediatric facial palsy requires a systematic diagnostic and multidisciplinary approach, as both aetiology and management vary. This review covers clinical diagnosis, indications for imaging, multidisciplinary follow-up, treatment options and prognosis. Severe cases benefit from corticosteroids; antivirals are reserved for Ramsay Hunt syndrome. Neuroborreliosis should be considered in endemic areas, even with initially negative serological tests. Early ophthalmologic care and multidisciplinary follow-up are essential to prevent complications.

Conclusion

Early, thorough evaluation and a multidisciplinary approach are essential to identify underlying causes of paediatric facial palsy. Corticosteroid use remains debated and varies across centres; based on our review, we propose an algorithm to guide management.

Introduction

Facial nerve palsy is a frequent presentation in the paediatric emergency ward, with an incidence that varies from 5 to 21 children per 100,000 children per year under the age of 18 due to variation in settings from different studies (1-3). Facial nerve palsy can be divided into congenital or acquired facial palsy, peripheral or central facial palsy. We excluded congenital facial palsy in this review. Peripheral facial palsy (PFP) and central facial palsy (CFP) differ both clinically and etiologically. To understand the difference between CFP and PFP, a quick anatomical review is needed. The facial nerve is the 7th cranial nerve, composed of fibres from the corticobulbar tract joining in multiple brainstem nuclei. The forehead muscles are innervated by fibres from both

cerebral hemispheres, while the inferior part of the face is innervated only by fibres from the opposite cerebral hemisphere as a result of the decussation of the fibres. Thus, a CFP resulting from a supranuclear lesion will lead to a palsy concerning the contralateral inferior part of the face, leaving the forehead muscles innervated by the fibres coming from the ipsilateral cerebral hemisphere. A PFP, resulting from a lesion under the nuclei, will lead to a palsy concerning both inferior and superior part of the ipsilateral face. Only a clinical examination will allow differentiation of both types (4). After its intracranial path, the facial nerve then enters the internal auditory canal into the petrous portion of the temporal bone. It exits the skull through the stylomastoid foramen and goes through the parotid gland where it divides into 5 branches which innervate the face muscles. Early differentiation between PFP and CFP is essential, as management pathways diverge significantly and delayed recognition of atypical or central causes remains a major source of morbidity in children (1,5). Most cases of PFP are Bell's palsy, but it is an exclusion diagnosis. Therefore, many aetiologies must be ruled out through further testing. According to several studies, the main causes are infectious diseases (1). In a non-Lyme endemic region, acute otitis media (AOM) is the most common, followed by herpes simplex virus (HSV) reactivation, varicella zoster virus (VZV) reactivation with or without Ramsay Hunt syndrome. Other viruses can be involved such as Epstein-Barr Virus (EBV), cytomegalovirus (CMV), coxsackie, human immunodeficiency virus (HIV), adenovirus (1,6). In an endemic region like central or eastern Europe, Lyme disease (Borrelia burgdorferi) has become one of the main causes (1,2). In this case, bilateral PFP is more frequent (4). Other causes of PFP are Guillain-Barré syndrome, trauma such as basal skull fracture or middle ear surgery, as well as malignant tumours of the temporal bone or parotid gland (1,6). CFP results from a central lesion, including vascular involvement, multiple sclerosis and less frequently, sarcoidosis. Neoplasms such as leukaemia or posterior fossa tumours, which account for 50% to 70% of all paediatric brain tumours, are also associated with cranial nerve impairment, most notably affecting the facial nerve, when located up the VII nerve nucleus (1,7). Posterior fossa tumours can also lead to PFP if affecting the VII nerve nucleus itself or beyond the nucleus. (7). The aim of this narrative review is to discuss the causes of facial palsy (FP) in children, the diagnostic criteria, and management strategies by comparing protocols from various reference centres and reviewing the literature published on the subject. Several clinical cases are presented to highlight the causes of FP that should not be overlooked. This study also proposes a management algorithm.

Methodology

We chose a narrative review because it allows flexible integration of heterogeneous evidence and clinical experience in an area with limited paediatric data, combining research studies, clinical guidelines, institutional protocols, and case reports to emphasize the importance of early diagnosis, multidisciplinary management, and recognition of less frequent aetiologies. We conducted a thorough search across electronic databases including PubMed, UpToDate, and the Cochrane Library using various terms related to "Facial palsy," such as "7th cranial nerve palsy" and "Facial paralysis," alongside phrases like "Management of Facial Palsy," "Treatment of facial palsy," and "Neuroborreliosis in children." We specifically targeted articles published after 2020 and written in English. We utilized the Scopus application to calculate CiteScore metrics, measuring the citation impact of the articles we included. To further enrich our review, we reached out to reputable children's hospitals to obtain their internal protocols for managing facial palsy. Protocols were selected based on their online availability and accessibility, and on inclusion of the authors' institution, the other major paediatric centre in Brussels, and a Flemish reference centre. Additionally, we meticulously reviewed the bibliographies of identified studies, review articles, and guidelines. From this comprehensive search, we identified 27 relevant articles and four guidelines that collectively offer a comprehensive overview of the management of FP in children. The four clinical cases presented are children who have been treated in "Hôpital Universitaire de Bruxelles" including the "Hôpital des enfants Reine Fabiola" and the "Hôpital Erasme", for whose consent has been obtained for the use of their data for this publication. We reviewed the English writing with ChatGPT and https://beta.springernature.com/pre-submission/writing-quality. The keywords were searched with MeSH on https://meshb.nlm.nih.gov/MeSHonDemand.

Diagnosis

A thorough medical history and clinical examination must be performed. The practitioner must review how the facial palsy (FP) started, its onset, progression, and associated symptoms such as fever, headache, ear pain, facial pain, hearing disorder or behavioural disorders. The child's medical history should be thoroughly reviewed, with particular attention to any previous episodes of similar symptoms, which should alert the practitioner. The clinical examination must include an ear, nose and throat (ENT) examination, an evaluation of periauricular vesicles or erythema migrans lesions and a full neurological examination. The facial nerve function is evaluated by assessing the forehead movements, elevating the brow, frowning, the ability to close the eye, open the mouth and puckering the lips (1,8). The FP is graded through the House-Brackmann (HB) scale from grade I characterized by a normal eye closure, normal mobility and without facial asymmetry to grade VI characterized by an incomplete eye closure, 0% of mobility and a facial asymmetry at rest. The HB grade should therefore be clearly recorded in the patient's medical file at each evaluation. We evaluated and compared the recommendations for complementary examinations from various university hospital centres across Europe (Belgium and France), Australia and America (9-13). Recommendations found in the literature led to the conclusion that it is necessary to conduct a lab testing for all children presenting with FP, including a full blood count, C-reactive protein (CRP), glycaemia, serological testing for mycoplasma, HSV, VZV, CMV, EBV and B. burgdorferi in regions endemic to Lyme disease (1). Additionally, a lumbar puncture with analysis of cytology, blood cultures, oligoclonal banding and B. burgdorferi serology should be performed if the clinician suspects meningitis or another central nervous system disease, or if the FP is bilateral, if another cranial nerve is affected or if an infection by B. burgdorferi is suspected (9-13, Table 1). Emergency imaging should not be performed as a routine evaluation, but should be guided by specific clinical indications or (Table 1 and 2):

- For children under 3 years of age without AOM.
- If there is a suspicion of a neurological cause, if the child presents with CFP, bilateral facial palsy, additional abnormal neurological findings such as concomitant paralysis of another cranial nerve, recurrent FP.
- A CT scan with contrast should be considered if the child presents with chronic otitis media, a cervical mass, a suspected mastoiditis, or if there is a history of temporal bone trauma or surgery (1,9-13).

Follow-up

Various specialists should be involved in the diagnosis and follow-up of children presenting with PFP. An ENT evaluation should be conducted promptly for every child presenting with PFP, within

TABLE 1: Diagnostic management of facial palsy recommended by different centres (9-13).

	Hôpital des Enfants Reine Fabiola, Brussels, Belgium	Université Catholique de Louvain, Brussels, Belgium	UZ Gent, Belgium	The royal children's Hospital Melbourne, Australia	Clinical Practice Guideline: Bell's Palsy - Otolaryngology–Head and Neck Surgery
Laboratory Testing	General blood test † + serology Lyme, HSV, HZV, CMV, EBV, Mycoplasma, mumps	General blood test + serology HSV, HZV, EBV, CMV, Mycoplasma, Lyme if evocative context (second test at 1 month if negative ‡)	General blood test + serology HSV, VZV, EBV, CMV, HIV, Syphilis, Lyme. If immunocompromised add adenovirus, parainfluenza, measles, mumps, rubella	If Suspected malignancy or other cause than Bell's Palsy, or commencing steroids: General blood test + serology HSV, HZV if vesicles are present	Routine laboratory testing is not required. Required if there is atypical presentation, suspected neoplasia, suggestive Lyme exposure.
Lumbar punction	If bilateral or balanced FP, other cranial nerve affected, signs of encephalitis/meningitis, suspected Lyme, suspected malignancy	If signs of meningitis/radiculitis, suspected Lyme.			
Imaging	MRI: if CPF, Other neurological abnormality § Cerebral CT scan if cranial bone trauma	CFP, other cranial nerve affected, mastoïditis, chronic otitis, cranial trauma, recurrence, worsening > 3 weeks. MRI or CT scan depending on the situation.	Cerebral CT scan if abnormal otoscopy, suspected cranial bone fracture, parotid or neck tumour. MRI if recurrency of facial palsy, HB grade 4, associated with hearing loss or vestibular syndrome with normal otoscopy, with central neurological symptoms, history of carcinoma, or no improvement after 6weeks/worsening after 2weeks. Ultrasound if suspected parotiditis or parotid tumour.	If other cause than Bell's Palsy is suspected	If cranial trauma, history of tumour, other cranial nerve affected, no sign of recovery after 3 months. Imaging of choice: MRI with and without contrast. If MRI is contraindicated: contrast-enhanced CT can be used.

† Blood test: Blood count, CRP, renal function, liver enzymes, electrolytes. ‡ Lyme serology can be negative if the exposition is less than 6 weeks' time. § Other neurological abnormality: other cranial nerve affected, cerebellar syndrome, meningeal syndrome, bilateral FP, myotatic areflexia.

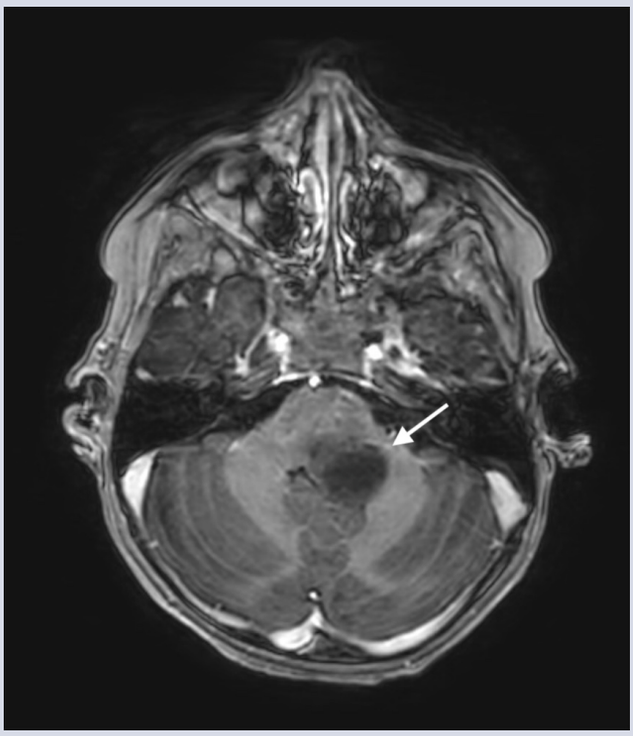
72 hours of onset. Urgent ENT evaluation is needed if the child presents with AOM, signs of mastoiditis, a cervical mass, a vesicular rash in or around the ear, loss of balance, hearing impairment or a history of head trauma. An assessment by a neurologist is urgently necessary for children under 3 years of age, if there is an additional abnormal neurological anomaly, if the child presents with CFP, or if there is a gradual deterioration of the FP. Imaging should not be routinely performed in children with typical peripheral facial palsy who show early and progressive clinical improvement. However, careful clinical follow-up remains essential. In accordance with published recommendations and institutional protocols, neuroimaging should be reconsidered not only in cases of worsening facial weakness or absence of improvement after 4 weeks, but also in cases of delayed or incomplete recovery when the clinical course deviates from the expected pattern (1,4,9–13). Although most children show clear improvement within the first weeks and achieve near-complete recovery within months (1,3), persistent significant weakness beyond 1 month, stagnation of recovery, or residual severe deficit (HB grade IV–VI) without continued improvement should prompt reassessment and discussion of brain MRI, even if the overall evolution appears globally favourable. The decision should be individualized and guided by the clinical trajectory, associated symptoms, and neurological examination findings.

Clinical Cases

Case 1

A 6-year-old male with no significant medical history who presented with a left PFP (HB IV), was started on prednisolone 2 mg/kg/day for a total of 10 days. Subsequently, the child went on a two-month vacation abroad, thus no reassessment was programmed. After two months, he still suffered a left FP and started to have balance disorders, muscular weakness in the left limb and was complaining of diplopia. On examination, he was noted to have an asymmetric smile, a loss of the nasolabial fold, but a complete eye closure and no decreased forehead movements. Thus the FP was assessed as a left CPF. Hemiparesis was noted in the left lower limb, along with a VI cranial nerve palsy. A CT-scan was performed, showing a solid expansive lesion in the brain stem. The MRI showed a 22 mm x 26 mm mass with no sign of hydrocephalus (Figure 1). The diagnosis of a H3 K27M-mutant diffuse midline glioma was established by biopsy. Unfortunately the child died 8 months later. This mutant is a high-grade glioma, grade 4 by the WHO classification, associated with a poor prognosis. The most common symptoms are cranial nerve palsy, with nerves VI and VII being the most commonly affected, along with ataxia (14). This clinical case highlights the importance of a meticulous clinical examination and the necessity of follow-up for

FIGURE 1: T1 weighted post contrast sequence on an axial plane with fat saturation. Left posterolateral portion of the pons. Visualization of a solid tumour in the right posterolateral portion of the pons, at the level of the middle cerebellar peduncles, encompassing the pontine nucleus of the left facial nerve as well as its fascicular segment.



all patients presenting with FP. It also underscores the possibility of a PFP resulting from a central lesion affecting the facial nerve. A neuro imaging must be performed if the PFP worsens over 3 weeks, or with no improvement after 4-weeks of onset, if another cranial nerve is damaged, or if the child presents with CFP (1,9).

Case 2

A 2-year-old toddler with no significant medical history presents at the emergency department for daily pyrexia for two weeks, left otalgia and left temporal headache. The child has recently been treated for AOM with amoxicillin. The child was prostrate, with a stiff neck, without any sign of mastoiditis, the eardrum was slightly erythematous and not bulging. A biology test was performed, which revealed a moderate inflammatory syndrome (CRP: 114 mg/L; white blood cell (WBC) count: 12180/µL) and a lumbar puncture which revealed a slight leukocytosis (WBC count: 21/µL). A broad spectrum antibiotic was started and the child was admitted to the hospital. The following day, the child developed left PFP (HB II). He underwent a brain CT scan (Figure 2) and a brain MRI which identified a collapsed formation at the petrous apex associated with osteitis (Figure 3). The ENT found an AOM that was not obvious in the first otoscopy and a trans tympanic ventilation tube was placed. The child was treated with ceftriaxone and metronidazole for a period of six weeks followed by an oral relay with cefuroxime. During hospitalization, the child developed keratitis of the left eye. The child has recovered all his facial motor skills but still presents a deafness for which the installation of a hearing aid is programmed. The interest of this clinical case is twofold. First, it evokes a rather rare complication of otitis associated with FP: petrous apicitis by extension of otitis. This highlights the importance of imaging and followed by a lumbar puncture if the child has signs of meningeal involvement with otitis. Secondly, it insists on the importance of applying artificial tears very regularly during the day and applying eye ointment and an eye patch during the night until complete recovery, since the consequences on the eye can be disastrous.

Case 3

A 15-year-old child with no significant medical history presented with right otalgia for 4 days, hypoacusis for 2 days, and a progressively worsening right PFP (HB grade III). On exam, he was found to have a right AOM without any associated rash. A lab testing showed no signs of inflammation and serology testing for VZV, HSV, EBV and B. burgdorferi came back negative. The child was discharged with corticosteroid treatment of methylprednisolone at 1 mg/kg/day for a total of 10 days and was scheduled for an appointment with an ENT specialist the following day. Upon examination, a painful vesicular rash on the right external ear was noted. The diagnosis of Ramsay Hunt syndrome was established, and aciclovir at 80 mg/kg/day for a total of 7 days was added to the corticosteroids treatment. Ramsay Hunt syndrome is caused by the reactivation of the VZV. The incidence is reported to be 2.7 per 100.000 children under the age of 10 (1). Herpetic vesicles are present in 80% of cases and usually appear several days after onset of FP, lasting 1-3 days (6). The take home message for this clinical case is the importance of scheduling an ENT evaluation, that eruptions do not appear after the visit to the emergency.

Case 4

An 8-year-old child with no significant history presented with right PFP (HB V) progressing over six days, as well as the emergence of a macular plaque rash on the right cheek progressing for the last 12 hours. Three days prior to presentation, there was paraesthesia noted in the region of the right trapezius muscle. A blood

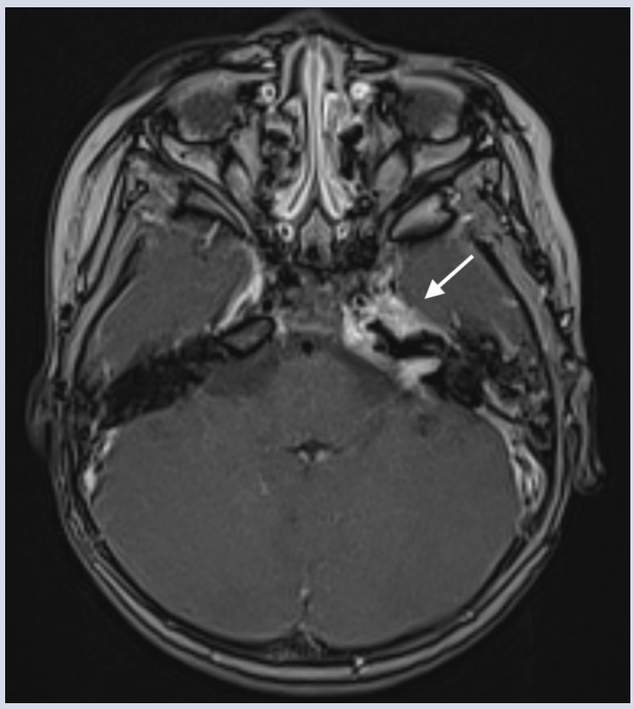
TABLE 2: Indications for imaging in paediatric facial palsy. Reference: Université libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), Service des urgences pédiatriques, Avenue J.J. Crocq 15 1020 Bruxelles – Belgium.

Imaging	When?
Brain + brain stem + temporal bone + parotid MRI T1 Weighted post-contrast sequences with fat saturation	Suspected inflammatory / neoplasia: - Atypical signs: bilateral FP, other cranial nerve affected - Suspected neoplasia; recurrency, CFP - Progression over 3 weeks or no improvement after 1 month of onset
Brain CT Scan with contrast	- Temporal bone trauma or surgery - ENT causes (chronic otitis media, suspected mastoiditis, ENT mass). > to rule out vascular complications such as intracranial venous thrombosis.

FIGURE 2: Non contrast CT scan, bone window. Axial sections. Erosion of the cortex of the left petrous apex (intact appearance on the right).



FIGURE 3: Non contrast CT scan, bone window. Axial sections. Erosion of the cortex of the left petrous apex (intact appearance on the right).



Axial T1 DIXON sequence (water-only image). Contrast enhancement of the bone marrow of the left petrous apex and left acousticofacial bundle and Meckel's cavum. Partial pneumatization of the petrous apex. Reactive dural enhancement. Asymmetric calibre of the left cavernous segment of the internal carotid artery, with a permeable appearance (arteritis).

test was performed, showing no signs of inflammation, and the serology testing for VZV, HSV, CMV, EBV and for B. burgdorferi were negative. An audiometry and tympanometry were performed and revealed normal results. The patient was discharged with a diagnosis of Ramsay Hunt syndrome and treated with corticosteroids and acyclovir for a week. Seven days later, the patient started to develop pain in the back and limbs without paraesthesia. No fever was noted. On exam, the patient presents with hyperesthesia in the neck, back and upper limbs. There was no observed weakness, and myotatic reflexes were normal. Right FP showed clear improvement. A brain MRI was performed and came back normal, as well as a second blood test. It was concluded to be neuropathic pain, and an outpatient MRI of the spine was scheduled. The patient was discharged and prescribed gabapentin and tier 1 analgesics. Seven days thereafter, the patient was evaluated by a neurologist, and a left PFP (HBIII) was noted. Neuropathic pain persisted, partially alleviated by gabapentin. The patient was admitted to expedite further evaluation. A series of additional examinations were conducted, including a normal MRI of the spine, a lumbar puncture revealing leukocytosis (111/µL WBC count) with lymphocyte predominance (100%), elevated cerebrospinal fluid (CSF) proteins levels (1.17g/ dL), and the presence of oligoclonal bands, as well as blood tests with serological analysis. Serological testing for both CSF (IgG 168 AU/ml) and blood (IgG 1019 AU/ml and IgM positive) came back positive for B. burgdorferi. The diagnosis of neuroborreliosis with bilateral PFP was established. Joint pain in the back and limbs raised suspicion of Banwarth syndrome. Meningoradiculitis was identified as one the manifestations of neuroborreliosis (17). Treatment with doxycycline for 28 days was initiated, resulting in favourable evolution without any sequelae. The interest of this clinical case is multiple. First, it stresses the importance of not excluding certain diagnoses only from serological testing. CSF serology for B. burgdorferi is sometimes negative at the beginning of the disease. Second, the majority of bilateral PFP has an identifiable cause and the association with Lyme disease is well known and must be always investigated (18,19). However, the history and initial clinical examination for Lyme disease is not specific. PFP may be the first manifestation of the infection, and there is rarely a history of recent tick bites or old migrant erythema (19). It should also be noted that the presence of oligoclonal bands is frequently observed in the CSF of patients with Lyme disease (20).

Treatment

The therapeutic approach to paediatric facial palsy depends on the underlying aetiology and severity, as summarized in Table 3. Management of peripheral facial palsy (PFP) must address two parallel objectives: (1) identification and treatment of the underlying cause and (2) prevention of complications directly related to facial weakness, particularly ocular damage. Due to incomplete eyelid closure, children are at risk of corneal dryness, keratitis and ulceration. Protective measures should therefore be initiated immediately in all patients with impaired eye closure, regardless of aetiology. Artificial tears should be administered regularly during the day, and lubricating ophthalmic ointment combined with eyelid taping or patching should be applied at night (Table 3) (2,9). Ophthalmologic assessment is warranted in cases of HB grade IV–VI or when corneal involvement is suspected. Regarding

TABLE 3: Treatment management of facial palsy recommended by different centres (6-9).

	Hôpital des Enfants Reine Fabiola, Brussels, Belgium	Université Catholique de Louvain, Brussels, Belgium	UZ Gent, Belgium	The royal children's Hospital Melbourne, Australia	Clinical Practice Guideline: Bell's Palsy - Otolaryngology–Head and Neck Surgery
Steroids	Oral prednisolone 1 mg/Kg/day (max 60 mg) for 10 days for HB 5-6 or for children more than 16 years old, within 72h of onset.	Oral prednisolone 2 mg/ Kg/day (max 64 mg) for 5 days, within 72h of onset. Extended to 10 days if painful or Ramsay Hunt Syndrome.	Prednisolone 2 mg/ Kg/day in 3 doses (max 70 mg) for 7 days, within 72h of onset (up to 7 days). Oral steroids if HB1-3. Intravenous steroids if HB ≥ 4 or suspect-ed VZV infection.	No consensus on the use of steroids in children due to lack of evidence.	No strict consensus on the use of oral steroids in children
Antivirals in combination with oral steroids	If Ramsay Hunt Syndrome: Acyclovir 20 mg/Kg/dose 4x/ day max 800 mg/ dose, for 7 days.	If Ramsay Hunt Syndrome: aciclovir 20 mg/Kg/ dose 3x/day (max 800 mg /dose) for 7 days.	If grade ≥ 4 or sus-pected ZVZ infection: Valacyclovir 3 x 1 g/day.	If vesicular rash is present.	If treated within 72 hours of onset of FP, in agreement with the patient as no real benefit has been proven.
Eye Care	For all patients : lubricating drops + ointment + occlusive bandage at night.	If incomplete eye closure: lubricating drops + ointment.	If incomplete eye clo-sure: lubricating drops + ointment + occlusive bandage at night.	If incomplete eye clo-sure: lubricating drops + ointment + occlusive bandage at night.	If incomplete eye closure: Lubricating drops and/or ointment
Surgical Decompression					Not recommended
Physical Therapy			If grade 4.		Not recommended

medications, two compounds are commonly used, although their indications in paediatrics are not clearly established.

1. Corticosteroids:

Corticosteroids have the effect of reducing the oedema of the facial nerve and therefore its compression. Their effectiveness has been repeatedly demonstrated in adults, and the latest Cochrane review mentions that there is no longer a need to prove their effectiveness in adults (21). Regarding pharmacological treatment (Table 3), corticosteroids remain the most debated intervention in children. A systematic review from 2012 identified all studies released between 2000 and 2010. Out of these 2293 studies, the quality and level of evidence, mainly consisting of small retrospective studies, did not provide a definitive answer regarding the efficacy of corticosteroid treatment in children (22). In 2022, an Australian study was published. This multicentre and double-blind study involving 187 randomized patients failed to demonstrate the efficacy of corticosteroids in children. The difference observed was not statistically significant, and in children, recovery is almost always complete (23). Nevertheless, this Australian study suffered from a limited number of participants. A Swedish study is currently underway with plans to include 500 children and adolescents aged 1 to 17. Results are expected at the earliest for 2026 (2). In children, the recovery from PFP is almost always complete, with cases of incomplete recovery being exceptionally rare. Therefore, it is generally unnecessary to overuse corticosteroids. While corticosteroids can be beneficial in certain cases, their effectiveness in children is not clearly demonstrated, and excessive use can lead to undesirable side effects. It is important to weigh the benefits and risks before prescribing them. Based on data from the literature and an intra-hospital consensus (Table 3), we propose treating only patients with a HB grade of IV or higher. We recommend administering corticosteroids (methylprednisolone) at a dose of 1 mg/kg/day (max 64mg) for 10 days if the patient presents within 72 hours of symptoms onset. For children aged 14 and older, we suggest following the adult treatment protocol and using corticosteroids regardless of the HB grade. However, if the child has a relative contraindication for corticosteroids administration (such as diabetes or gastro-intestinal contra-indications), we advise against treatment.

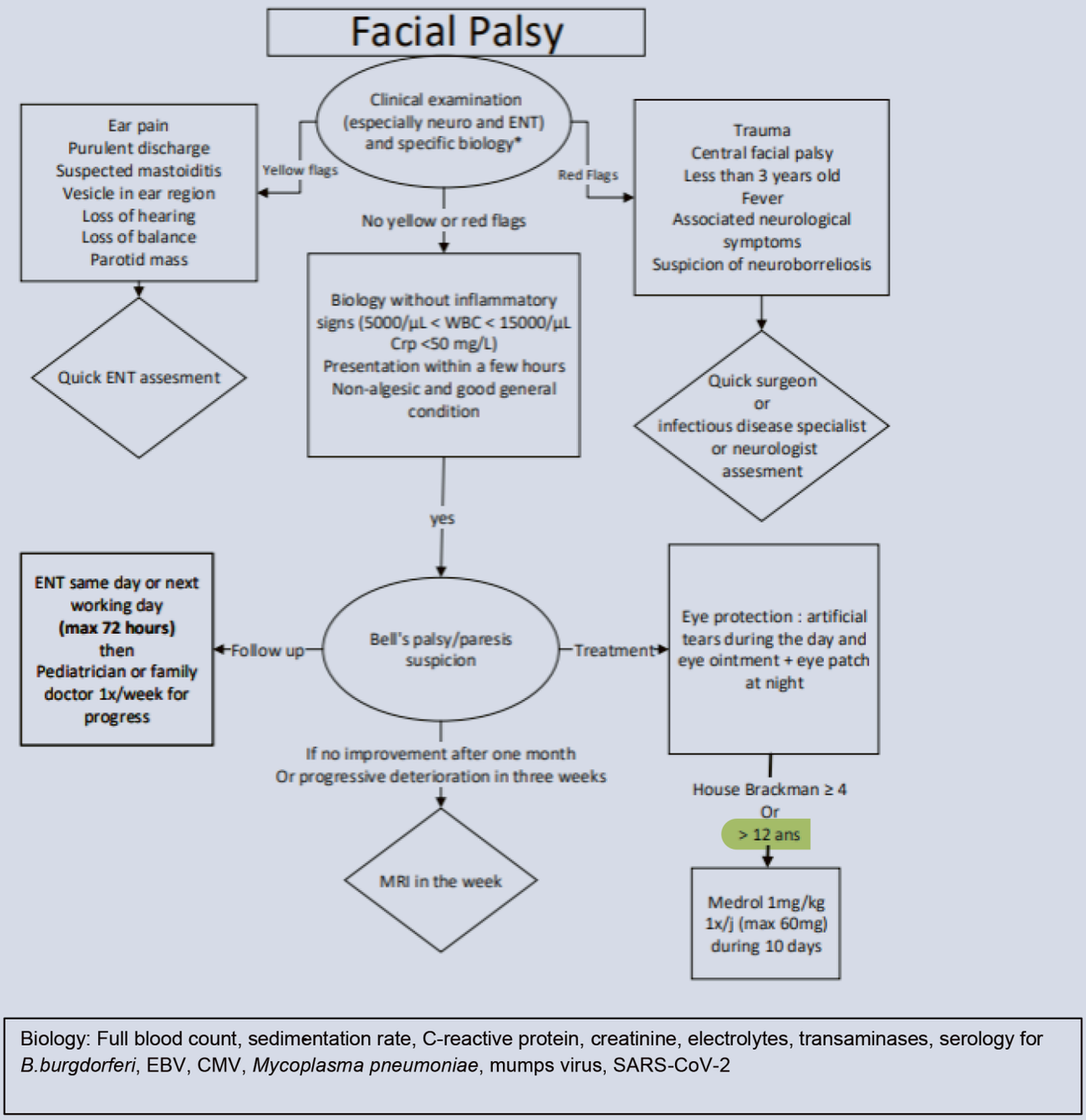
2. Antiviral treatment

We conducted a thorough review of the latest systematic reviews and meta-analysis concerning the use of antivirals (aciclovir, valaciclovir, famciclovir) for treating PF in adults, either as monotherapy or in conjunction with corticosteroids. These antivirals function by impeding HSV infection through the inhibition of DNA polymerase, thus hindering its replication. Upon comparing the recovery of facial function using the HB scale, it was concluded that antivirals alone yielded no benefit compared to placebo, the efficacy of corticosteroids alone is superior over antivirals alone, and there were no significant differences in recovery rates between corticosteroids alone or in combination with antivirals, though a slight benefit cannot be entirely ruled out (9,21-23). No similarly significant studies have been conducted in children. Therefore, and based on the intra-hospital consensus we reviewed (Table 3), we recommend supplementing corticosteroid treatment with an antiviral only in cases suspected to be of viral origin (such as Ramsay Hunt syndrome). Specifically, we recommend acyclovir at a dose of 20 mg/kg/dose 4 times a day with a maximum of 3200 mg/day, administered for a total duration of 7 days (24).

3. Physiotherapy and facial exercise

A 2011 Cochrane review concluded that high-quality evidence supporting physical therapy in Bell's palsy was lacking (25). More recently, an updated systematic review by Khan et al. reported emerging evidence suggesting potential benefits of facial exercise therapy, including when initiated early in recovery (26). However, heterogeneity in study design and methodological limitations prevented firm conclusions. In 2023, Nakano et al.

FIGURE 4: Management algorithm for paediatric facial palsy.



conducted a systematic review and meta-analysis including seven randomized controlled trials in adults and reported that physical therapy may reduce non-recovery rates (RR 0.51, low-certainty evidence) and improve Sunnybrook facial grading scores. Nevertheless, the certainty of evidence was rated as low or very low due to high risk of bias, imprecision, and heterogeneity in timing and therapeutic protocols (27). Importantly, the optimal timing for initiating physiotherapy remains uncertain, even in adults. Included studies-initiated therapy at varying time points, ranging from the acute phase to several months after onset. Concerns have been raised that inappropriate or forceful exercises during the early inflammatory phase may promote maladaptive motor patterns or synkinesis. In children, where spontaneous recovery is generally excellent, evidence remains extremely limited (1,3). Therefore, facial physiotherapy should not be systematically initiated during the acute phase but rather considered on a case-by-case basis, particularly in children with delayed recovery, residual weakness, or emerging synkinesis, and in those able to actively cooperate with therapy. In our institution, physiotherapy is proposed mainly in cases of prolonged or incomplete recovery, with initial sessions focused on education and gentle, supervised exercises to be continued at home (10).

4. Electrostimulation

At present, there is no clinical evidence supporting efficacy (25). Recently, a randomized controlled study was conducted with adults and appears to show some efficacy but their cohort was

small. Additional studies are needed to offer this type of therapy to the patient and even more in children because recovery is almost always complete after one year (28).

Neuroborreliosis

The prevalence of borreliosis varies depending on the country. For instance, countries like Finland or Sweden have a very high prevalence of borreliosis, whereas no cases have been reported in Australia. Consequently, diagnostic procedures differ between countries based on the varying presence of B. burgdorferi (29). In Belgium, 10% of ticks are infected with B. burgdorferi, and there is no apparent increase in incidence (30). In neuroborreliosis, the challenge lies in its diagnosis and treatment. Serological blood and/or CSF tests may yield negative results, which do not rule out early stages of Lyme disease. The antibody response initiates within the first days of infection, often remaining below the laboratory's detection threshold if tested too early. It is recommended to use a combination of ELISA and Western blot techniques for antibodies detection (STTT: standardized 2-tier testing: double testing by ELISA and Western-Blot). The mainstay remains the detection of intrathecal antibodies, although recent studies have shown that the sensitivity ranges between 55 and 80% and is lower in patients with shorter symptom durations. Therefore, it is recommended to repeat serological tests 2-4 weeks later if initial results are negatives but the context is evocatory of Lyme disease. A promising new technique, the C6 ELISA Test, is proposed to replace the STTT and intrathecal antibody detection, though further studies are necessary to validate its efficacy (29). Moreover, most cases of FP related to neuroborreliosis do not present recent tick bites or erythema migrans. A retrospective US study identified certain risk factors neuroborreliosis-related FP, including headache and/or pyrexia, seasonal occurrence (June to October in Belgium), bilateral FP, erythema migrans or recent tick bite (16). For additional testing, blood serology or CSF analysis can be performed. Lumbar puncture may reveal lymphocytic pleocytosis with hyperproteinorrachia. The IgG CSF/IgG index blood may be significantly elevated, and the presence of oligoclonal bands is sometimes observed. However, these results are not always positive, and repeated analysis may be necessary. Regarding treatment, there is ongoing debate regarding the use of intravenous versus oral antibiotic therapy. Clinical trials in Europe suggest that oral doxycycline is comparable to intravenous antibiotics, although it is only used in children over 8 years old, with ceftriaxone being preferred for younger children (29). The efficacy of corticosteroids, however, remains uncertain (16). Thus, we recommend treating patients with suspected neuroborreliosis on a case-by-case basis, consulting with your institution's paediatric infectious disease specialist. A 2008 study shows an excellent recovery rate at 6-month follow-up (31).

Prognosis

The recovery rate in children presenting with PFP is excellent and most children show complete recovery within 6 months, although some studies indicate mild dysfunction at follow-up (2,3,24,30). Possible persisting symptoms include impaired eye closure, affected pronunciation, minor nerve dysfunction, and synkinesis (2,29,31).

Limitations

There are a few limitations to our review. First, we sought expert opinions for subjects still under debate in the literature, such as the utility of corticosteroids in treating FP in children. Second, the proportions of causes differ between regions where Lyme disease is endemic and those where it is not, and the literature does not always account for this variation. Third, the HB scale is not entirely objective, which can affect the consistency in the initiation of treatment.

Conclusion

FP is an uncommon but clinically significant presentation in the paediatric emergency setting, with multiple potential aetiologies that require careful differentiation. Distinguishing central from peripheral facial palsy is essential, as management strategies differ substantially. Bell's palsy remains a diagnosis of exclusion. A structured approach based on thorough medical history, detailed neurological and ENT examination, and systematic grading using the House-Brackmann scale is crucial. Complementary investigations should be guided by clinical findings and risk factors. Neuroimaging and lumbar puncture must be considered in cases of bilateral palsy, central signs, associated cranial nerve involvement, atypical progression, or absence of improvement after 4 weeks. Eye protection measures are mandatory in all patients with incomplete eyelid closure. Regarding pharmacological treatment, we recommend corticosteroids (1 mg/kg/day, max 64 mg for 10 days) in children with severe PFP (HB grade IV–VI) when initiated within 72 hours of symptom onset. For adolescents aged 14 years and older, adult protocols may be followed. Antiviral therapy should be reserved for suspected viral aetiologies such as Ramsay Hunt syndrome. Current evidence does not support the systematic use of physiotherapy or electrostimulation in the acute phase. While emerging adult data suggests a potential benefit of facial exercise therapy, the certainty of evidence remains low and paediatric data are lacking. Physiotherapy may therefore be considered on a case-by-case basis, particularly in children with delayed recovery, residual weakness, or synkinesis. Finally, we propose a practical management algorithm to assist clinicians in the evaluation and treatment of paediatric facial palsy (Figure 4).

Statements

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BESCHERM

ALLE BABY'S* TEGEN RSV†

†LAGERE-LUCHTWEG AANDOENINGEN VEROORZAAKT DOOR RSV



Patiëntweergave. Dit is een fictief patiëntgeval, uitsluitend bedoeld ter illustratie.

Plan Beyfortus® idealiter vóór aanvang van het RSV-seizoen:

- ✓ Eenmalige injectie voor het hele seizoen (ten minste 5-6 maanden)
- ✓ Dosering op basis van gewicht: 50mg (<5kg) of 100mg (≥5kg)
- ✓ Terugbetaald voor alle baby's in hun eerste RSV-seizoen** en voor kwetsbare kinderen in hun tweede seizoen

SOPHIA

- Geboortedatum: 15 augustus (vóór het RSV-seizoen)
- Geboortestatus: A terme (39 weken), normaal geboortegewicht
- Woont samen met beide ouders en een broer van 3 jaar
- Ging binnen drie maanden na de geboorte naar de crèche
- Was niet beschermd tegen RSV
- Werd in december opgenomen in het ziekenhuis wegens RSV-LRTD

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†Beyfortus® is geïndiceerd voor de preventie van lagere-luchtwegaandoeningen veroorzaakt door RSV* bij:[1]
i. Pasgeborenen en zuigelingen tijdens hun eerste RSV-seizoen.
ii. Kinderen tot 24 maanden oud die kwetsbaar blijven voor ernstige RSV-ziekte tijdens hun tweede RSV-seizoen.

▾Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden. Zie rubriek 4.8 voor het rapporteren van bijwerkingen. **NAAM VAN HET GENEESMIDDEL** Beyfortus 50 mg oplossing voor injectie in een voorgevulde spuit. Beyfortus 100 mg oplossing voor injectie in een voorgevulde spuit. **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING** Beyfortus 50 mg oplossing voor injectie in een voorgevulde spuit Elke voorgevulde spuit bevat 50 mg nirsevimab in 0,5 ml (100 mg/ml). Beyfortus 100 mg oplossing voor injectie in een voorgevulde spuit Elke voorgevulde spuit bevat 100 mg nirsevimab in 1 ml (100 mg/ml). Nirsevimab is een gehumaniseerd immunoglobuline G1 kappa (IgG1κ) monoklonaal antilichaam dat geproduceerd wordt uit ovariumcellen van de Chinese hamster (Chinese hamster ovary, CHO) met behulp van recombinant-DNA-technologie. 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) (zie rubriek 4.4). Voor de volledige lijst van hulpstoffen, zie rubriek 6.1. **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 blootstelling bij zuigelingen van < 1 kg hogere blootstellingen opleveren dan bij zuigelingen die meer wegen. De voordelen en risico's van het gebruik van nirsevimab bij zuigelingen van <1 kg moeten zorgvuldig worden afgewogen. Er zijn beperkte gegevens beschikbaar over extreem premature zuigelingen (zwangerschapsduur < 29 weken) jonger dan 8 weken. Er zijn geen klinische gegevens beschikbaar over zuigelingen met een postmenstruele leeftijd (zwangerschapsduur bij geboorte plus chronologische leeftijd) van minder dan 32 weken (zie rubriek 5.1). 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 eertse 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 bijwerking was licht tot matig van intensiteit. Aanvullend werden pyrexie en injectieplaatsreacties binnen 7 dagen na toediening gemeld met een prevalentie van respectievelijk 0,5% en 0,3%. Injectieplaatsreacties waren niet ernstig. Lijst van bijwerkingen Hieronder staan de bijwerkingen die zijn gemeld bij 2.966 voldragen en premature zuigelingen (zwangerschapsduur, Gestational Age (GA) ≥ 29 weken) die nirsevimab kregen in klinische onderzoeken en tijdens het toezicht na het in de handel brengen (zie rubriek 4.4). 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 - Overgevoeligheida a Bijwerkingen uit spontane melding Huid- en onderhuidaandoeningen · Soms – Rashb b Rash is gedefinieerd door de volgende gegroepeerde voorkeurstermen: rash, maculo-papulaire rash, vlekkerige rash Algemene aandoeningen en toedieningsplaatsstoornissen · Soms – Injectieplaatsreactiec ; 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 MEDLEY bij 918 zuigelingen met een verhoogd risico op ernstige RSV ziekte, onder wie 196 extreem premature zuigelingen (GA < 29 weken) en 306 zuigelingen met chronische longziekte van prematuriteit of hemodynamisch significante aangeboren hartziekte die hun eerste RSV seizoen ingingen, die nirsevimab (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). Kinderen 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 corticosteroiden (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 respiratoire syncytiale virusinfectie van de onderste luchtwegen (RSV LRTI). 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 wordt 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: 03/2026. Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau http://www.ema.europa.eu

RSV, Respiratoir Syncytieel Virus; **LRTD,** Lower Respiratory Tract Disease
*tijdens hun eerste RSV-seizoen **Éénmalige terugbetaling voor het eerste RSV-Seizoen en bij jonge kinderen (<2 jaar) die een hartoperatie ondergaan met cardiopulmoniare bypass in hun eerste of tweede RSV-seizoen, of jonge kinderen (<2 jaar) die kwetsbaar blijven voor ernstige RSV-ziekte tijdens hun tweede RSV-seizoen, (zoals beschreven in de aanbevelingen van de HGR (advies 9760)). Toediening voor de start van het RSV-seizoen of vanaf de geboorte voor zuigelingen geboren in het RSV-seizoen.
Referentie: 1. Beyfortus® SKP, 03/2026.

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REVIEW ARTICLE

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Non-Invasive Measurement of Cortisol in Children with Adverse Childhood Experiences: A Systematic Review

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Keywords

Adverse childhood experiences; Childhood trauma; Biomarkers; Hair cortisol concentration; Salivary cortisol

Abstract

Purpose

Adverse Childhood Experiences (ACEs) encompass various traumatic events during childhood, linked to adverse health outcomes in later life. Traditional screening methods have possible pitfalls, leading to a growing interest in the use of biomarkers.

Methods

A comprehensive literature review was conducted resulting in the inclusion of 27 studies examining biomarkers of toxic stress in children. These studies employed diverse methodologies, including hair and saliva sampling techniques, and utilized various assessment tools for childhood adversity.

Results

The studies analyzed 1,787 hair samples and 4,170 saliva samples for associations between childhood adversity and cortisol. Hair cortisol concentration (HCC) showed a robust positive correlation with cumulative adversity, while salivary cortisol measures showed a less consistent correlation to adversity.

Discussion

Age, gender and adversity influence the hypothalamic pituitary adrenal (HPA) axis. Hair cortisol emerged as a possible biomarker for chronic stress exposure, while salivary cortisol measures offered insights into acute stress responses with conflicting results. The discrepancies in findings highlight the need for further research to elucidate the complex interplay between childhood adversity and cortisol dynamics, informing targeted interventions to mitigate long-term health effects.

Introduction

Adverse Childhood Experiences (ACEs) encompass traumatic events and chronic stressors occurring during childhood, including physical, emotional, or sexual abuse, parental neglect, household dysfunction, and exposure to violence or substance abuse (1–3). The first ACE study was published in 1998 and since then research has extensively documented the profound impact of ACEs on physical, emotional, and cognitive development, correlating with an increased risk of physical and psychological morbidity, and premature mortality in early adulthood (4–6). Effectively identifying and mitigating these adversities, particularly in paediatric healthcare, remains a complex challenge due to their multifactorial nature and the limitations of current screening approaches (4–7). Traditional screening methods, often reliant on self-reporting or clinical interviews, are prone to recall and reporting bias, stigma, and subjective interpretation (8,9). Additionally, the potentially invasive nature of some assessments may retraumatize vulnerable children and undermine the therapeutic relationship between healthcare providers and patients (10). In light of these challenges, there is growing interest in biomarkers, such as hair and salivary cortisol, as non-invasive screening tools for ACEs in children (8,11). Cortisol, a stress hormone, can be measured in hair and saliva to offer objective insights into individuals' long-term and acute stress experiences (2,3,12). These biomarkers present advantages, including potential for objective measurement and ability to capture chronic and acute stress responses over time (13). Biomarkers such as hair and salivary cortisol are investigated as non-invasive tools for screening ACEs. Cortisol measurement in hair and saliva

TABLE 1: Development of search query

Designated number	Search query component	explanation
#1	"Adverse childhood experiences" OR "ACEs" OR "Childhood trauma" OR "childhood adversity"	This part of the search query includes multiple synonymous terms related to adverse childhood experiences (ACEs) or childhood trauma.
#2	"biomarkers" OR "Cortisol" OR "Hair cortisol" OR "salivary cortisol" OR "stress biomarkers" OR "Cortisol levels" OR "non-invasive screening methods"	the search is broadened to include various terms related to biomarkers and cortisol, which are indicators of biological processes, particularly stress. Including terms like "Hair cortisol," "salivary cortisol," and "stress biomarkers" ensures coverage of specific types of biomarkers relevant to the study of childhood trauma.
#3	"Children" OR "paediatric population" OR "paediatric screening"	This part of the search query specifies the population of interest, focusing on articles related to children or the paediatric population. It ensures that articles discussing biomarkers and childhood trauma are relevant to the paediatric context.
#1 AND #2 AND #3	("Adverse childhood experiences" OR "ACEs" OR "Childhood trauma" OR "childhood adversity") AND ("biomarkers" OR "Cortisol" OR "Hair cortisol" OR "salivary cortisol" OR "stress biomarkers" OR "Cortisol levels" OR "non-invasive screening methods") AND ("Children" OR "paediatric population" OR "paediatric screening")	

correlate with long-term and acute stress, offering advantages in capturing objective measurement of chronic and acute responses. Advancing knowledge of these biomarkers, alongside consideration of demographic and psychological variables (1), may enable early detection and intervention strategies for ACEs, reducing the long-term sequelae of childhood trauma. This review aims to explore the use of hair and salivary cortisol as biomarkers for ACEs in children, examining their efficacy, feasibility, and ethical considerations within paediatric care.

Methods

Search strategy

A systematic literature review was conducted between June and September 2024. Based on a scoping search, keywords and synonyms were identified for three domains: non-invasive cortisol measurement, adverse childhood experiences, and childhood context (Table 1). The population was defined as individuals younger than 18 years, thereby including infants, children, and adolescents irrespective of whether specific age-related keywords were explicitly included in the search terms. Searches were run in PubMed, Embase, and Web of Science, with queries iteratively refined for relevance (Table 2). Controlled vocabulary terms (e.g., MeSH) were not included in the search strategy.
Based on the scoping phase, the final search strategy yielded studies across a broad range of ages and contexts and was considered sufficiently comprehensive for this systematic review.

Study selection

The search was conducted between June 2024 and September 2024 and identified 363 articles. After removing duplicates, titles and abstracts were screened against predefined criteria by two independent reviewers (MD, LH), with disagreements resolved by a third (ADG). Studies were eligible for full-text review if they included participants younger than 18 years; employed case-control, cross-sectional, longitudinal, or randomized controlled design; were published in peer-reviewed journals, and available in English. Exclusion criteria included non-human studies; case reports, reviews, or meta-analyses; interventions involving medication or treatment; absence of ACE reporting; or lack of adjustment for confounders. Sixty-three studies met initial criteria, but eleven lacked full text availability. Ultimately, 27 articles were included (PRISMA diagram, Fig. 1). Abstract and full-text screening were conducted using Rayyan software (14). Before submission in October 2025, the search was repeated and no new articles were included.

Data extraction

MD extracted data on the characteristics of the report, the study population and outcome parameters. These data were verified for accuracy and completeness by LH and ADG. A risk of bias assessment was using the Newcastle-Ottawa Scale for observational studies (15).

Protocol

Prior to initiation of the review process, the protocol for this study was published on PROSPERO (CRD42024571586).

Results

Study characteristics

From the initial yield of the search strategy, 300 studies were excluded, primarily due to the wrong population (n=144), wrong outcome (n=96), inappropriate study design (n=36) or the absence of reported ACEs (n=36). The assessed risk of bias in the selected studies was low overall. However, some studies selectively sampled participants from hospital settings or via social services, potentially introducing selection bias. Consequently, the study population may not fully represent broader community samples. Scores are summarized in Table 3.

Demography of study participants

The demographic characteristics of study participants are summarized in Table 4. The 27 studies included in this review encompass a total of 1787 assessments of hair and 4170 assessments of saliva samples. Of hair samples, 36.8% (N=657) were from boys, 49.5% (N=884) from girls, and 13.8% (N=246) were not specified. The gender difference may be explained by insufficient hair availability for sampling or refusal for cosmetic reasons. Saliva originated from 35.7% boys (N=1488) and 38.5% girls (N=1606) (25.8% unspecified; N=1076). Gender was not reported in a study where participants were infants (1) and by several studies where gender of the participants was specified for the whole study population, but not for the population whose test samples were eligible for analysis (11,16–18). Participants from a wide range of age groups were included, from infants (youngest group mean age 12.4 months) (1), over toddlers (2,19–21) and school children (13,22–28) to adolescents(11,16,17,22–24,26,27,29–35) (eldest group aged 12-21 years old).

Assessment of adverse childhood experiences

Heterogeneity existed in the methodology for assessment of childhood adversity. Some studies developed their own questionnaire and divided adversities into multiple categories (1,2,19,20,24,25,32). Other authors used established instruments, including the Childhood experiences of Care and Abuse interview (CECA) (17,30,33,36), the Early Life Stress Questionnaire (ELSQ) (35), the Trauma Symptom Checklist for Children (TSCC) (34), the Childhood Trauma Questionnaire (CTQ) (31,37–39), the Lifetime Incidence of Traumatic Events Parent-report (LITE-PR) (13), the Early Trauma Inventory (ETI) (22,26) and the Life Experiences Survey (21). Any categories of adversity reported further in this review are taken from the original research. Few studies considered the temporal relation between the onset of adversities and cortisol measurements. Bosch et al. questioned participants across developmental stages and reported differences in cortisol profiles by timing of adversity (32). Do Prado et al. separately questioned stress levels over the past 12 months but observed no case-control differences (39). Some authors report timing of adversity as a variable in their questionnaires, without integrating this into analyses (11,21,28,35). None of the remaining articles reported timing of adversity.

Non-invasive measurement of cortisol

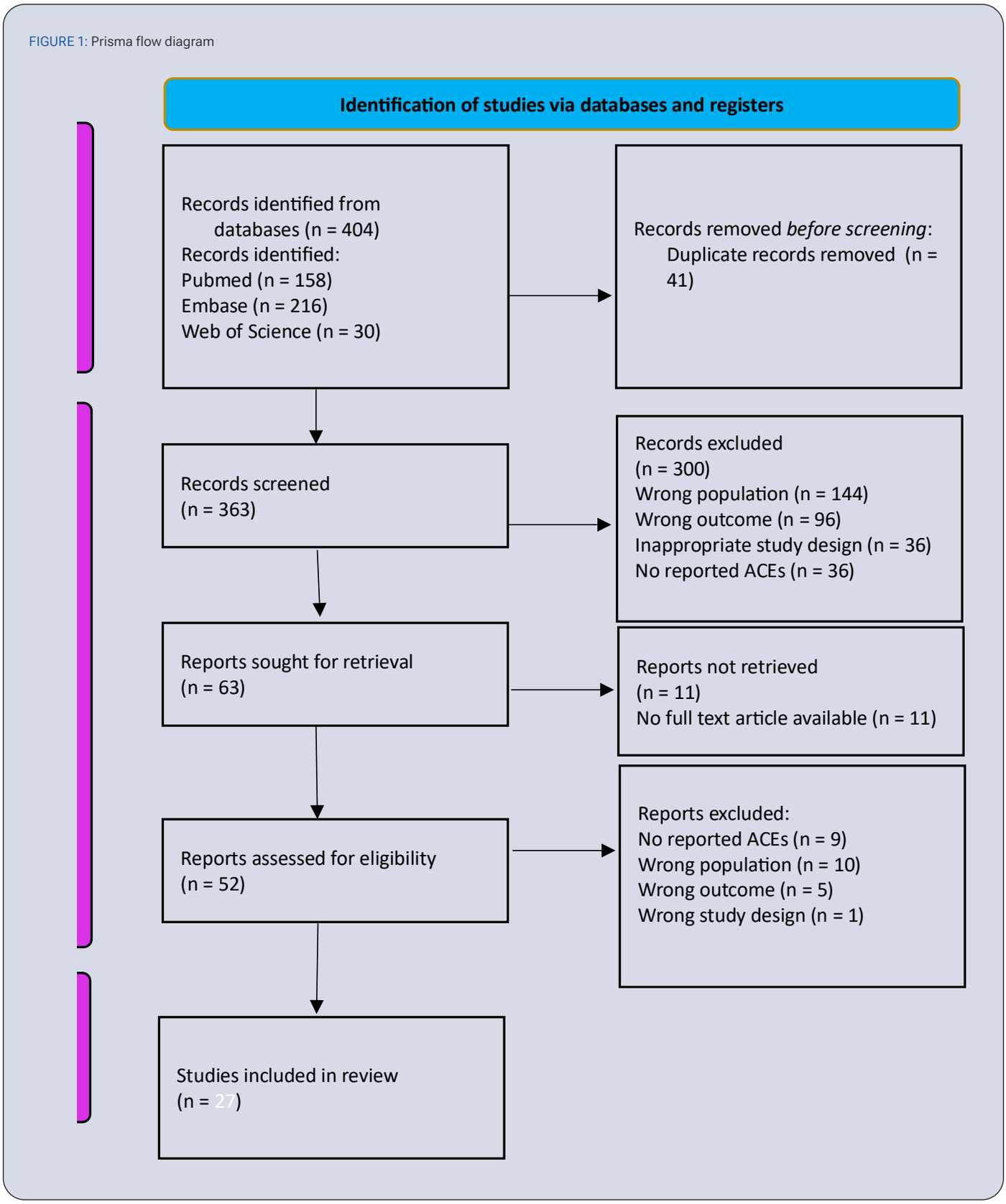
Hair cortisol

Nine studies measured hair cortisol concentration (HCC) (1,2,11,17,19,20,26,30,39), comprising 1787 samples and 35.0% of all cortisol measurement. Sampling was generally uniform with hair collected from the posterior vertex and analysis of the proximal 3 cm. Bryson et al. sampled from the parietal or temporal regions if posterior vertex samples were insufficient (2,20). Van Dammen et al. analysed only the first cm of hair due to a higher number of short hair samples (11). Multiple studies reported positive correlations between ACEs and HCC, of which two in the context of psychiatric comorbidity (17,30), discussed in section 3.4.3. Bhopal et al. reported a strong association between cumulative adversity and hair cortisol in infants. The mean HCC was 6.26 pg/mg (SD 3.01). Each additional adversity corresponded to a 6.1% increase in cortisol levels (95% CI 2.8 – 9.4, p<0.001). The authors structured ACEs in multiple categories, of which HCC changes were most pronounced in relationships, child, and socioeconomic adversities (1). Bryson et al. linked unsafe living conditions to elevated cortisol levels in 2- and 3-year-olds. Mean HCC was 1.04 pg/mg (SD 0.97) for children living in a safe place versus 1.63 pg/mg (SD 0.96) for those who did not. This finding remained significant after adjustment for confounders (β=0.57, 95% CI=0.08–1.07, p=0.023), however without significant correlation to other adversities. Adverse experiences were associated with externalizing symptoms (b=0.41; 95% CI 0.15 to 0.66; no absolute numbers reported), but hair cortisol was not considered a mediating factor (2,20) In a small cohort, Simmons et al. reported significantly higher mean HCC in males than females (5.78 SD 3.88 vs 2.95 pg/mg SD 3.64) and found lifetime trauma positively associated with HCC. Greater trauma exposure, both in frequency and type, predicted elevated HCC (β=0.23, CI 0.01-0.36, p=0.04)(13). A follow-up study confirmed this association and further showed that positive parental behaviours, including nurturing behaviour (b=−0.28, 95% CI -0.50 to -0.06, p=0.014) and maternal emotional coaching (b=−0.25, 95% CI -0.48 to -0.03, p=0.028), correlated with lower HCC (19). In the research of Van Dammen et al. on the contrary, median HCC was significantly higher in female than male participants, respectively 3.6 pg/mg vs 2.4 pg/mg. Total adversity scores were not significantly associated with hair cortisol levels in adolescents. In this population only boys exposed to person-related adversity exhibited statistically significant higher levels of hair cortisol (B=0.016, p=0.007) (11). Hartmann do Prado et al. found that adolescents experiencing early life stress as assessed by the Childhood Trauma Questionnaire had significantly higher HCC (x^2=8.58, p=0.003) (39). Taken together, most studies suggest a positive association between cumulative adversity and hair cortisol concentrations, particularly in younger populations. However, substantial heterogeneity exists in absolute values, effect sizes, and sex-specific findings, limiting comparability across studies.

TABLE 2: Database search strategy

Search query number	database	Search query component	results	Results imported into EndNote
1	PubMed	#1 AND #2 AND #3	150	150
2	Embase	#1 AND #2 AND #3	915	0
3	Embase	'Childhood adversity' AND ('salivary cortisol' OR 'hair cortisol') AND 'child'	74	74
7	Web of Science	#1 AND #2 AND #3	139.072	0
8	Web of Science	childhood adversity hair cortisol salivary cortisol child (ALL FIELDS)	29	29

FIGURE 1: Prisma flow diagram



Salivary cortisol

Diurnal pattern analysis

Fourteen studies measured the diurnal pattern of salivary cortisol (1,11,17,18,22,23,27,28,30,31,34–36,40), reporting data for 1977 participants (33.2% of cortisol measurement). Timing of sampling differed among study groups. The timing of cortisol sampling is summarized in Table 5. Five studies were conducted in het context of psychiatric comorbidity, discussed in section 3.43. (17,27,30,31,35). Valentino et al. saw significantly lower morning cortisol levels in maltreated children aged 3-6 years old, compared to controls (mean 0.32 mg/mL (SD=0.32) vs 0.48 mg/mL (SD=0.52), SE=0.16, p=0.04). Midday and evening cortisol

showed no significant difference (40). Marques-Feixa et al. identified blunted decline of salivary cortisol during the day and thus a higher cortisol area-under-the-curve (AUC) in maltreated children and adolescents, when analysed in an ANOVA test. This result showed dose-response effects for severity (F=6.349, p=0.002) and frequency (F=6.068, p=0.003) of maltreatment. When differentiating age groups, cortisol levels were higher in adolescents compared to younger children (18). Kuhlman et al found trauma-specific differences in a cohort of 9 to 16-year-olds, with non-intentional trauma linked to a steeper diurnal slope (non-intentional × Time b=−.037, t (103.3) =−2.36, p=02). Age and sex were not found to be significant predictors of the cortisol awakening response (22). Kaess et al. observed an elevated cortisol awakening response only in girls with higher Childhood Trauma Questionnaire (CTQ) scores (B=-0.652/β=-0.026, p=0.047) (37). In 15 participants living in residential care homes for abused adolescents, mean cortisol AUC correlated with internalizing symptoms (r=0.56, p<0.05) (34). Several studies report trends in results without reaching statistical significance. These results must be interpreted with caution. Bhopal et al. reported correlation between adversity and a blunted diurnal cortisol slope in infants with small effect sizes. The overall mean saliva AUC in their cohort was 1.29 mcg/dL (SD 0.47), with 60% showing a cortisol slope smaller than 0.01 mcg/h and 15.3% showing a raising slope instead of the hypothesized decline (1). No significant relation between fetal or childhood psychosocial adversity and cortisol could be demonstrated by Isaksson et al. in children and adolescents with ADHD, values were not reported (27). Van Dammen et al. reported a trend towards a lower AUC for adolescent boys with environment-related adversity (b=-9.37; SE=5.07; p=0.08) compared to their female counterparts (11). In conclusion, ACEs show correlation to diurnal salivary cortisol in most research. While several studies report altered diurnal slopes or cortisol awakening responses, there is little reproducibility of results with authors finding both hypo- and hypercortisolism. This variability suggests that diurnal cortisol patterns may reflect complex, context-dependent adaptations rather than a uniform biomarker signal.

Stress test

Twelve studies measured reactivity of salivary cortisol to a stressor (16–18,21,22,24–26,28,32,33,38), reporting data for 2193 participants (36.8% of cortisol measurements). Different stressors were used, from social or physical standardized stress tests to other specific tasks with saliva samples being collected before and after exposure. Exact timing differed among study groups. Details of sampling are summarized in Table 5. Three studies conducted in the context of psychiatric comorbidity are discussed in section 3.4.3 (17,24,33). A longitudinal cohort study by Bosch et al. revealed that cortisol reactivity varied by the timing of childhood adversity. Pre- and postnatal stress were linked to heightened responses (F=5.17, p=0.006), while late-childhood adversity correlated with higher baseline levels (F=8.08, p=0.005) and adolescent adversity to lower baseline levels (F=4.8, p=0.03). No difference was reported in relation to biological sex (32). Marques-Feixa et al. describe a blunted cortisol response among participants aged 7-17 years exposed to ACEs (F 4.530, p=0.002), despite higher perceived stress (F=9.129, p=0.007) as assessed by the Trier Social Stress Test (TSST) (18). Comparable results are described by Sumner et al. When comparing participants with or without a history of maltreatment in an ANOVA test, F=5.05, p=0.02, with lower levels of cortisol at the second (p=0.07) and third timepoint of measurement (p=0.01).

TABLE 3: Risk of bias assessed using the Newcastle-Ottawa Scale (1: selection, 2: comparability, 3: exposure)

Cohort studies					Case-control studies				
Author	Year	1	2	3	Author	Year	1	2	3
Reichl(25)	2024	**	**	**	Chung (31)	2023	**	**	***
Bhopal (1)	2019	****	**	**	Harkness (29)	2010	****	*	***
Bosch(28)	2012	***	**	****	Marques-Feixa (14)	2021	**	**	**
Bryson (2)	2019	***	**	****	Weems (13,19)	2009	***	*	**
Bryson (16)	2020	***	**	****	Reichl (13)	2019	*	**	*****
Gustafsson (30)	2010	*	*	****	Valentino (36)	2015	***		****
Iob (21)	2021	***	**	***	Weems (20)	2009	***	*	**
Kaess (33)	2017	****	*	****	Peckins (24)	2015	***	*	**
Kuhlman (18)	2015	**	**	***	Isaksson (23)	2013	****	*	*
Kuhlman (22)	2018	***	**	***					
Llorens (27)	2022	***	*	***					
Oriana Linares (34)	2012	**	*	***					
Reichl (26)	2016	**	**	***					
Simmons (4)	2016	****	*	***					
Simmons (15)	2019	*	*	***					
Van Dammen (5)	2020	****	**	****					
Winiarski (17)	2018	***	**	***					
Hartmann do Prado (35)	2017	****	**	***					
Sumner (12)	2014	****		*****					

They found no difference in baseline cortisol, confidence intervals were not reported (16). A twin cohort study of 11-year-olds reported significantly lower cortisol (β=-0.576, p=0.049) in children with ≥3 ACEs, albeit with a small effect size. The strongest association was linked to bullying. This was borderline associated with depressive symptoms at age 21 (25). Peckins et al recruited children between 9 and 12 years old via Child and Family Services and performed a TSST. A blunted cortisol response was more often observed in participants experiencing maltreatment versus healthy controls with statistically significant findings (p<0.05, OR=0.41) (28). According to Winiarski et al., cortisol reactivity moderated the relationship between early life stress and aggression in toddlers (aged 2.5-5.5 years old). A higher rise in cortisol in response to a stress test was associated with more symptoms of aggression only in the presence of early life stress with a coefficient of -0.078 (SE=0.038, p=0.039) (21). In an investigation of adolescent girls from a high-risk population for both childhood adversities and dating perpetration, girls experiencing ACEs showed a significantly higher cortisol reactivity to stress with a steeper cortisol slope (β= 0.947, SE=0.274, p=0.001) (38). Kuhlman et al. demonstrated trauma-specific cortisol responses. Physical abuse was linked to a steeper cortisol peak (p=0.02), while emotional abuse was associated with a slower post-stressor decline (p=0.03) (22). A follow-up study found that the type of abuse influenced psychological symptoms. A raised HPA reactivity combined with physical abuse was associated with more externalizing symptoms (p=0.027) (26). As with the previously discussed diurnal cortisol patterns, cortisol reactivity to stress shows a correlation to ACEs in most studies. However, the direction of this association is inconsistent, with both heightened and blunted responses reported. These findings likely reflect differences in timing, type, and chronicity of adversity, as well as developmental and individual factors.

Psychopathology as co-morbidity

As previously mentioned and documented in literature, experiencing ACEs heightens the risk of developing psychiatric disorders. Evidence from a large population-based study in Canada substantiates this association, demonstrating, a strong correlation between child abuse and various mental conditions (6). In line with these findings, several authors have explored the role of psychopathology on the HPA axis in the presence of ACEs. In a subgroup of children with ADHD, childhood adversity was positively correlated with a higher morning increase in salivary cortisol (r=0.19, p=0.041), which could not be demonstrated in control participants without ADHD diagnosis (27). In a sample of adolescents with ADHD (aged 14-17 years), higher salivary cortisol at awakening was associated with more inattentive symptoms, only in the presence of maltreatment (β=-0.398, p=0.035). In this study group a strong correlation between salivary cortisol and fasting plasma cortisol (p<0.001) was demonstrated (31). Maltreated adolescents with moderate to severe depressive symptoms showed a higher baseline salivary cortisol (p<0.01, η^2=0.08) in research by Harkness et al., but lower cortisol reactivity to stress (p<0.005, η^2=0.64) (33). Weems et al. noted distinct diurnal cortisol patterns in children with PTSD symptoms, including a steeper initial decline and a subsequent rise at night. HLM estimation of a curvilinear pattern resulted in a coefficient of 0.03 when comparing children with vs without PTSD (SE=0.01, p=0.013) (23,24). Children with functional neurological disorder (FND) were investigated by Chung et al. A reduced cortisol awakening response was reported in children with FND, particularly in those with more ACEs using a Pearson correlation test (r=-0.6, p=0.02) (35). Adolescents engaging in NSSI (non-suicidal self-injury) reported significantly higher ACEs related to antipathy and physical maltreatment (p<0.01 and p=0.04 respectively) in comparison to healthy controls. No significant association between hair cortisol and NSSI was observed, nor between salivary cortisol and child abuse. A significant relation of the diurnal slope of salivary cortisol levels to child abuse was found, where adolescents engaging in NSSI had a steeper diurnal slope in the presence of abuse (β=-0.47, p=0.02). On the contrary, healthy controls had a flattened slope although these results did not reach significance (β=0.27, p=0.06) (30). In comparison to their siblings, adolescents engaging in NSSI had higher ACE scores (z=- 2.73, 95% CI -2.05 to -0.34, p<0.01) and HCC levels (z=- 2.57, 95% CI -0.41 to -0.06, p=0.01) (17). Finally, emotional abuse and non-intentional trauma have been established to correlate with internalizing symptoms (respectively p=0.001 and p=0.017) (26). Collectively, we conclude that different psychiatric disorders have an influence on the HPA axis and that this modification shows a correlation to the presence of ACEs. However, the correlation differs among different studies and few patients are included, warranting caution in generalizing conclusions.

Discussion

This review synthesizes the current literature investigating non-invasive cortisol measurement as potential biomarkers for stress in children with ACEs. Across 1,787 hair samples and 4,170 saliva samples, these studies provide valuable insights into the complex relationship between childhood adversity and cortisol dynamics across developmental stages and socio-cultural contexts. Age critically influences cortisol regulation due to maturation of the HPA- axis (1,11,13). Including participants from infancy to adolescence increases generalizability but complicates comparison due to age-related variability. Timing of adversity is an important parameter to consider, as demonstrated by Bosch et al. (32), yet rarely addressed in the existing literature. Gender differences are evident, with for example Van Dammen et al. reporting higher mean HCC in female participants, and Simmons et al. in males (11,13). These sex-specific differences highlight an important limitation in the use of cortisol as a biomarker. Variability in HPA-axis functioning between males and females suggests that cortisol cannot be interpreted uniformly across populations. This limits its utility as a standalone biomarker and underscores the need for age- and sex-specific reference frameworks when considering clinical application. The studies reviewed employed diverse methods to assess ACEs, including standardized questionnaires or study-specific instruments. While these yield cumulative adversity scores, they often fail to capture individual stress perception, limiting precision (11). Distinguishing ACEs from trauma shows a need for standardized tools reflecting their multifaceted nature. Person- and environment-related adversities differently impacted cortisol regulation, underscoring the complexity of assessing childhood adversity. HCC demonstrated strong associations with cumulative adversity, indicating its potential as a biomarker for chronic stress. Previous literature on ACEs has already supported the biology of stress, where physiological stress responses become detrimental when chronically activated (7). Elevated HCC was especially found in younger children, with variations by gender and adversity type. Associations in adolescents were less consistent (1–3,13,19,34,39). Salivary cortisol findings were mixed, with both blunted diurnal slopes or altered AUC metrics, and found elevated cortisol awakening responses (1,11,22,34,37,40). Many lacked statistical significance. Similarly, reactivity to stress tests showed mixed results, with both heightened and blunted reactivity reported, potentially influenced by age, gender, trauma type, and timing (16,18, 21,22,25,32,38) . This suggests limited reliability of salivary cortisol as an ACE biomarker. ACEs-related psychiatric disorders, including NSSI, ADHD, and depression, show distinct cortisol patterns, underscoring the need to account for these comorbidities.

TABLE 4: Demographics of study participants.

Author	Year of publication	Number of patients	Age	Gender	Method of cortisol analysis	Number of samples	Gender
Bhopal	2019	1693	median 12,4m	n/a	Hair	712	371F, 341M
Bryson	2018	603	2y	n/a	Hair	319	186F, 133M
Bryson	2019	500	2-3y	n/a	Hair	297	180F, 117M
Simmons	2018	60	mean 4,25y	34F, 26M	Hair	60	34F, 26M
Simmons	2016	70	mean 9,5y	56F, 14M	Hair	70	56F, 14M
Reichl	2019	64	12-17y	n/a	Hair	63	n/a
Van Dammen	2020	190	12-18y	116F, 74M	Hair	183	n/a
Hartmann do Prado	2017	243	13-17	n/a	Hair	57	15F-15M (case), 18F-9M (control)
Reichl	2016	26	14-18y	24F, 2M	Hair	26	24F, 2M
Bhopal	2019	1350	median 12,4m	n/a	Saliva - diurnal	752	353F, 399M
Valentino	2015	92	3-6y	25F-24M (case) - 23F-20M (control)	Saliva - diurnal	92	25F, 24M (case) - 23F, 20M (control)
Isaksson	2013	418 (197 ADHD /221 HC)	6-17y, mean 11,9y	49F, 148M (case); 129F, 92M (control)	Saliva - diurnal	400	191 (case), 209 (control)
Marques-Feixa	2023	187	7-17y	108F, 79M	Saliva - diurnal	178	n/a
Kuhlman	2015	121	9-16y	59F, 62M	Saliva - diurnal	121	59F, 62M
Weems	2008	41 (26 case/ 15 control)	10-16y	10F, 16M (case), 5F-10M (control)	Saliva - diurnal	41	10F, 16M (case),5F, 10M (control)
Van Dammen	2020	190	12-18y	116F, 74M	Saliva - diurnal	92	n/a
Gustafsson	2010	15	13-19y	14F, 1M	Saliva - diurnal	15	14F, 1M
Llorens	2022	76	14-17	22F, 54M	Saliva - diurnal	76	22F, 54M
Reichl	2016	52	14-18y	48F, 4M	Saliva - diurnal	52	48F, 4M
Reichl	2016	26	14-18y	24F, 2M	Saliva - diurnal	26	24F, 2M
Chung	2023	78 (41 FND/ 37 HC)	11,3-16,1y	n/a	Saliva - awakening response	63	26F, 6M (FND) - 23F 8M (HC)
Kaess	2017	238	14-16	122F, 116M	Saliva -awakening response	69	30F, 39M
Winiarski	2018	219	2,5-5,5y	110F, 109M	Saliva - stress test	219	110F, 109M
Peckins	2015	454	9-12y	212F, 242M	Saliva - stress test	454	212F, 242M
Kuhlman	2015	121	9-16y	59F, 62M	Saliva - stress test	121	59F, 62M
Kuhlman	2018	121	9-16y	57F, 64M	Saliva - stress test	121	57F, 64M
Iob	2021	300	11y	180F, 120M	Saliva - stress test	290	173F, 117M
Bosch	2012	1816	11-21y	926F - 890M	Saliva - stress test	471	245F, 226M
Reichl	2019	64	12-17y	n/a	Saliva - stress test	64	n/a
Harkness	2010	71	12-21y	48F, 23M	Saliva - stress test	71	48F, 23M
Sumner	2014	168	13-17y	94F, 74M	Saliva - stress test	158	n/a
Reichl	2016	52	14-18y	48F, 4M	Saliva - stress test	184	n/a
Oriana Linares	2013	40	mean 16,63y	40F	Saliva - stress test	40	40F
Llorens	2022	76	14-17y	22F, 54M	Fasting blood sample	76	22F, 54M

TABLE 5: Sampling protocols for salivary cortisol.

Author	Year of publication	Type of sampling	Timing of sampling	Type of stressor
Marques Feixa	2023	Saliva - diurnal	1 day; awakening, +30 min, before lunch, before bedtime	
Marques Feixa	2023	Saliva - stress test	stress test at 16:00; -30 min, immediately before stressor, +15 min, + 30 min	Trier Social Stress Test
Chung	2022	Saliva - awakening response	awakening, 30 min after awakening	
Llorens	2022	Saliva - diurnal	2 consecutive days; awakening, +30 min, +60 min, 22:00	
Iob	2021	Saliva - stress test	Baseline, immediately after stressor, +10 minutes	computer game
Van Dammen	2020	Saliva - diurnal	1 weekday; awakening, + 30 min, 12:00, 20:00	
Bhopal	2019	Saliva - diurnal	2 consecutive days; 8:00, 12:00, 16:00	-
Bosch	2019	Saliva - stress test	Pre-test, immediately after, +20 min, +40min	Groninger Social Stress test
Reichl	2019	Saliva - stress test	Before and after CECA interview	CECA interview
Kuhlman	2018	Saliva - diurnal	2 consecutive weekdays; awakening, +45 min, before dinner, before bedtime	
Kuhlman	2018	Saliva - stress test	Baseline at -30min, immediately before stressor, +25min, +35min, +45min, +55min, +65min	Socially-evaluated Cold Pressor Task
Winniarski	2018	Saliva - stress test	Baseline, 20 minutes after completing stress test	Laboratory temperament assessment battery
Kaess	2017	Saliva - diurnal	2 consecutive days; awakening, +30 min, +60 min, 20:00	
Reichl	2016	Saliva - diurnal	3 consecutive days; awakening, +30 min, +60 min, before bed	
Peckins	2015	Saliva - stress test	"-45 min, -10 min, immediately after stressor, +10 min, +20min, +30 min	Trier Social Stress Test
Valentino	2015	Saliva - diurnal	2 consecutive weekend days; awakening, before lunch, before bedtime	
Sumner	2014	Saliva - stress test	test between 14:00 en 19:00; pre-test, immediately after, +20 min	Trier Social Stress Test
Isaksson	2013	Saliva - diurnal	Weekday; awakening, +30min, 16:00, bedtime	
Oriana Linares	2013	Saliva - stress test	"- 45 min, -25 min, -5 min, +20 min, +40 min, +60 min"	Viewing of video of a teen dating argument that escalates into severe physical aggression
Kuhlman	2012	Saliva - stress test	Pre-test, +25min, +35min, +45min, +55min, +65min	Socially-evaluated Cold Pressor Task
Gustafsson	2010	Saliva diurnal	3 weekdays, 8:30, 10:30, 21:00	
Harkness	2010	Saliva - stress test	Baseline, 10 min after first stressor, 20 min after first stressor	Trier Social Stress Test
Weems	2008	Saliva - diurnal	3 days; before breakfast, before lunch, before dinner, before bedtime	

Future studies should examine whether cortisol profiles predict psychiatric risk or can guide interventions targeting HPA-axis dysregulation. The studies reviewed employed diverse methods to assess ACEs, ranging from study-specific questionnaires to validated instruments such as the CTQ, CECA, and ETI. While these tools capture important aspects of adversity, substantial heterogeneity exists in their conceptual scope and operationalization. Importantly, many instruments focus primarily on trauma-related exposures (e.g. abuse and neglect), whereas broader ACE frameworks also include household dysfunction and environmental adversity. Trauma-focused questionnaires may fail to capture the breadth of ACEs, highlighting the need for validated and standardized assessment tools. In addition, ACEs are often summarized as cumulative scores, which improves feasibility but may obscure important dimensions such as timing, chronicity, severity, and developmental context of adversity. This is particularly relevant in paediatric research, where exposure assessment may rely on self-report, proxy report, or study-specific classifications, each with distinct risks of underreporting or misclassification. Importantly, validated tools for childhood victimization do exist, as illustrated by Afifi et al., who used the Childhood Experiences of Violence Questionnaire, a valid and reliable instrument for assessing youth victimization (6). The absence of the original ACE questionnaire (as published by Felliti et al.) in the included studies may reflect its limited applicability in paediatric populations, where proxy reporting and ethical considerations

complicate its use. However, this variability in measurement tools reduces comparability across studies and may contribute to inconsistent findings regarding cortisol associations. This review has several important limitations. First, most included studies were cross-sectional in design, which limits causal inference and hampers the ability to disentangle temporal relationships between adverse childhood experiences and cortisol dynamics. Caution is needed to not overinterpret correlation as causation, as has been highlighted in previous observational research (6,7). Second, substantial heterogeneity was observed in both exposure and outcome assessment. Variability in ACE definitions, measurement instruments, and reporting approaches complicates direct comparison across studies. In parallel, differences in cortisol assessment, including timing of sampling, biological matrices, and laboratory methodologies, may have contributed to inconsistent findings. The wide age range of participants further complicates interpretation, given the developmental changes in HPA-axis functioning throughout childhood and adolescence. Third, selection bias may have influenced the results. Several studies recruited participants through clinical services or social care systems, potentially leading to an overrepresentation of children with more severe adversity or maladaptive coping mechanisms. This may limit the generalizability of findings to broader community populations exposed to less severe or more heterogeneous forms of adversity. Fourth, important confounding factors, including medication use, socioeconomic status, nutritional status, sleep patterns, and diurnal variation, were inconsistently reported and controlled for across studies, further limiting comparability and interpretation. Finally, although the search strategy was predefined, it may not have captured all relevant literature. The absence of broader constructs such as "early life stress" and the limited use of controlled vocabulary (e.g., MeSH terms) may have reduced the sensitivity of the search. Future research should explore mediators and moderators, including genetics, parenting styles, social support, and psychiatric symptoms, and prioritize longitudinal designs to clarify the long-term impact of ACEs on cortisol dynamics. Standardized cortisol sampling and analysis protocols are needed to improve comparability and clinical utility, and interdisciplinary collaboration is essential to translate these findings into practice. Cortisol may help identify ACE-related risk but cannot capture the full complexity of adversity alone. HCC shows promise as a retrospective marker of cumulative stress. However, its clinical use requires further validation, and distinguishing adaptive from maladaptive responses remains challenging, as both hypo- and hypercortisolism occur following adversity. Particularly in saliva, non-invasively measured cortisol is unlikely to serve as a reliable standalone biomarker for ACEs. Instead, it may be more informative as part of a multi-biomarker framework integrating physiological, psychological, and environmental measures. Subsequently, trends on a community or population-based level may be more of interest than the individual's value. This is in line with critiques of the ACE framework as a probabilistic, population-level construct rather than a tool to diagnose individual vulnerability. When using the ACEs framework for policy making, caution should be taken to avoid stigmatization of families and vulnerable children (7).

Conclusion

This systematic review highlights the complex impact of childhood adversity on cortisol regulation and underscores the utility of non-invasive cortisol measurements, particularly HCC, as biomarkers for chronic stress. By advancing our understanding of the physiological pathways linking early adversity to health outcomes, these findings might provide a foundation for targeted interventions to mitigate the long-term effects of ACEs on physical and mental well-being. The clinical application of cortisol as a diagnostic or prognostic tool requires further refinement, including standardization of measurement protocols and a deeper understanding of individual variability in stress responses.

Statement

The authors have no conflicts of interest to disclose relating to the topic discussed in this manuscript.

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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 Oligosaccharides ***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**

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Tuberculous Osteomyelitis with Associated Cutaneous Abscessation: A Paediatric Case Report of Extrapulmonary Tuberculosis

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Keywords

Paediatric Tuberculosis; Extrapulmonary Tuberculosis; Tuberculous Osteomyelitis; Case Report

Abstract

Tuberculosis remains a global health concern, with children at higher risk of extrapulmonary involvement. An 8-year-old immunocompetent girl, originating from Eritrea, presented with painful ankle swelling. Imaging showed osteomyelitis and systemic calcifications. Mycobacterium tuberculosis was isolated from surgical drainage. She was diagnosed with tuberculous osteomyelitis and scrofuloderma in the context of miliary tuberculosis, though a metastatic abscess could not be excluded. Tuberculosis should be considered in children from endemic regions presenting with persistent osteoarticular or cutaneous lesions to ensure early diagnosis and prevent complications.

Background

Tuberculosis (TB) continues to represent a major public health concern. According to the World Health Organization, one-quarter of the global population is infected with Mycobacterium tuberculosis, of which an estimated 10% are children. In 2023, one million paediatric TB cases were reported worldwide, of which 200,000 died due to untreated or complicated disease. The highest incidence rates were observed in South-East Asia and Africa, however TB has also re-emerged as a concern in high-income countries, largely due to international migration and increased global travel. In 2025, children accounted for 4% of newly reported tuberculosis cases in the WHO European Region, representing a 10% increase in incidence compared with 2023 (1, 2). TB is a contagious bacterial infection caused by M. tuberculosis, transmitted primarily via infectious respiratory particles. Paediatric TB progression differs from adults: while approximately 10% of adults develop disease, usually from reactivation, up to 50% of immunocompetent children develop disease, typically from primary infection. Furthermore, extrapulmonary TB is more common in children, occurring in up to 54% of cases versus 16% in adults. Mediastinal/hilar lymph nodes are involved in 50% of the cases, while 20% show extrathoracic disease, most often cervical lymphadenitis (3, 4). Diagnosing TB in children remains challenging due to the nonpulmonary subtle presentation. The increasing number of TB cases among children in Europe underscores the need for heightened awareness to enable timely diagnosis of this preventable and curable disease, thereby limiting disease progression and reducing associated morbidity and mortality.

Case report

In April 2025, an 8-year-old girl presented to the emergency department of Hôpital Universitaire des Enfants Reine Fabiola in Brussels Belgium with right ankle pain following a sprain. The patient, born in Eritrea, lived in Uganda for seven years before arriving in Belgium in February 2025. No symptoms were reported prior to the injury. Apart from minimal swelling, no additional clinical signs were observed on admission. Initial X-ray suggested a possible fracture after which a cast was applied. Subsequent clinical follow-up was reassuring. In June 2025, the patient re-presented with persistent right ankle pain, without associated swelling or cutaneous manifestations. Repeat X-ray was reassuring and conservative management was advised. In July 2025, the patient re-presented with a painful swelling of the right ankle persisting for five days. Apart from fatigue, there were no signs of weight loss, fever, or other systemic symptoms. Vitals signs were within normal limits. Clinical examination showed two ~4 cm abscesses medio-posterior on the right ankle with surrounding erythematous, painful skin (Figure 1). Lung auscultation revealed mild right-sided crackles, and painless bilateral cervical lymphadenopathy was present. The remainder of the examination was unremarkable. Ankle X-ray suggested osteomyelitis (Figure 2), after which MRI confirmed osteitis with suspected fistulized Brodie's abscess. Chest X-ray (Figure 3) and subsequent

FIGURE 1: Photos of clinical examination of the right ankle retrieved during admission.

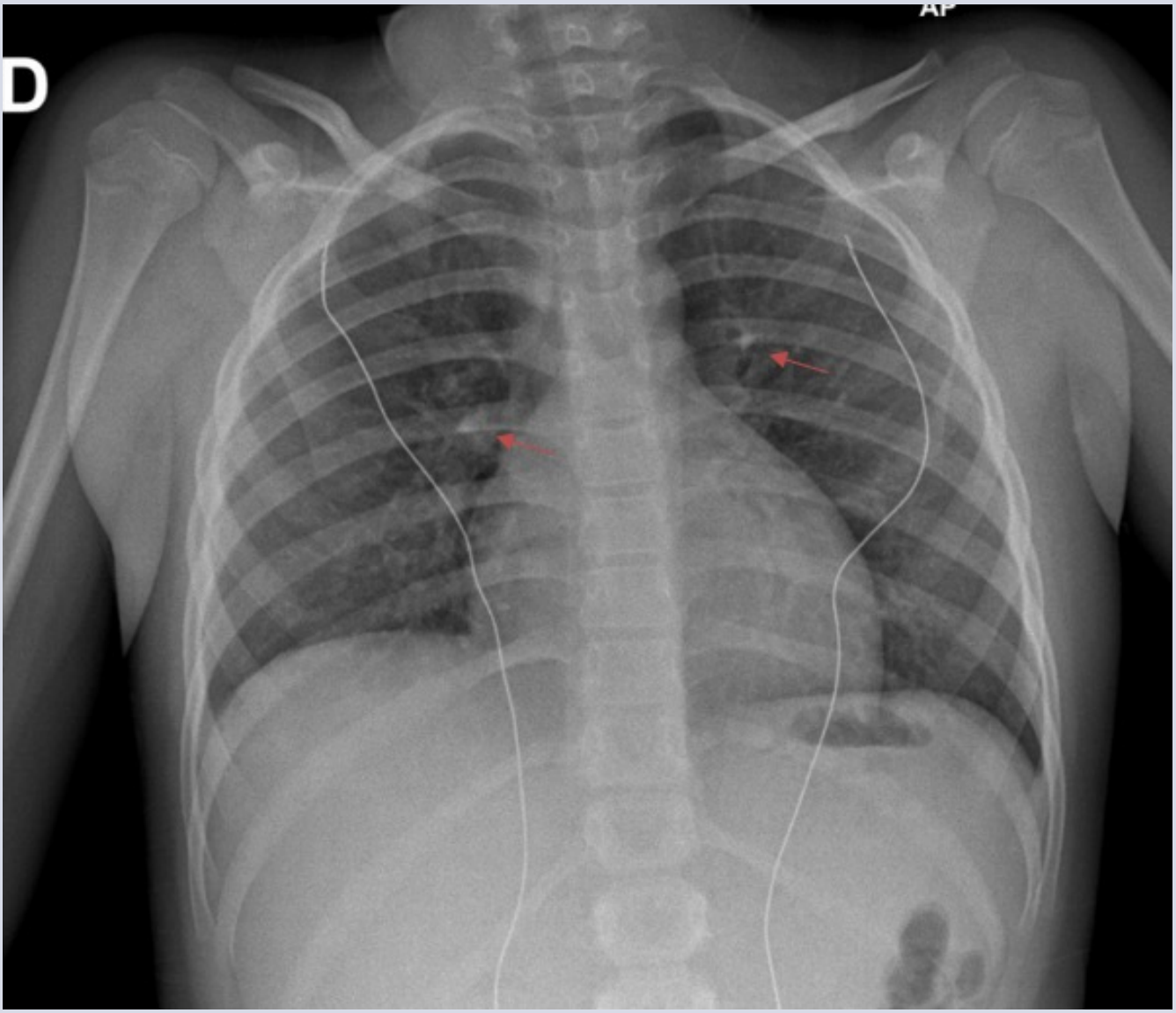


CT revealed pulmonary, mediastinal, hilar, hepatic, and splenic calcifications. Blood investigations, including complete blood count, C-reactive protein, renal and hepatic function, extensive serology (including HIV), as well as superficial smears and gastric aspirates, were negative. Tuberculin skin test was positive (induration size undocumented), no interferon-gamma release

FIGURE 2: Results of X-ray of the right ankle: Osteolytic lesion at the distal metaphysis of the right fibula. Periosteal apposition. Significant swelling of the soft tissues around the malleolus.



FIGURE 3: Results of chest x-ray: Calcifications in the upper left lobe and middle right lobe. Examination within normal limits.



assay was performed. M. tuberculosis was confirmed by culture obtained from surgical drainage (consisting of evacuation of purulent secretions through two skin incisions over the affected area, followed by curettage and irrigation with physiological saline and povidone-iodine). With all the clinical findings, radiological and microbiological results, the patient was diagnosed with tuberculous osteomyelitis. The patient was hospitalized for a total of 2 months and received antituberculosis quadritherapy, resulting in total resolution of clinical symptoms and signs.

Discussion

This case illustrates an uncommon presentation of extrapulmonary TB in an immunocompetent child without comorbidities. As mentioned earlier, paediatric TB progresses rapidly after primary infection with more frequent extrapulmonary manifestations compared with adults. Children under the age of five are at highest risk for dissemination, but extrapulmonary disease may also occur in older immunocompetent children. The true global burden of paediatric extrapulmonary TB remains uncertain due to underdiagnosis and incomplete reporting (1-5). Osteoarticular TB accounts for 5% of all TB and 10% of paediatric extrapulmonary cases. Although the initial ankle sprain may have been coincidental, the possibility that antecedent trauma facilitated the invasion of M. tuberculosis within osseous tissue cannot be excluded. If so, this case could be consistent with post-traumatic osteoarticular tuberculosis, a rare and frequently misdiagnosed subtype due to its variable clinical presentation thereby underscoring the importance of a thorough medical history (6). Clinical presentation of osteoarticular TB is typically insidious, with progressive joint pain, swelling, and decreased range of motion. Systemic symptoms are often absent, radiological findings nonspecific, and microbiological yield is limited due to the pauci-bacillary nature of osteoarticular lesions. Pathophysiologically, synovial invasion triggers chronic inflammation, pannus formation, fibrosis, and progressive destruction of cartilage and bone. Early radiographic changes are nonspecific and include joint effusion, soft tissue swelling, juxta-articular osteopenia, and peripheral erosions. Definitive diagnosis requires microbiological confirmation and/or histopathological evidence of caseating granulomas (1, 6-8). In this patient, imaging findings and microbiological culture confirmed TB osteomyelitis. Cutaneous TB is rarer: 1% of all TB; and 10% of paediatric extrapulmonary TB. Pathophysiologically, cutaneous TB occurs mostly due to contiguous spread from an

underlying focus or hematogenous/lymphatic dissemination but can also occur due to direct inoculation though extremely rare (1, 3-5). In our patient, MRI suggested fistulisation of osteomyelitis to the overlying skin, consistent with scrofuloderma, the most frequent form of cutaneous TB in children. However, the clinical presentation also raised suspicion of a tuberculous gumma (i.e. a metastatic tuberculous abscess), a rare form accounting for 1–2% of all cutaneous TB cases. These lesions typically begin as cold, painless subcutaneous nodules that liquefy into abscesses and may perforate the skin, forming sinus tracts and ulcerations. Metastatic tuberculous abscesses may occur during established TB or, more rarely, as the first manifestation of disseminated disease. Although usually associated with immunocompromised or malnourished patients, several cases in immunocompetent hosts, including children, have been reported. Diagnosis of cutaneous TB remains challenging due to its variable morphology and broad differential diagnosis. Ziehl–Neelsen staining is positive in fewer than 50% of cases, while cultures are positive in up to 85%. Histopathology typically reveals granulomatous inflammation with or without caseation in over 80% of cases (9-11). In this case, histopathological examination was not performed to confirm TB (no rationale for omitting this investigation was specified). This case report has several limitations. As a single paediatric case, it limits generalizability to other children with extrathoracic tuberculosis; however, it underscores the ongoing problem of underdiagnosis and highlights the need to consider a broad differential diagnosis, even with subtle clinical signs. Furthermore, histopathological examination was not performed, although it was not required to establish the diagnosis and would not have distinguished scrofuloderma from metastatic abscess. Finally, reliance on surgical culture for confirmation limits the applicability of these findings to broader clinical practice, yet it emphasizes that negative microscopy of superficial smears or gastric aspirates do not exclude tuberculosis when clinical suspicion is high.

Conclusion

Extrapulmonary TB in children remains diagnostically challenging due to its nonspecific clinical manifestations. This case highlights the importance of maintaining a high index of suspicion for TB in children from endemic regions presenting with persistent joint pain and/or cutaneous abscesses, even in the absence of systemic symptoms. Increased awareness of atypical presentations will facilitate timely diagnosis and management, thereby reducing morbidity and preventing long-term sequelae.

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CASE REPORT

Belg J Paediatr. 2026;28(2): p.187-192

Challenges in Diagnosing and Treating Early-Stage Streptococcal Toxic Shock Syndrome: about an Invasive Group A Streptococcal Case Report

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Keywords

Group A Streptococcal Infections; Streptococcal Toxic Shock Syndrome; Hemodynamics; Abscess; Anti-Bacterial Agents; Intravenous Immunoglobulins; Child

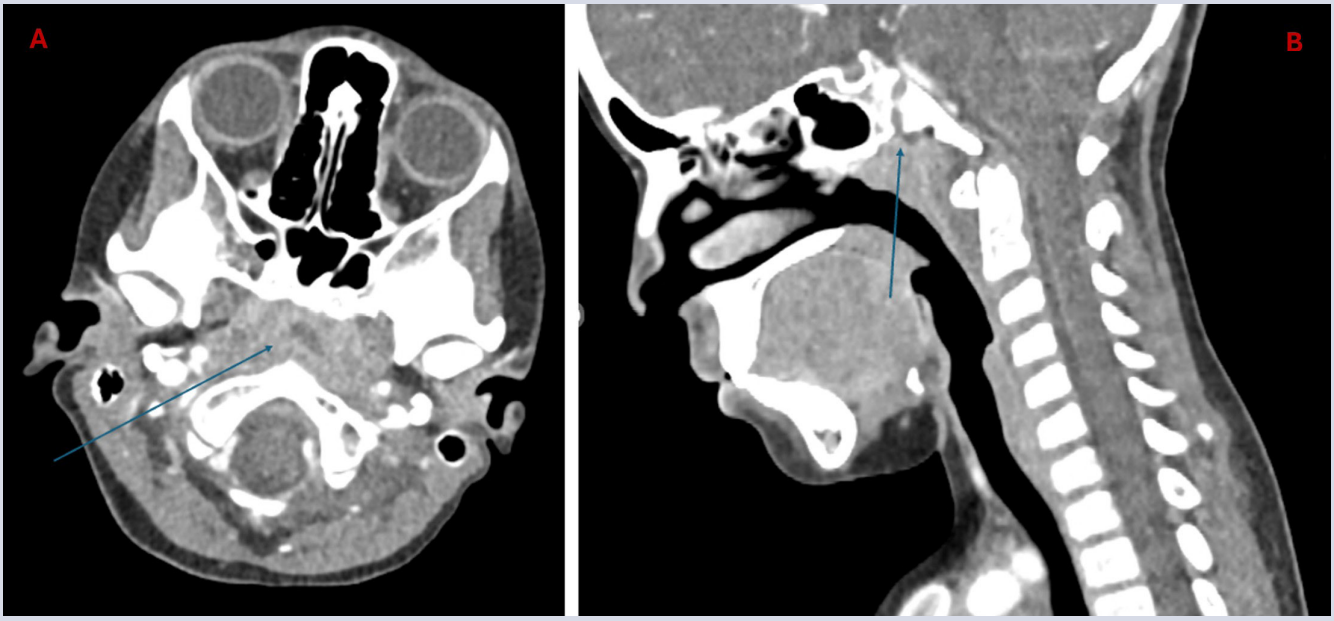
Abstract

We report the case of a 7-year-old girl with severe torticollis caused by invasive Group A Streptococcal infection (iGAS) complicated by early Streptococcal Toxic Shock Syndrome (STSS). Despite the absence of hypotension, she developed multiorgan damage. Imaging revealed multiple abscess at the base of the skull. Rapid intravenous antibiotics and supportive care led to full recovery. This case illustrates the diagnostic challenges of atypical STSS and emphasizes the importance of early recognition and treatment, particularly given the recent rise in paediatric iGAS cases across Europe following the COVID-19 pandemic.

Introduction

Invasive Group A Streptococcal infections (iGAS) are defined by the presence of GAS in a normally sterile site or, in a non-sterile site when associated with toxin production leading to Streptococcal Toxic Shock Syndrome (STSS). iGAS carries a mortality rate of 8% to 17%, if not promptly treated. Among the key virulence factors of GAS protein M enables tissue colonization and immune evasion, while toxins trigger the massive immune response underlying STSS. Moreover, some strains produce toxins that act as superantigens, causing a massive immune response leading to STSS. iGAS combined with STSS is associated with a higher mortality rate estimated between 30% to 70% (1,2). After the COVID-19 lockdown, several European countries reported a marked increase in paediatric iGAS cases. In France and the Netherlands, the incidence was twice the pre-pandemic levels. Pneumonia with empyema, almost always linked to a respiratory virus, was the predominant presentation. The reasons for this surge remain unclear, though early data do not indicate association with a specific protein M type (3,4). We describe the case of a child with an iGAS osteoarticular infection who exhibited early signs of STSS. This occurred in Brussels during the early

FIGURE 1: Cervicofacial injected CT Scan: axial cut (A) and sagittal cut (B).

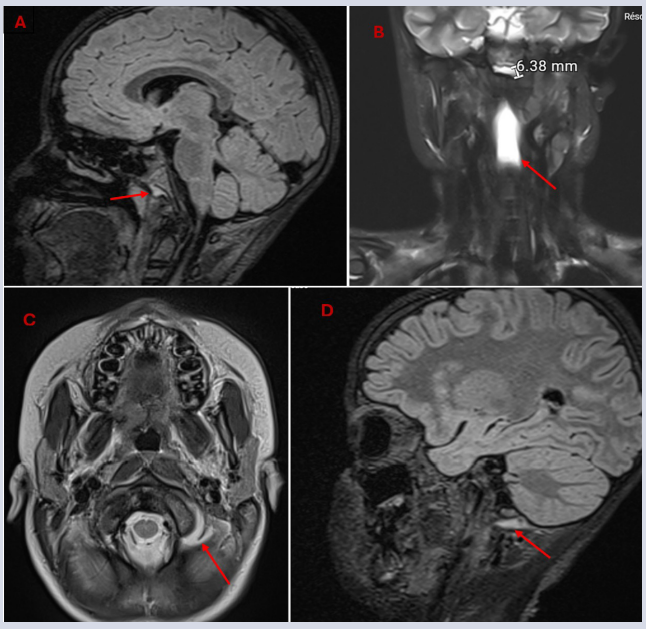


post-pandemic period and is therefore relevant in this epidemiological context. We aim to emphasise the importance of early recognition and treatment of iGAS and STSS.

Case report

A seven-year-old girl was admitted to our paediatric department after suffering from torticollis for four days. She had been scratched in the neck by another child three days before the cervical pain started. She had no history of fever, no relevant medical background, and had not travelled recently. On the first day of cervical pain, a muscular contracture was identified and symptomatic treatment was recommended. She returned to the emergency room within two days because she started vomiting and her pain worsened. The physical examination revealed torticollis with impairment of both active and passive neck mobility. No cervical mass was identified clinically. She still had no fever, no rash and no neurological impairment. However, her blood sample showed significant inflammation with a C-reactive protein level of 200 mg/L (N ≤ 5,0 mg/L) and leukocytosis of 16400/μL (N 4500-13500/μL) of which 15300/μL were neutrophils (N 1500-7000/μL). She was admitted at this point to investigate the origin of such severe inflammation in the setting of a torticollis. Intravenous analgesics were given. She developed a sudden fever of 40°C six hours after admission. A cervical CT scan with contrast injections (Figure 1) revealed multiple small abscesses at the skull base, including one anterior to the clivus. A lumbar puncture showed no cerebrospinal fluid abnormalities. An MRI scan was performed on day 4 to evaluate the extent of the infection and assess for the presence of intramedullary lesions. Presphenoidal and multiple prevertebral collections extending from C1 to C4 were detected, associated with left occipito-atlantoid arthritis (Figure 2). The blood culture returned positive for Group A Streptococcus in less than 36 hours. Empirical ceftriaxone was initiated and subsequently switched to high-dose cefazolin once GAS had been identified. Early multiorgan involvement (liver, lungs, kidney and coagulation) in the absence of haemodynamic instability raised suspicion of STSS and prompted the addition of clindamycin on day one. No soft tissue necrosis or skin rash was observed. Indeed, hepatic cytolysis peaked at five times the baseline level within 48 hours. She also had altered hepatic function, with prothrombin time (PT) at 35% upon admission. On day two she developed a capillary leak syndrome with renal impairment. She presented with oedema of the face and extremities, became oliguric (diuresis less than 0.5 ml/kg/h), and gained 4% of her initial weight. Transient hypertension was noted during this period with a systolic blood pressure of 140 mmHg (> p 99). Furosemide and nifedipine were added. Laboratory tests showed hypoproteinaemia, hypoalbuminemia (minimal at 28 g/L on day two), microscopic haematuria and

FIGURE 2: Cervicofacial MRI with multiple prevertebral presphenoidal collections (A: T1 FLAIR sagittal cut; B: T2 Coronal cut with fat suppression). Cerebral MRI with arthritis of the left occipito-atlantoid joint (C: T2 MRI axial cut; D: T1 FLAIR MRI sagittal cut).

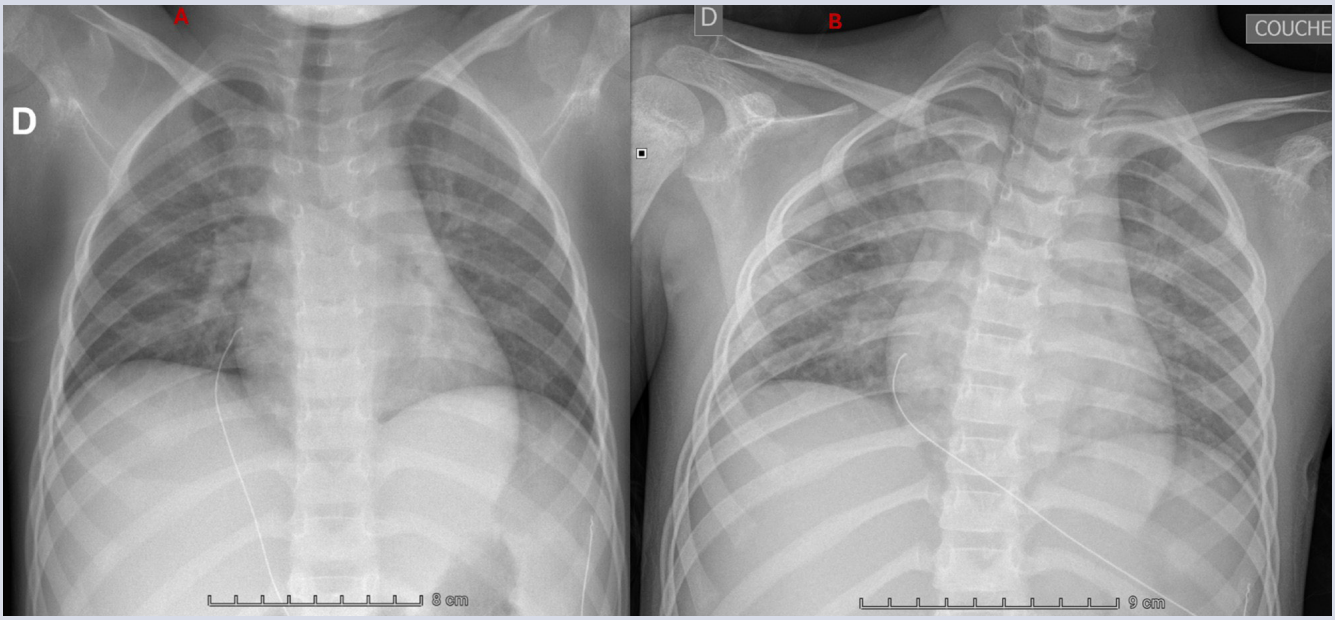


proteinuria (proteinuria/creatinuria ratio of 483 mg/g). Although her serum creatinine remained normal, the combination of these findings with addition of the renal ultrasound showing bilateral cortical hyperechogenicity suggested possible glomerular involvement. She also exhibited signs of acute respiratory distress syndrome (ARDS), with bilateral hypoventilation and desaturation to SpO2 85% requiring low-flow oxygen (maximum 2L/min). A chest X-ray on day two showed diffuse bilateral coalescent opacities (Figure 3). In this context intravenous methylprednisolone was added for three days, which allowed for a quick resolution of symptoms; oxygen was stopped after 36 hours. Echocardiography confirmed preserved cardiac function. As her clinical status improved rapidly, the administration of intravenous immunoglobulins (IVIG) was cancelled. Cytolysis was fully resolved after one week, and PT returned to normal after three days. After one week, she had regained a good general state and full neck mobility. She received high-dose intravenous cefazolin for 28 days, while clindamycin was stopped after 10 days. Household contacts received 7 days of oral cefadroxil as post-exposure prophylaxis as soon as the GAS was identified in blood cultures. A follow-up MRI scan on day 13 showed resolution of the prevertebral collection, although the presphenoidal collection and occipito-atlantoid arthritis were still present. An MRI scan on day 21 showed only partial regression of the infectious lesions, so that IV treatment was continued for a total of 28 days. The girl was then discharged with a further four weeks of oral antibiotics. An MRI scan after 8 weeks confirmed complete resolution of both the abscesses and septic arthritis.

Discussion

After the COVID-19 pandemic, a rise in paediatric iGAS was reported across Europe. iGAS may progress to severe manifestations such as STSS, whose early recognition is critical for prognosis. According to the CDC criteria, a confirmed case of STSS requires isolation of GAS from a sterile site, hypotension, and at least two additional clinical or laboratory abnormalities, including renal impairment, coagulopathy, hepatic involvement, ARDS, macular rash or soft tissue necrosis. However, these criteria were primarily designed for epidemiological surveillance and may lack sensitivity in early clinical stages. Although mandatory in formal definitions, hypotension may be delayed and should not preclude early treatment when clinical suspicion is high (2,5). In our case, iGAS was confirmed by positive blood cultures, and STSS was suspected based on multiple organ involvement (liver, lungs, kidney and coagulation). The absence of skin rash, a frequent and early sign of STSS in children, complicated the distinction between STSS and sepsis with multiorgan failure. However, the absence of haemodynamic instability prior to or concurrent with multiorgan damage was considered consistent with STSS. In STSS, the GAS toxins act as superantigens triggering uncontrolled T-cell activation and massive cytokine release through dysregulation of immune signalling pathways. This exaggerated host immune response drives organ dysfunction and contributes substantially to mortality (6). Failure to identify STSS may delay targeted toxin-suppressive interventions and worsen prognosis. Of note, although our patient did not strictly meet the CDC creatinine threshold for renal impairment, she exhibited oliguria, haematuria, proteinuria, oedema, transient hypertension, all suggestive of glomerular involvement. Toxin-mediated renal injury may precede measurable renal failure and remain clinically significant even without fulfilling formal thresholds. In our case, the favourable outcome following timely antibiotics and supportive therapy suggests that early intervention may prevent progression to haemodynamic shock. Clindamycin was promptly added on day one upon suspicion of STSS. Its efficacy lies in its ability to inhibit streptococcal toxin and cytokine production, and it also has excellent tissue penetration, particularly relevant in deep cervical infection. Unlike beta-lactams, its activity is not affected by high bacterial inoculum (Eagle effect). In combination with high-doses beta-lactams, conferring rapid bactericidal activity, clindamycin constitutes the best synergistic regimen to reduce STSS-related mortality, as highlighted by the meta-analysis of Laho et al. (7). Although bactericidal antibiotics such as beta-lactams may theoretically increase toxin release through bacterial lysis, this concern is outweighed by the well-established survival benefit of early and aggressive antimicrobial therapy, as delays are consistently associated with increased mortality. The role of intravenous immunoglobulins (IVIG) in severe iGAS, particularly STSS, remains controversial. Given their safety profile and the severity

FIGURE 3: Chest X Ray (A: the day of admission; B: on day two of the stay).



of the disease, many experts, including in our country, recommend IVIG for cases of involving haemodynamic instability, ICU admission, STSS or necrotizing fasciitis (7). Although our patient fulfilled criteria suggestive of STSS and received clindamycin, the absence of shock and the rapid clinical improvement under antibiotic therapy led to withhold IVIG administration, balancing potential benefit against uncertain evidence in non-fulminant presentations. Invasive GAS infections are often considered more difficult to eradicate and are associated with a high risk of recurrence, often justifying prolonged antibiotic courses, particularly in deep-seated infections. In osteoarticular infections, treatment duration is generally guided by radiological and clinical evolution. However, imaging abnormalities may persist despite clinical recovery. As highlighted in paediatric guidelines, this can lead to unnecessarily prolonged antibiotic therapy (8). In our case, the persistence of cervical arthritis on imaging led us to continue the treatment until resolution was achieved, given the limited reliability of clinical assessment for our patient's deep-seated infection. The recent PEGASUS study, covering 1721 paediatric iGAS cases across 14 European countries, reported a marked post-pandemic surge of iGAS with heterogeneous clinical presentations. Ear, nose and throat (ENT) infections, in particular deep cervical and head and neck infections, as in our patient, accounted for over a quarter of cases in this outbreak. Their data also illustrated the wide range of iGAS presentations, identified previous chickenpox as a risk factor and further emphasized the importance of recognising atypical or incomplete presentations of STSS (9). Our patient was infected with a strain of GAS carrying emm4 gene. This is one of the five most common protein M gene subtypes associated with iGAS. Strains belonging to this emm-type are frequently capsule negative. Flores et al. reported that such capsule-negative emm-types are increasingly associated with invasive paediatric infections, possibly through enhanced toxin production and alternative virulence mechanisms compensating for the absence of a capsule (10). In the Netherlands, a novel capsule-negative emm4 lineage was identified and associated with the post-pandemic increase in iGAS incidence, suggesting that specific genetic lineages may have contributed to this epidemiological pattern (11). In Belgium, however, data from the national surveillance system did not reveal significant pattern in emm-type distribution during this period (12). Although the absolute risk of secondary iGAS infection among contacts remains low, it is significantly higher than in the general population. This justifies targeted prophylaxis for close contacts of patients with severe GAS infection including STSS. However recommendations for post-exposure prophylaxis remain inconsistent across European countries, despite evidence supporting its effectiveness (7). In our case, household contacts received 7 days of oral cefadroxil. Current Belgian guidance also emphasises prompt case notification to health authorities, as well as prophylaxis for close contacts (12). This case highlights the diagnostic challenge of early or atypical STSS and underscores the importance of prompt recognition to guide appropriate management. Although iGAS incidence has declined following the post-pandemic surge, recent Belgian data indicate that rates remain persistently elevated in children (13). The underlying reasons for this sustained increase remain incompletely understood. This case report aims to contribute to ongoing clinical awareness and supports the need for continued surveillance and systematic reporting of iGAS to better characterize its evolving epidemiology.

Statement

Written informed consent was obtained from the parents of the children who served as subjects of this case report study.

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Belg J Paediatr. 2026;28(2): p.193-198

Dynamic Monitoring and Risk Assessment of Fatigue in Survivors of Childhood Cancer

PhD thesis presented on 24/11/2025 at KU Leuven, Leuven, Belgium

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Keywords

Childhood Cancer; Cancer Survivorship; Late Effects; Fatigue

Abstract

Background
Persistent fatigue is one of the most common and burdensome late effects in childhood cancer survivors (CCS), yet its mechanisms remain poorly understood.

Methods
This PhD combined longitudinal surveys, physical fitness testing, blood biomarkers, and real-time ecological momentary assessment with wearable monitoring in adolescent and young adult CCS, with comparisons to healthy controls.

Results
Fatigue was highly prevalent, multidimensional, and fluctuated markedly over time. Psychological distress, poor sleep, and reduced physical fitness were key modifiable contributors. Biomarker analyses revealed biological alterations and two distinct subgroups, underscoring fatigue heterogeneity.

Conclusion
Fatigue in CCS is a dynamic, multifactorial condition requiring systematic screening and personalized, multidisciplinary care.

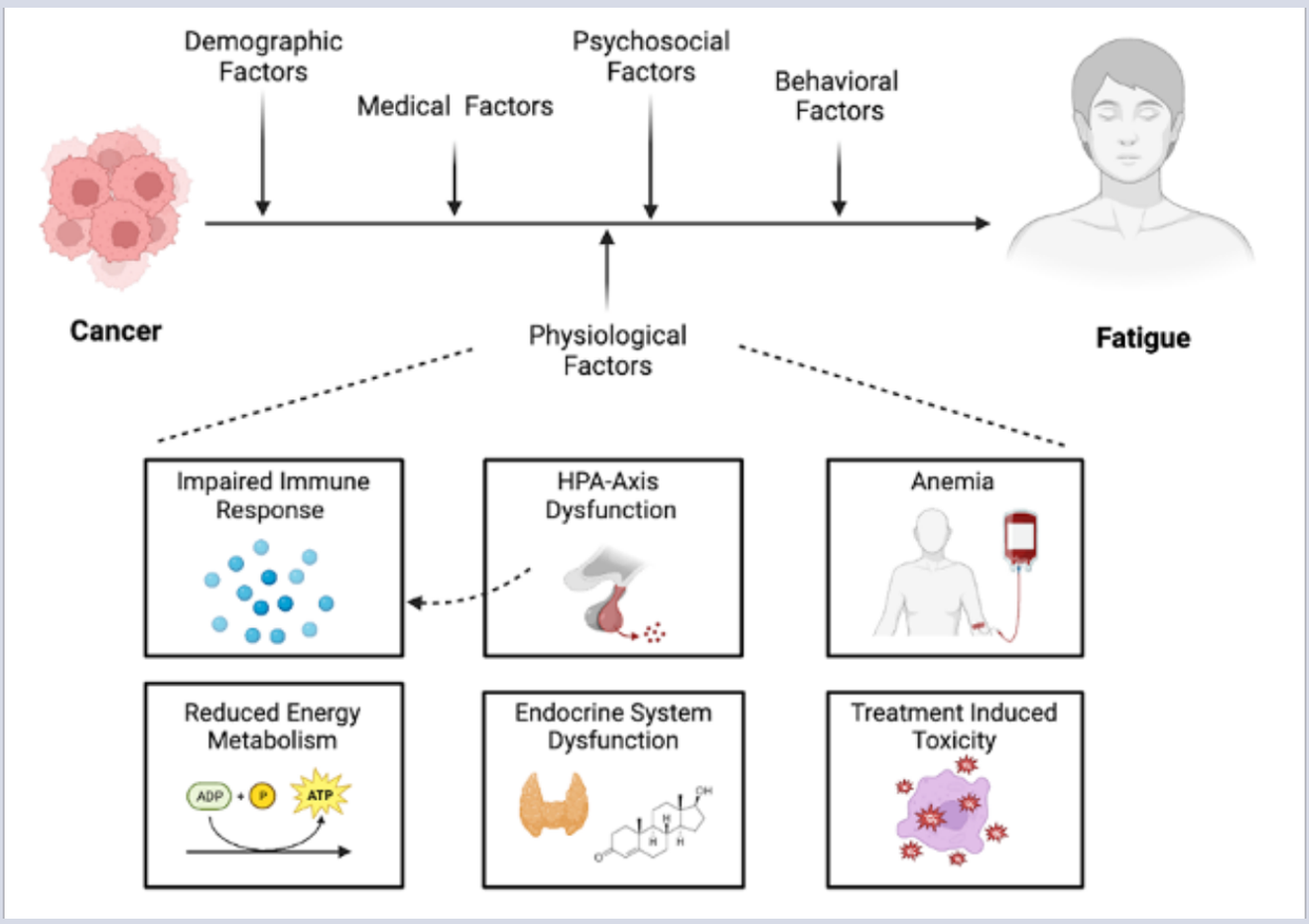
Introduction: fatigue as a key survivorship issue

Thanks to major advances in pediatric oncology, survival rates for childhood cancer now exceed 80%. As a result, increasing attention is being paid to the long-term consequences of cancer and its treatment. Many survivors experience late effects that persist well into adolescence and adulthood, affecting daily functioning and quality of life (1). Among these late effects, fatigue stands out as one of the most common and burdensome, yet it often remains underrecognized in clinical practice. Fatigue in childhood cancer survivors (CCS) is not simply a transient or benign symptom. It can persist for years after treatment completion, interfere with school participation, social engagement, emotional well-being, and cognitive functioning, and significantly reduce overall quality of life (2). Importantly, fatigue may occur even in survivors without active disease, clear medical complications, or abnormal routine clinical findings. This makes fatigue challenging to recognize, explain, and manage in routine follow-up care. The etiology of fatigue in CCS is complex and multifactorial. Psychological, behavioral factors and biological alterations all appear to contribute. Moreover, fatigue is not static: it fluctuates over time and across contexts. This PhD dissertation aimed to advance understanding of fatigue in CCS by investigating its psychological, behavioral, biological, and momentary contributors, using a combination of longitudinal surveys, physical fitness testing, biomarker analyses, and real-time monitoring with ecological momentary assessment (EMA) and wearable devices.

Fatigue is more than “being tired”

Fatigue in CCS is best understood as a multidimensional symptom. Survivors may experience physical fatigue, characterized by reduced endurance and rapid exhaustion, as well as cognitive

FIGURE: Overview of hypothesized mechanisms involved in fatigue.



The origin, duration and severity of fatigue is an interplay of physiological factors, demographic factors (e.g. sex and age at diagnosis,...), medical factors (e.g. type of diagnosis and treatment, pre-existing health conditions,...), psychosocial factors (e.g. anxiety, depression, stress, social isolation and support,...) and behavioral factors (e.g. physical activity, sleep patterns,...). This figure was created with BioRender.

fatigue, manifesting as concentration difficulties, mental slowness, or "brain fog." Emotional exhaustion and reduced motivation are also commonly reported. These dimensions often co-occur but do not necessarily evolve in parallel. In pediatric survivorship research and clinical care, fatigue is typically assessed using questionnaires that capture both a global fatigue score and domain-specific subscales. For example, the PedsQL Multidimensional Fatigue Scale distinguishes between general fatigue, sleep/rest fatigue, and cognitive fatigue (3). Such multidimensional assessment is crucial, as different fatigue domains may have different contributors and clinical implications. An additional challenge is that fatigue fluctuates markedly over time (4). Survivors frequently report variations within a single day, influenced by sleep, activity, emotional stress, and situational demands. A survivor may therefore appear relatively well during a clinic visit, while experiencing substantial fatigue-related impairment in daily life. Recognizing fatigue as a dynamic symptom rather than a stable trait is essential for adequate assessment and care.

Psychological distress as a long-term contributor

Psychological factors play an important role in fatigue among CCS. Cancer diagnosis and treatment represent potentially traumatic experiences, and a substantial proportion of survivors report ongoing cancer-related distress years after treatment completion. This includes fear of cancer recurrence and post-traumatic stress symptoms. In our longitudinal study of adolescent and young adult CCS, fear of cancer recurrence and post-traumatic stress symptoms were found to predict higher fatigue levels one year later (5). These associations persisted even after accounting for baseline fatigue, highlighting distress as a genuine risk factor rather than a mere consequence of fatigue. Survivors who worried more about their health or experienced intrusive memories related to cancer were more likely to report persistent fatigue over time. Resilience, defined as the ability to recover from stress, was associated with lower concurrent fatigue levels. However, resilience did not buffer the impact of cancer-related distress on future fatigue. This suggests that while resilience is beneficial, it may not be sufficient to offset the effects of ongoing psychological distress. For pediatricians, these findings underscore the importance of considering psychological well-being when survivors present with fatigue. Persistent fatigue should prompt questions about health-related worries, traumatic stress, and emotional burden, even years after treatment.

Modifiable behavioral and physical contributors

Beyond psychological distress, several modifiable behavioral and physical factors contribute to fatigue in CCS. Among these, sleep

quality and physical fitness emerged as particularly important (6). Compared to healthy peers, CCS reported significantly higher levels of fatigue across all domains (general (44.7% vs. 23%), sleep/rest (55.3% vs. 30.8%), cognitive (64.7% vs. 29.3%) and total (56.5% vs. 25%) fatigue). Poor sleep quality was strongly associated with higher fatigue, especially sleep/rest fatigue and general fatigue. Disturbed or insufficient sleep can exacerbate daytime tiredness, impair emotional regulation, and reduce cognitive functioning, creating a vicious cycle that maintains fatigue. Physical fitness also played a key role. Lower cardiorespiratory fitness, assessed using cardiopulmonary exercise testing (VO_2 peak), was associated with higher fatigue levels. Survivors with reduced endurance reported more fatigue, even when accounting for other factors. Importantly, fatigue was closely linked to broader outcomes, including reduced quality of life, emotional difficulties, and cognitive complaints. These findings highlight that fatigue should not be viewed in isolation. Instead, it often reflects a broader pattern of reduced physical reserve and impaired recovery. From a clinical perspective, this supports the integration of sleep assessment, physical activity promotion, and rehabilitation strategies into survivorship care.

Fatigue in daily life: insights from ecological momentary assessments and wearables

Traditional questionnaires provide valuable information about overall fatigue levels but fail to capture short-term fluctuations and contextual influences. To address this limitation, this PhD used ecological momentary assessments (EMA) combined with wearable monitoring to study fatigue as it unfolds in daily life. Using a smartphone app, CCS reported their fatigue multiple times per day, while a wearable device continuously tracked sleep, heart rate, and physical activity. These intensive measurements revealed pronounced within-day and day-to-day variability in fatigue, demonstrating that fatigue is not simply a stable background characteristic but a dynamic experience. Importantly, most variability in fatigue reflected within-person fluctuations rather than stable differences between survivors. For general fatigue, 71% of the variability occurred within individuals over time (and 29% reflected between-person differences). For cognitive fatigue, 69% of the variability occurred within individuals over time (and 31% reflected between-person differences). In other words, fatigue is not only about who is more fatigued on average, but also very much about when a survivor is more fatigued. Within-person analyses showed that sleeping longer than usual predicted lower next-day fatigue for both general and cognitive fatigue, while higher prior tension predicted higher subsequent fatigue in both domains. Importantly, recent physical activity showed opposite associations depending on the fatigue domain: taking more steps in the preceding two hours was associated with higher momentary general fatigue, but lower momentary cognitive fatigue. In addition, general fatigue increased across the day with a nonlinear late-day acceleration, whereas this diurnal pattern was not observed for cognitive fatigue. For clinicians, these results emphasize that timing and context matter. Because a large part of fatigue reflects short-term fluctuations, a single fatigue score may miss clinically relevant patterns. Fatigue complaints may depend on recent sleep, activity, and stress, which are not always apparent during clinic visits. Although EMA and wearables are not yet standard tools in clinical practice, they illustrate how fatigue monitoring could evolve toward more personalized and timely assessment.

Biological alterations and fatigue heterogeneity

Biological mechanisms are increasingly recognized as contributors to fatigue in cancer survivors. Our systematic review of the literature identified consistent associations between fatigue and inflammatory cytokines, hypothalamic–pituitary–adrenal axis dysregulation, oxidative stress, and neurotrophic alterations, although pediatric data remain limited (7). In our biomarker analyses comparing CCS to healthy controls, Gfap, total tau and MCP-1 differed between groups. Furthermore, clustering analyses revealed two biologically distinct subgroups among CCS: an inflammatory-dominant subgroup and a glial-associated subgroup. Despite these biological differences, fatigue severity did not differ between the subgroups. This finding highlights the heterogeneity of fatigue. Similar levels of fatigue may arise from different underlying biological pathways, underscoring why no single biomarker can fully explain or predict fatigue (8). Clinically, this reinforces the need for multifactorial assessment and cautions against overly reductionist explanations.

Clinical implications for pediatric practice

Fatigue should be considered a core outcome in survivorship care. Pediatricians play a key role in recognizing and addressing fatigue, particularly as survivors transition from oncology-centered care to general follow-up. Several practical implications emerge from this work: (a) fatigue should be systematically screened, even in survivors who appear medically stable, (b) persistent fatigue warrants assessment of psychological distress, sleep quality, and physical functioning, (c) because fatigue fluctuates over time, clinicians should explore patterns and triggers (e.g., time of day, recent sleep, activity, or stress) rather than relying on a single global fatigue score, (d) normalizing severe fatigue as "part of survivorship" may delay appropriate support, (e) multidisciplinary approaches, including psychological support, sleep interventions, physical rehabilitation, and guidance on

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activity pacing, are likely to be most effective. Addressing fatigue early and in a time-sensitive manner may help prevent secondary consequences such as school difficulties, social withdrawal, and reduced participation in physical activity.

Future perspectives

Looking ahead, digital tools such as smartphone apps and wearable devices offer promising opportunities for real-time fatigue monitoring and personalized intervention. Combined with biomarker-informed phenotyping, such approaches could enable earlier identification of high-risk survivors and more tailored support. Ultimately, improving fatigue management is essential for preserving quality of life and long-term functioning in this growing survivor population.

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Belg J Paediatr. 2026;28(2): p.199-202

Real-world Evidence from Diabetes Technology in Type 1 Diabetes: Towards Clinically Meaningful, Person-centered and Healthcare-informing Insights

PhD thesis presented on 28 November 2025 at KU Leuven, Leuven, Belgium

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Keywords

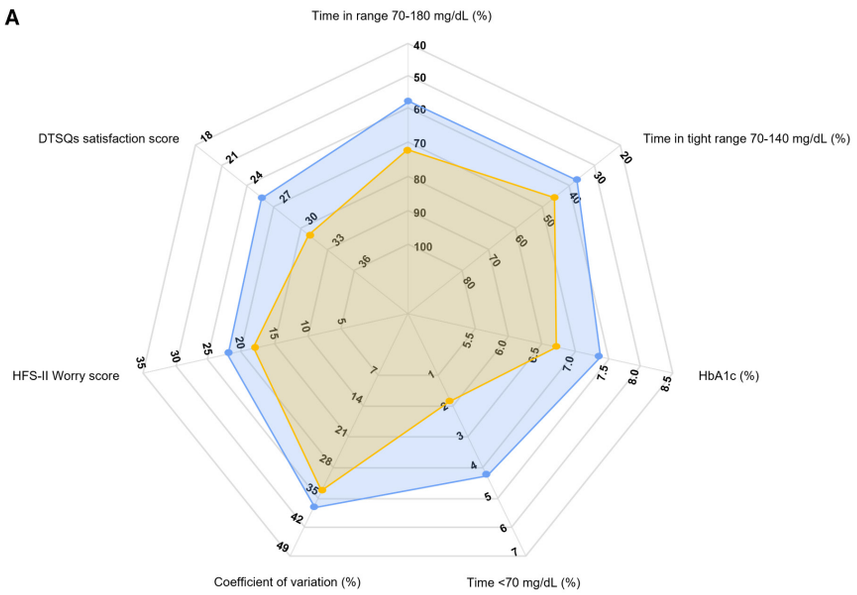
Type 1 diabetes; Technology; Real world evidence

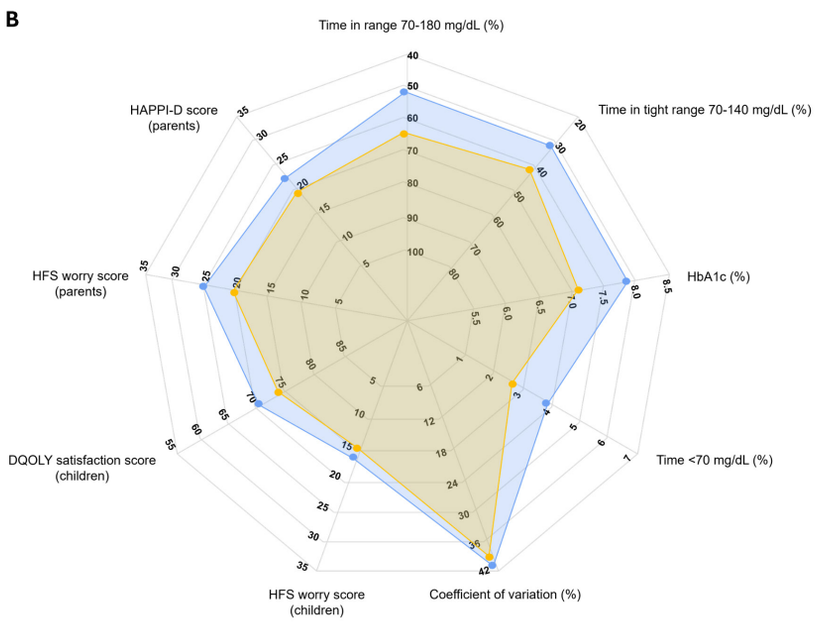
Introduction

Type 1 diabetes (T1D) is caused by a cellular-mediated autoimmune destruction of the insulin producing β-cells of the islets of Langerhans in the pancreas, leading to an absolute endogenous insulin deficiency. Consequently, people with T1D require lifelong intensive insulin therapy to manage their blood glucose levels and minimize the risk of acute (severe hypoglycaemic event (SHE), diabetic ketoacidosis (DKA)) and chronic diabetes complications (retinopathy, nephropathy, neuropathy and cardiovascular disease). Insulin can be administered via multiple daily injections (MDI) or an insulin pump, both requiring regular self-monitoring of blood glucose levels to adjust insulin doses accurately. This can be done via capillary finger pricks or continuous glucose monitoring (CGM) systems, which use a subcutaneous sensor to provide real-time glucose readings. Since the landmark Diabetes Control and Complications Trial established that high haemoglobin A1c (HbA1c; a marker for average blood glucose over the preceding 2-3 months) is strongly associated with an increased risk of developing chronic diabetes complications, monitoring HbA1c has become the gold standard for evaluating glycaemic management and guiding therapeutic decisions in people with T1D, with international guidelines recommending a target value of <7% for HbA1c. The wealth of data generated by CGM has led to the implementation of additional parameters beyond HbA1c, including the time in range parameters (time in range (TIR; glucose 70-180 mg/dL), time in hypoglycaemia (glucose <70 mg/dL and <54 mg/dL) and time in hyperglycaemia (glucose >180 mg/dL and >250 mg/dL)). These measures of short-term glycaemic management complement HbA1c by providing a more comprehensive assessment of an individual's glycaemic profile, addressing the limitations of relying solely on HbA1c. More recently, time in tight range (TITR; glucose 70-140 mg/dL) has been introduced as a marker of normoglycemia. The introduction of automated insulin delivery (AID) systems has fundamentally transformed diabetes management. By integrating CGM data with algorithm-driven insulin delivery, these pumps automatically adapt basal insulin to achieve predefined glucose targets or target ranges. However, current AID systems still require users to manually enter carbohydrate intake and accept a system-generated bolus advice at mealtimes, as well as to announce physical activity in order to appropriately adapt insulin delivery during exercise. Several randomized controlled trials (RCTs) have consistently demonstrated the superiority of AID systems over other intensive insulin regimes in improving glycaemic management, minimizing hypoglycaemia, and enhancing person-reported outcomes (PROs) across all age groups with T1D. While RCTs remain the gold standard for evaluating efficacy and safety of novel interventions, their strict inclusion criteria and controlled settings may limit the generalizability of findings to routine clinical practice. In contrast, real-world studies capture outcomes in broader and more heterogeneous populations in everyday settings, better reflecting variations in demographics, comorbidities, behaviour, and adherence.

Aim

In the context of T1D care, technologies such as CGM, insulin pumps, and AID systems are particularly powerful sources of real-world data, systematically generating detailed, high frequency information on glucose levels, insulin delivery patterns, and user behaviour. The overall aim of this PhD thesis was to leverage real-world data from diabetes technology to generate clinically meaningful, person-centred, and policy-informing evidence for people with T1D. Specifically, the current PhD research was structured around two aims: 1) to validate the clinical relevance of TITR and TIR as key measures of glycaemic management alongside HbA1c, and 2) to evaluate the real-world effectiveness, safety, usability and cost-effectiveness of AID therapy across different age groups with T1D.





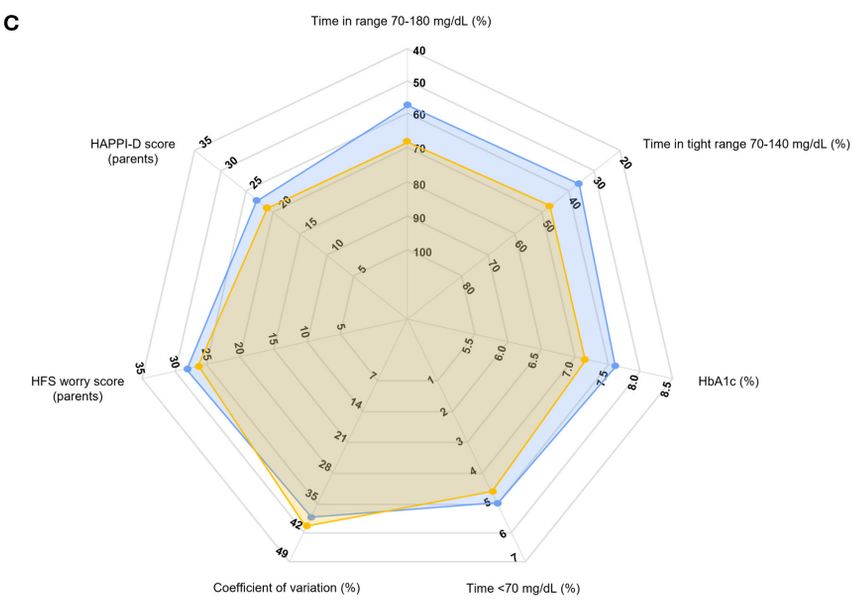
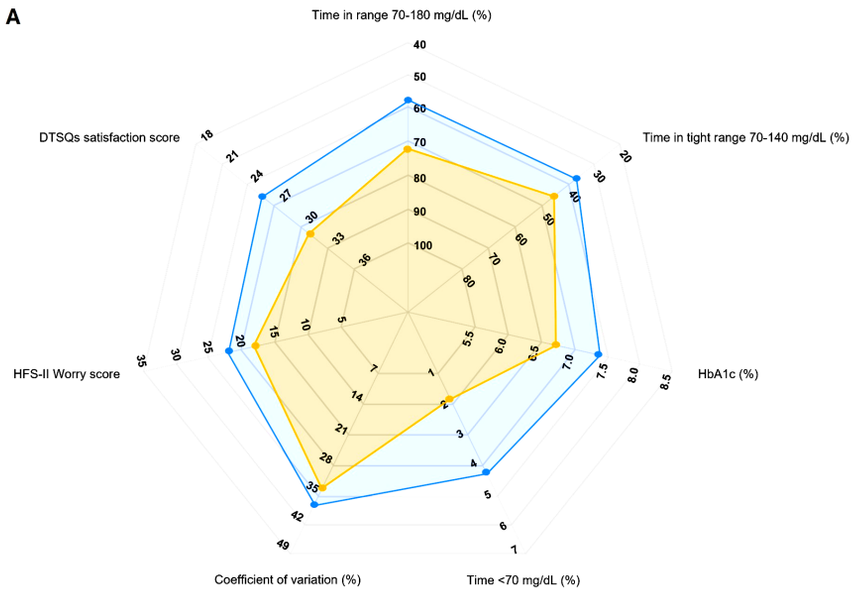
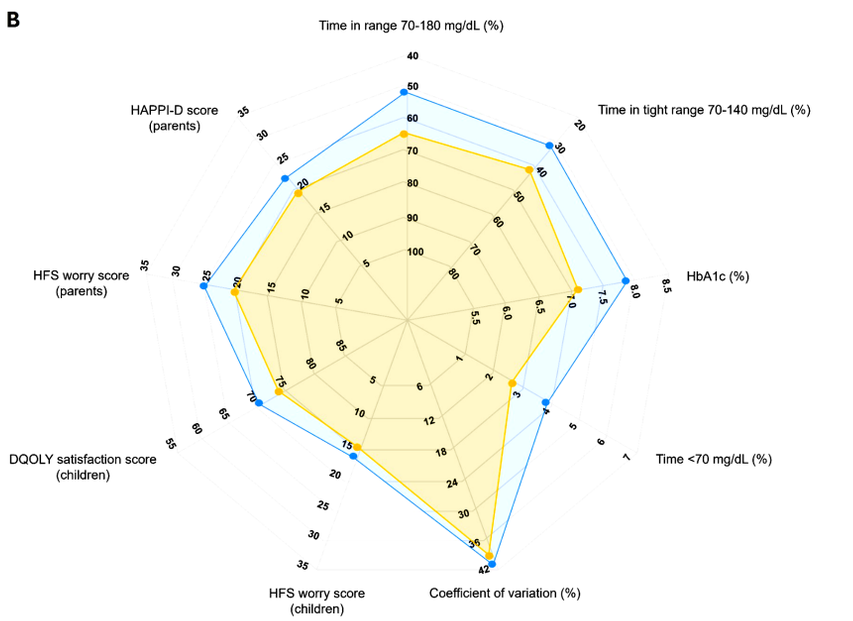
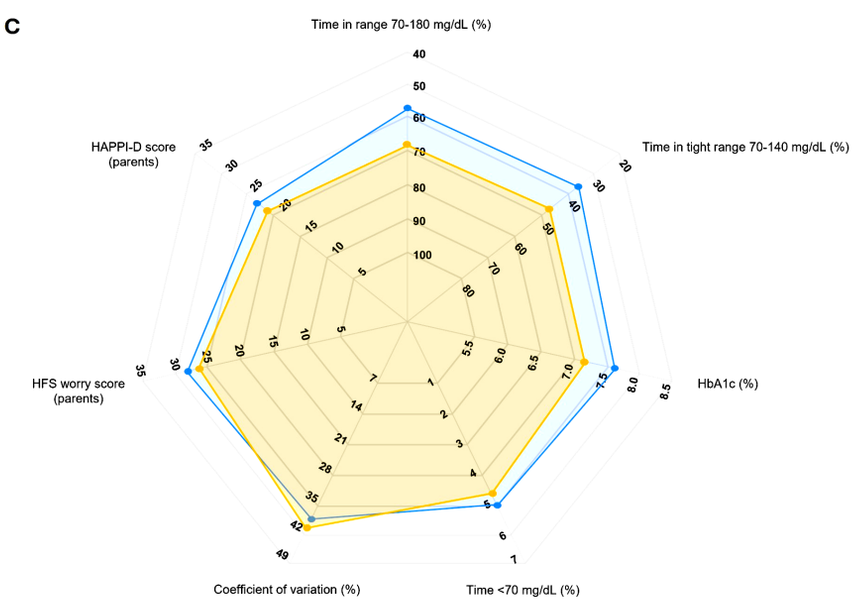


FIGURE 1: Radar plots showing the overall performance of AID systems across the three INRANGE cohorts: adults on Tandem Control-IQ (A), children aged ≥6 years on Tandem Control-IQ (B) and children aged 2-6 years on Medtronic 780G. Each axis represents a diabetes metric for which the outcomes are compared at start (blue) with those at 12 months (yellow). AID, automated insulin delivery; HbA1c, haemoglobin A1c; HFS, Hypoglycaemia Fear Survey; DTSQs, Diabetes Treatment and Satisfaction Questionnaire status; HAPPI-D, part of the HAPPI-D Protocol (Hvidøre, Adolescent, Parent, Professional, Instrument, Diabetes); DQOLY, the Diabetes Quality of Life for Youth questionnaire.


A
Time in range 70-180 mg/dL (%)
Time in tight range 70-140 mg/dL (%)
HbA1c (%)
Time <70 mg/dL (%)
Coefficient of variation (%)
HFS-II Worry score
DTSQs satisfaction score


B
Time in range 70-180 mg/dL (%)
Time in tight range 70-140 mg/dL (%)
HbA1c (%)
Time <70 mg/dL (%)
Coefficient of variation (%)
HFS worry score (children)
DQOLY satisfaction score (children)
HFS worry score (parents)
HAPPI-D score (parents)


C
Time in range 70-180 mg/dL (%)
Time in tight range 70-140 mg/dL (%)
HbA1c (%)
Time <70 mg/dL (%)
Coefficient of variation (%)
HFS worry score (parents)
HAPPI-D score (parents)

Results

To address the first aim, a cross-sectional analysis was conducted with data from 808 adults with T1D who participated in the RESCUE and FUTURE real-world studies at the University Hospitals of Leuven to evaluate the association of CGM-measured TITR and TIR with the presence of various micro- and macrovascular complications. Both TITR and TIR were found to be inversely associated with the presence of microvascular complications (retinopathy, nephropathy and peripheral neuropathy) and a cerebrovascular accident. Specifically, a 10% increase in TITR or TIR was related with 23.8% and 17.2% lower incidences, respectively, of any microvascular complication and 34.9% and 25.1% lower incidences, respectively, of a cerebrovascular accident. Our findings demonstrated that glycaemic management cannot be adequately summarized by a single metric such as HbA1c. Instead, TITR/TIR and HbA1c should be interpreted as complementary measures within a multifactorial framework to estimate complication risk and guide personalized treatment strategies (1). For the second aim, the multicentre, prospective, observational INRANGE study was set up to assess real-world changes in glycaemic outcomes and PROs over one year following initiation of AID therapy. The study included three cohorts: adults using the Tandem Control-IQ, children aged ≥6 years using the Tandem Control-IQ and young children aged 2-6 years using the Medtronic 780G. Data were collected from system initiation through 12 months of routine clinical follow-up as part of standard care. For the first cohort, a total of 473 adults on Tandem Control-IQ were included, of whom 453 (95.8%) completed the 12-month follow-up and 20 (4.2%) discontinued system use. The primary endpoint, TIR, increased from 58.8% at start to 72.1% at 4 months (p<0.001) and remained stable at 12 months (70.9%, p<0.001 vs start). HbA1c decreased from 7.4% to 6.7% and time <70 mg/dL from 4.2% to 1.9% (all p<0.001 vs start). Participants reported more diabetes-related quality of life, higher treatment satisfaction, and reduced fear of hypoglycaemia. The number of self-reported SHEs decreased significantly in the year following AID initiation (15.7 per 100 person-years [PY]) compared to the year before (37.5 per 100 PY, p=0.002). Work absenteeism declined significantly from 116 to 69 days per 100 PY (p=0.034) (2). The paediatric cohort on Tandem Control-IQ included 114 children, of whom 108 (94.7%) completed the 12-month follow-up, 5 (4.4%) discontinued system use and 1 (0.9%) was lost to follow-up. Despite lower TIR (51.6%) and higher HbA1c (7.8%) at start compared with adults, similar relative improvements were observed after one year (TIR 64.4%, HbA1c 7.1%; all p<0.001 vs start). Children were more satisfied with their current treatment and experienced less impact of diabetes on their daily life, while they reported no effect of system use on diabetes-related or hypoglycaemia-related concerns. Parents experienced less burden of diabetes on the quality of life of their child and family and they reported fewer worries about hypoglycaemia. Significant reductions in school absenteeism among children (287 vs 30 days per 100 PY, p=0.001) and work absenteeism among parents (247 vs 47 days per 100 PY, p<0.001) were observed (3). The final cohort included 114 children aged 2-6 years using the Medtronic 780G off-label at the time of the study. Over 12 months, 5 children (3.4%) discontinued system use and 2 (1.3%) were lost to follow-up. TIR increased from 56.8% to 66.6% and HbA1c decreased from 7.6% to 7.2% (all p<0.001 vs start). Time <70 mg/dL remained stable (5.0% at start vs 4.6% at 12 months, p=0.172). Use of the system was associated with a reduction in diabetes-related parental burden, whereas no significant change in hypoglycaemia-related parental fear was observed. No hospitalizations for SHEs occurred during follow-up, and one hospitalization for DKA due to infusion set occlusion was reported, supporting the safety of the system in this age group. A positive effect on school or daycare absenteeism in children (591 vs 278 days per 100 PY, p=0.006), as well as work absenteeism in parents (687 vs 430 days per 100 PY, p=0.043) was observed (4). The overall performance of AID systems across the three INRANGE cohorts is summarized in Figure 1 using radar plots. Finally, the cost-utility of Tandem Control-IQ relative to MDI and standard insulin pump therapy (both in combination with CGM) was evaluated in adults with T1D in Belgium using data from the adult INRANGE cohort as input into the validated IQVIA Core Diabetes Model. Tandem Control-IQ yielded 19.50 quality-adjusted life years (QALYs) vs 17.92 for MDI and standard insulin pump therapy plus CGM, with total costs of €193,588 and €160,129, respectively, resulting in an incremental cost-utility ratio (ICUR) of €21,111/QALY. Scenario analyses confirmed the robustness of these findings across alternative assumptions: MDI + CGM as sole comparator (ICUR: €41,701/QALY), reduced HbA1c efficacy (ICUR: €25,967/QALY), and a 20-year time horizon (ICUR: €30,183/QALY). Overall, the QALY gains achieved with Tandem Control-IQ were sufficiently large to offset the additional costs of AID therapy, keeping the ICURs below commonly accepted thresholds (5).

Conclusion

This PhD thesis highlighted the power of real-world data generated by diabetes technologies to provide clinically relevant, person-centred, and policy-informing insights into T1D care. By validating novel glycaemic metrics, confirming the real-world benefits of AID systems across different age groups, and establishing their economic value, this research bridged the gap between evidence from RCTs and routine practice. Collectively, our findings underscored the importance of integrating real-world evidence into clinical and policy decision-making, with the ultimate goal of optimizing individualized diabetes management and improving long-term outcomes for people living with T1D.

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12:45 - 13:30	Lunch
13:30 - 13:35	Opening & Introductie
13:35 - 15:00	Casussen en wetenschappelijke projecten
15:00 - 15:30	Pauze
15:30 - 16:45	Prosa: van theorie naar Praktijk naar Beleid Dr. Heidi Devos - Dr. Kate Sauer Lies Cremers - Prosa verpleegkundige UZ Leuven
16:45 - 17:30	Jeugdgezondheidszorg voor schoolgaande kinderen in Vlaanderen (VWVJ) Dr. Anouk Vanlander - Dr. Alexandra Seghers
17:30 - 18:00	Prijsuitreiking en slotwoord

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i. Les nouveau-nés et les nourrissons lors de leur première saison à risque de VRS
ii. Les enfants jusqu'à l'âge de 24 mois qui restent vulnérables à une infection sévère à VRS pendant leur deuxième saison à risque

▾Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Les professionnels de la santé déclarent tout effet indésirable suspecté. Voir rubrique 4.8 pour les modalités de déclaration des effets indésirables. **DÉNOMINATION DU MÉDICAMENT** Beyfortus 50 mg solution injectable en seringue préremplie. Beyfortus 100 mg solution injectable en seringue préremplie. **COMPOSITION QUALITATIVE ET QUANTITATIVE** Beyfortus 50 mg solution injectable en seringue préremplie : Chaque seringue préremplie contient 50 mg de nirsévimab dans 0,5 mL (100 mg/mL). Beyfortus 100 mg solution injectable en seringue préremplie Chaque seringue préremplie contient 100 mg de nirsévimab dans 1 mL (100 mg/mL). Le nirsévimab est un anticorps monoclonal humain de type immunoglobuline G1 kappa (IgG1κ) produit dans des cellules d'ovaires de hamster chinois (CHO) par la technologie de l'ADN recombinant. 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) (voir rubrique 4.4). Pour la liste complète des excipients, voir rubrique 6.1. **FORME PHARMACEUTIQUE** Solution injectable. Solution limpide à opalescente, incolore à jaune, de pH 6.0. **INDICATIONS THÉRAPEUTIQUES** Beyfortus est indiqué pour la prévention des infections des voies respiratoires inférieures dues au virus respiratoire syncytial (VRS) : - Chez les nouveau-nés et les nourrissons au cours de leur première saison de circulation du VRS. – 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 administré par voie intramusculaire pour les nourrissons dont le poids est <5 kg et une dose unique de 100 mg administré par voie intramusculaire pour les nourrissons dont le poids est <5 kg. Beyfortus doit être administré 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 sasion 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 contrôlés sont répertoriés par classe de systèmes d'organes (SOC) MedDRA. Au sein de chaque SOC, les termes préférentiels sont présentés par fréquence décroissante puis par gravité décroissante. La fréquence de survenue de chaque effet indésirable est définie comme suit : très fréquent (≥1/10) ; fréquent (≥1/100 à <1/10) ; peu fréquent (≥1/1 000 à <1/100) ; rare (≥1/10 000 à <1/1 000) ; très rare (<1/10 000) et fréquence indéterminée (ne peut être estimée à partir des données disponibles). Affections du 1 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 nourissons 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). Enfants qui demeurent vulnérables à une infection sévère due au VRS au cours de leur deuxième saison de circulation du VRS La sécurité d'emploi a été évaluée au cours de l'étude MEDLEY chez 220 enfants porteurs de maladie pulmonaire chronique du prématuré ou d'une cardiopathie congénitale hémodynamiquement significative qui ont reçu du nirsévimab ou du palivizumab au cours de leur première saison d'épidémie à VRS et qui ensuite ont reçu du nirsévimab lors de leur deuxième saison d'épidémie à VRS (180 sujets ont reçu du nirsévimab pendant les saisons 1 et 2, 40 ont reçu du palivizumab pendant la saison 1 et du nirsévimab pendant la saison 2). Le profil de sécurité du nirsévimab chez les enfants l'ayant reçu pendant leur deuxième saison d'épidémie à VRS était 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 (IVRI 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 : 03/2026. Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu

VRS, virus respiratoire syncytial; **IVRI,** Infection Virale Respiratoire Inférieure
*pendant leur première saison VRS **Remboursement unique pour la première saison VRS et chez les jeunes enfants (<2 ans) qui subissent une chirurgie cardiaque avec circulation extracorporelle pendant leur première ou deuxième saison VRS, ou les jeunes enfants (<2 ans) qui restent vulnérables à une maladie grave due au VRS pendant leur deuxième saison VRS, (comme décrit dans les recommandations du CSS (avis 9760)). Administration avant le début de la saison VRS ou dès la naissance pour les nourrissons nés pendant la saison VRS.

Reference: 1. Beyfortus®. Résumé des Caractéristiques du Produit (RCP) de l'UE, 03/2026

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