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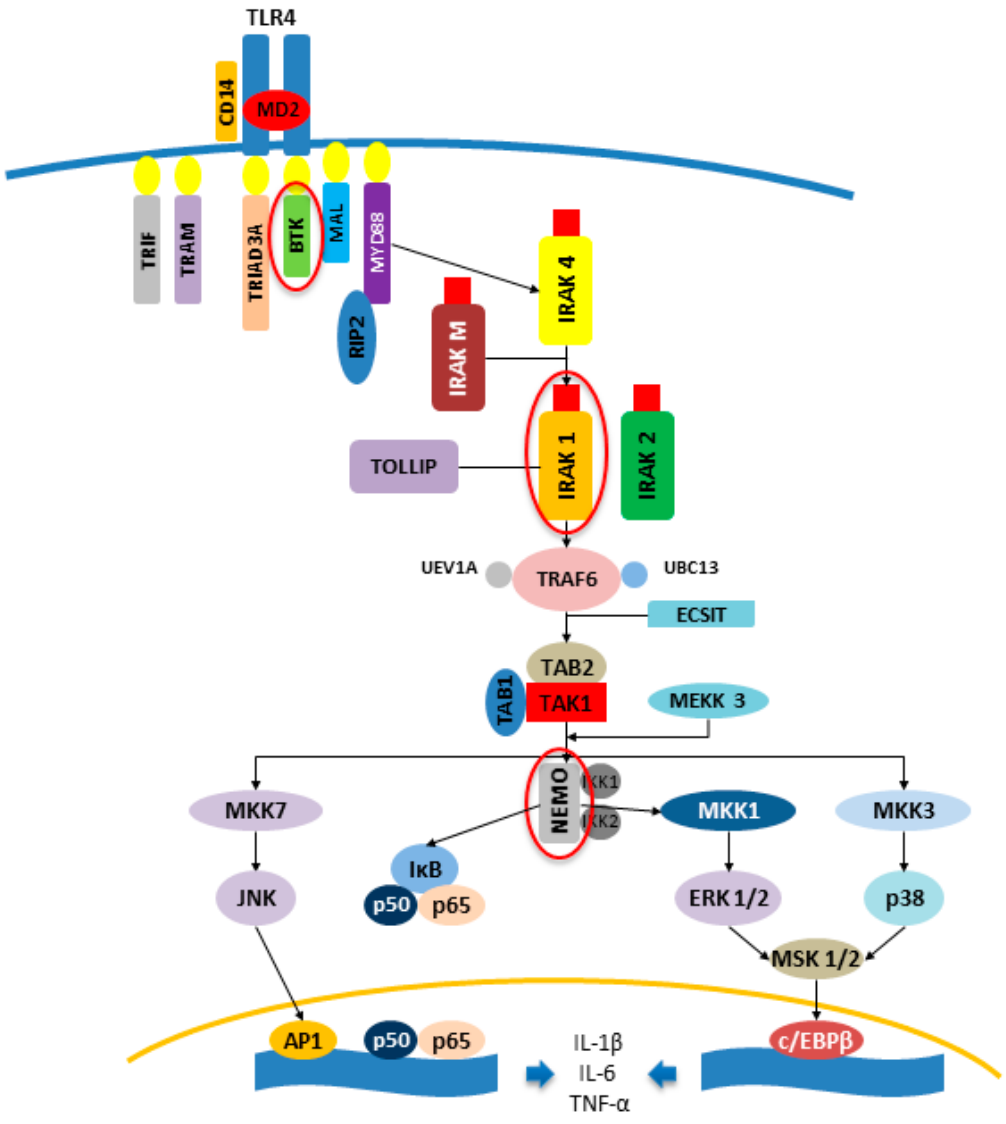





Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

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# Editorial

Dear Colleagues,
For many of us, the past few weeks will be clouded by sad feelings.
We are indeed in deep mourning.
One of our colleagues, Dr Wivine Marion, neonatologist in CHC, Rocourt and Namur was brutally killed on November 1th 2018. We refer to the hommage in this issue by Pierre Maton, CHC-Rocourt and Elisabeth Henrion, CHC-Namur. They make a call to cultivate: "l'éducation à la parentalité, le respect de l'autre, en particulier du sexe opposé".
On October 31th 2018 professor Linda De Meirleir, specialised in pediatric neurology and metabolic diseases, and head of the UZ Brussel Paediatric Neurology, passed away. In the tribute written by our president, Anne Malfroot, Linda is described as "a remarkably courageous, dynamic, no-nonsense multitasker and as a deeply dedicated, caring an beloved colleague, mother, and wife who lived a rich life full of joy, laughter, and love".
On behalf of the editorial board and the whole pediatric community we present to their closests relatives and families our sincere condolences. The crying emptiness in our heart will be filled by warm memories.

In our peer-reviewed Belgian Journal of Paediatrics a diversity of manuscripts is published: Original Articles, Reviews and State of the Art papers, Short Communications, Case Reports. Our traditional and recurring sections are well known: Theme's, Campaign, Surgeon's Corner, Made in Belgium, Paediatric Cochrane Corner.
In the current winter issue of the BJP we launch a new topic: ***"Focus on Symptoms"***.
Starting from common complaints and symptoms with which clinicians are regularly confronted, the author offers a short, schematic or algorithmic approach.
***We kindly invite our readers to send us proposals for further topics.***
Two interesting manuscripts deal with diagnosing Mycobacterial infections in children, with data about local experience. One of two consecutive manuscripts deals with diagnosing. The second contribution will be published in our next issue. In another original paper, guidelines and a risk assessment tool are described for the follow-up of children with pulmonary arterial hypertension .
A case report draws our attention on therapeutic "like-a-looks", with possible dangerous complications.
On occasion of the past World Prematurity Day , 17th November 2018, a short communication highlights this year's motto: "Working together: Partnering with families in the care of small and sick newborns".
That men and women are different doesn't need much discussion. In our current Made in Belgium authors focus on the role of the X chromosome in sex differences in pediatric inflammatory diseases. Very exciting!
In the Cochrane Corner Section the recent update regarding glucocorticoids for croup is presented and commented

The editorial board and the secretary wish to thank all the authors, guest editors and especially the dedicated reviewers for their commitment to the BJP during the past year. We are convinced that this official publication of the Belgian Society of Paediatrics responds to a need to unite in a scientific way Belgian researchers, trainees and health care professionals involved in the care, well-being and prevention of diseases in infants, children and adolescents in Belgium. Communication on homegrown research and local experiences stimulates and supports each other. The BJP also offers an easy accessible national forum to interesting and practice-oriented scientific papers in paediatrics in addition to other international and sometimes more subspecialised sources.

Via the website, members of the Belgian Society of Paediatrics have access to the online version of the BJP, CEBAM, E-learnings, protocols, guidelines, information about awards and prices, educational and training courses, congresses and power point presentations.

We hope that the last issue of the year 2018 will pique the scientific and clinical interest of our readership.

**Don't forget to register for the next annual congress of the Belgian Society of Paediatrics. March 21-22, 2019 : The Egg, Brussels**

On behalf of the editorial board, we wish you all a very happy and prosperous New Year, with a lot of pleasant experiences.
Nadine Francotte, Mark Wojciechowski, Anne Rochtus, Christophe Barrea, Natacha Meignen.

Samy Cadranel and Marc Raes, chief editors

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

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

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# Obituary

## TRIBUTE TO Prof. Dr. LINDA DE MEIRLEIR
## 1954-2018

It is with immense sadness that we announce our much loved and highly appreciated colleague Linda De Meirleir, pediatric neurologist, passed away October 31, 2018, after a long and courageous battle with illness.

She was the founder and the head of the Paediatric Neurology Clinic and Metabolic Diseases of the UZ Brussel.

She was happily married to Jacques De Greve and mother of Laura and Ben.

She obtained her medical degree at the Vrije Universiteit Brussel in 1979 and became a specialist in Neuropsychiatry in 1984. Subsequently she was accepted as a clinical fellow in Paediatric Neurology at the Hospital for Sick Children, University of Toronto, Canada 1984-1985, and received a Foreign Research Fellowship Award from the Hospital for Sick Children Foundation Toronto 1985-1986. Her research resulted among other in the characterization of the pyruvate dehydrogenase E1 alpha subunit gene in patients with a pyruvate dehydrogenase complex deficiency. Returned to Brussels, she continued her research and obtained in 1993 her PhD in medical sciences at the VUB, under the supervision of Prof. Brian H. Robinson. In 1997 she obtained her specialization degree in Paediatric Neurology.

Her main scientific activities involved the intensive investigation of inborn errors of metabolism resulting in congenital lactic acidose syndromes including the clinical, biochemical and molecular aspects of mitochondrial respiratory chain defects and pyruvate dehydrogenase deficiency and also in lysosomal storage disorders.

But Linda was more than an excellent scientist and clinician. She was a committed ambassadress of pediatric neurology and metabolic disorders around the globe, to ensure patients received the best possible care. She was a women of action: problems were to be solved, challenges to be met. Whenever she had the occasion, she would stage the international pediatric neurology scene for her colleagues here in Belgium. She was the founder and President of the metabolics.be and a long-time President of the Belgian Society of Pediatric Neurology BPNS.

She served as a member of several International Working Groups for mucopolysaccharidoses, mitochondrial disorders, urea cycle disorders, and organic acidurias to develop consensus statements and improved standards of care for newborn screening, diagnosis, management and interventional clinical trials in children with these rare disorders. She was an active member of multiple International Societies and Networks in the field among which the European Paediatric Neurology Society EPNS and the International Child Neurology ICNA.

She was the head of the UZ Brussel Paediatric Neurology team that she built and trained, including a lot of colleagues who moved to other places to promote expertise in Paediatric Neurology throughout the country and beyond. She was able to make the most of others, appreciating and respecting them, and to focus the energies of their co-workers and colleagues on a common objective. She was a highly energetic and dynamic team builder and spearheaded the development of the multidisciplinary Centers for Developmental Disorders, Metabolic Diseases, Neuromuscular Diseases and a clinic for Learning Disabilities in addition to general Pediatric Neurology, expanding her Division from a staff of two to 40 members. Linda was also Director of the Brussels Neonatal Screening Center from 2012 and Director of Rare diseases UZ Brussel from 2017.

In Belgium, but also from the international community, she is appreciated not only for her professional, but especially for her human qualities: "Above all, Linda had a great heart and generosity of spirit that touched all of those who knew her and for whom she made the world a brighter place. She was a person of rare integrity, quiet dignity and deep humanity, which was present in all of her actions, with a vibrant creative mind which, when combined with her intense dedication, energy, and advocacy, led to her many successful altruistic endeavors. Linda is recognized internationally for her excellence as a highly gifted and compassionate clinician and inspirational teacher as well as a strong clinician-researcher who has impacted the lives of so many children and their families within Belgium and throughout the world, as well as those of her colleagues and the many trainees she has fostered. Linda will be remembered as a remarkably courageous, dynamic, no-nonsense multitasker and as a deeply dedicated, caring and beloved colleague, mother, and wife who lived a rich life full of joy, laughter, and love. She was devoted to her family and her friends and an ardent sailor with a true 'joie de vivre'. A peacekeeper and a passionate unifier. "as wrote Dr. Ingrid Tein, president of the International Child Neurology Association, in her international tribute*.

We have lost a colleague who enjoyed the respect and appreciation of everyone who knew her.
We will continue to pay tribute to her legacy, she will always be with us.
Our hearts and thoughts go out to her husband and her children.

Anne Malfroot
President Belgian Society of Paediatrics

*Source https://icnapedia.org/explore/articles/news/entry/2018/11/04/linda-joanna-de-meirleir-1954-2018

# Obituary

## Wivinne Marion 1.4.1976-1.11.2018

Comment imaginer devoir écrire un jour l'éloge funéraire d'un membre de son équipe arrachée à la vie dans d'aussi odieuses circonstances. Sans doute, est-ce nécessaire avant tout pour ne pas que sa vie se résume à un affreux fait divers. Parce qu'au-delà de la peine, de la douleur, mais aussi de la colère, il reste la joie de l'avoir connue et la chaleur de souvenirs.

Le Dr Wivinne MARION a profondément marqué chacun des services où elle a travaillé. Assistante déjà, son style « détonnant » interpellait mais très rapidement son dynamisme, son envie d'apprendre et son intelligence brillante effaçaient tout le reste. Elle développe assez vite une attirance marquée pour la néonatologie, discipline où ses qualités humaines et sa soif d'exigence allaient pouvoir s'épanouir au mieux.

A la fin de sa formation, après un an passé dans le service néonatal de Rocourt, elle décida de parfaire sa formation en néonatologie au CHUV de Lausanne pour explorer au mieux les techniques d'investigations en neurologie périnatale. Comme à cœur vaillant rien n'est impossible, c'est avec un fils encore nourrisson et son mari en formation en France qu'elle partit à l'assaut de la Suisse, avec l'aide précieuse de sa maman, marque déjà de l'importance qu'elle attachait à la famille, ce que sa famille lui rendait bien.

Après un an de *fellowship*, riche de nouvelles expériences, elle a rejoint l'équipe du NIC de Rocourt. Pendant 10 ans, elle fut sur tous les fronts. Entre l'échographe et le *Cerebral Function Monitoring* (CFM), le cerveau de nos tout petits n'avait plus de secret pour elle. Elle a aussi beaucoup réfléchi à la nutrition néonatale et son importance pour la croissance cérébrale. Toujours désireuse d'apprendre, elle voulait aussi transmettre : avec beaucoup de patience et un esprit de synthèse remarquable elle a créé à Rocourt le « vademecum du service néonatal », dont profitent encore aujourd'hui toutes les équipes partenaires du service. Non contente de cela, elle assurait également une consultation de l'ONE (de nouveau la famille : bon sang ne pourrait mentir, avec une maman elle-même TMS).

En 2015, lassée des trajets quotidiens vers Liège, et désireuse de rendre à sa famille un peu du temps que son métier lui prenait, c'est au NIC du CHR de Namur qu'elle décida de poursuivre sa carrière. Fidèle à elle-même c'est avec enthousiasme et passion qu'elle s'occupa des petits Namurois. Elle en profita pour vivre d'autres aventures, notamment l'enseignement puisqu'elle dispensa des cours de néonatologie à la Haute école de la Province dès l'année académique 2015-2016. Ses élèves comme ses collègues et les membres de son équipe, tous étaient ravis. Que dire de ses patients…

Nous avions l'impression que dans sa ville natale, elle coulerait à jamais des jours tranquilles. Mais Wivinne n'était pas femme à se contenter du quotidien d'un travail. Une autre passion la titillait de plus en plus. Les revues de couture se mêlaient aux revues scientifiques, la machine à coudre côtoyait le stéthoscope : d'abord des déguisements pour ses enfants, puis des blouses, des robes et bien plus encore, ...une petite entreprise naissait.

Cette vie d'enthousiasme et de projets s'est arrêtée brutalement ce 1er novembre, lors d'un jogging matinal qui ressemblait à tous les autres. Au-delà de la peine, de la colère, des souvenirs, cette disparition horrible doit nous confronter à nos choix de vouloir en faire toujours plus pour nos patients. Cultivons l'éducation à la parentalité, au respect de l'autre, en particulier du sexe opposé. Renforçons la prévention chez l'adolescent contre l'abus d'alcool et de substances illicites. Donnons ces clés aux enfants et aux adolescents d'aujourd'hui, ils seront les adultes de demain.

Pour Wivinne, in memoriam.

Dr. Pierre Maton
Service de néonatologie
CHC-St Vincent
207 rue F. Lefebvre - 4000 Rocourt

Dr. Elisabeth Henrion
Pédiatre-Néonatologue
CHR de Namur
185 Avenue Albert 1er - 5000 Namur


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# DYNAMICS IN PEDIATRICS

21 & 22.03.2019

THE EGG, Brussels

www.bvksbp2019.be

BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE
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**Registrations opening**
15 October 2018

**Abstracts submission deadline**
21 December 2018

**Organizing Committee (UZ Leuven):**

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Gunnar Buyse, MD PhD
**Congress President, UZ Leuven**

Anne Malfroot, MD PhD
**President BVK/SBP**

# Save the date

## January 26, 2019

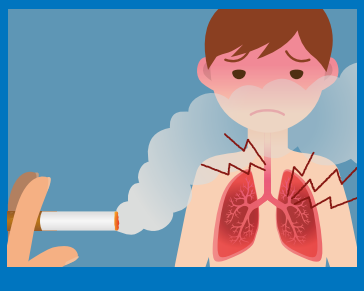
Invitation à la Matinée Liégeoise de Pneumologie et Allergologie Pédiatrique - site Citadelle

# Matinée Liégeoise de Pneumologie et Allergologie Pédiatrique

Samedi 26 janvier 2019 - De 8h30 à 12h30

CHR Liège - Salle Cathédrale (route 012)

Boulevard du 12ème de Ligne 1 - 4000 Liège

## PROGRAMME

| | |
|---|---|
| 08h30 | Accueil Café |
| 09h00 | Introduction - *Dr H. Boboli, pneumologue pédiatre* |
| 09h15 | L'asthme en âge pré-scolaire : que dire aux parents ?<br>*Dr A. Janssen, pédiatre, en formation de pneumologie pédiatrique* |
| 09h55 | Allergie à l'œuf et vaccination : il ne faut plus choisir !<br>*Dr A. Van Rymenam, allergologue pédiatre* |
| 10h35 | Tabac et pédiatrie : pour une génération sans fumée ...<br>*Dr I. Jamin, cardiologue, tabacologue*<br>*C. Collard, infirmière pédiatrique, tabacologue* |
| 11h15 | Pause Café |
| 11h30 | Ateliers pratiques - Choix entre 2 ateliers<br>Atelier 1 : Épreuves fonctionnelles respiratoires<br>Atelier 2 : Dispositifs et chambres d'inhalation<br>Atelier 3 : Éducation thérapeutique : Mesures d'éviction des acariens |
| 12h30 | Fin |

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# May 23, 2019

## 7th Symposium of Ethics in the Neonate and the Child

## "Fetal Abnormality: from TOP to bottom"

C.H.U. *de Charleroi*

To pinpoint the most controversial aspects of the management of severe fetal anomalies - from termination to continuation of pregnancy - we will have the honour to welcome fetal medicine experts like Prof **Catherine DONNER** (Brussels) and Prof **Eva PAJKRT** (Amsterdam), experts of neonatal medicine such as Prof **Jean-François MAGNY** (Paris) and Dr **Pierre BÉTRÉMIEUX** (Rennes), but also a perinatal pedopsychiatrist Prof **Luc ROEGIERS** (Brussels), a philosopher Prof **Michel DUPUIS** (Brussels, Paris) and a lawyer, Me **Sylvie TACK** (Gent, Antwerpen), all involved in this specialized field.

Yet we also count on **Eric BOEVER**'s verve, journalist at RTBF, on the interviews of parents confronted with these realities, and of course on the public's active participation to animate this today's debate.

Looking forward to seeing you there,

Serge VANDEN EIJNDEN, Eric CAVATORTA NICU, CHU Charleroi

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# Formation FAPS

# 2019 - 2020

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There are ten 2-day modules from January 2019 to February 2020.

The formation offers a high level of training, given by Belgian and French experts.

Therapy theory and practice, as well as sharing experiences, are the pillars of this formation.

Ethical consideration is also very important.

A University certificate (ULB) is obtained at the end of the formation.


Contact : FAPS asbl • Mme Marion Faingnaert • Marion.faingnaert@gmail.com
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# Challenges in Diagnosing Mycobacterial Infections in Children.

Siel Daelemans, Linde Peeters, Hanneke Eyns, Elke De Wachter, Anne Malfroot

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## Key words

tuberculosis, non tuberculous mycobacteria, children

## Abstract

Mycobacterial infections are an important disease worldwide. Tuberculosis (TB) is the best known, being a leading cause of human morbidity and mortality. In addition, nontuberculous mycobacteria (NTM) are emerging as globally significant pathogens, especially in developed countries and in particular in children.
Diagnosis of mycobacterial infection is challenging, especially in children, as they can present with unspecific symptoms mimicking other infectious or non-infectious diseases. Other challenges and difficulties include obtaining specimens for culture, microbiological confirmation and identification of the mycobacterial species.
A case series of eight recent cases illustrating these challenges is presented

## Introduction

The *Mycobacterium* genus is a diverse group of bacilli consisting of multiple different species, with the newest identified species being discovered only in recent years. They belong to the acid- and alcohol-fast Gram-positive organisms.[1]

The most important impact on human morbidity and mortality worldwide is caused by the *Mycobacterium tuberculosis* complex, which contains multiple species (such as *Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum*, etc.) and causes tuberculosis (TB). *Mycobacterium leprae* is a related species, causing leprosy. These species cannot exist as free-living organisms in nature and are transmitted person-to-person.[1-6]

Another group of *Mycobacteria spp.* are the nontuberculous mycobacteria (NTM), a broad classification of approximately 186 species, with the majority of disease in humans being caused by fewer than twenty species.[3,7] They differ from the *M. tuberculosis* (*Mycobacterium tuberculosis*) complex in epidemiology, pathophysiology, clinical manifestations and therapy.

Mycobacterial infections can mimic many other infectious and non-infectious diseases.[4,7-9] In low-incidence countries there is limited awareness of mycobacterial infections in children among health care workers. Knowledge of the extend of mycobacterial infections is essential for correct diagnosis. Therefore, an overview of pathophysiology and clinical presentations is provided and pitfalls in diagnosis are illustrated based on some recent cases of a single centre.

### Epidemiology of mycobacterial infections

Although the global incidence of **TB** is declining worldwide, it is still the ninth leading cause of death, and the leading cause from a single infectious agent, ranking above Human Immunodeficiency Virus (HIV).[10] The fastest decline of TB is seen in low incidence countries, like Belgium where incidence was 10/100 000 persons per year in 2016, with 100 new cases of children (<15 years of age) that same year.[11] However, in large capital cities of several low-incidence European countries a disproportional high rate of TB has been noted in recent years, due to an increase of TB among vulnerable groups (for example migrants, prisoners, drug users or homeless people).[12,13] TB in children, especially below five years of age, suggests recent transmission of infection by an adult, although the child is often the first diagnosed. Therefore childhood TB is a proxy measure of TB infection control in the community.[4] Notification of TB is mandatory worldwide.[5,14]

The notification of NTM infection cases, on the contrary, is not mandatory.[5] Literature on NTM infections in humans is therefore limited (in contrast to TB).[7] This hampers the accurate knowledge of the impact of **NTM** infections on public health. Nevertheless, it is largely accepted that in western developed countries the prevalence of these infections is growing, especially in children, whereas TB follows the opposite trend.[1,2,5,7] Incidence in children is reported between 0,6 – 2,1/100 000/year.[7]

### Pathophysiology of mycobacterial infections

**NTM** are ubiquitous in the environment, and can be found in water (fresh or salt water, but also in tap water or showerhead sprays), soils, domestic and wild animals, milk and food products.[2,3,5,7] Some are rapid growing (e.g. M. abcessus), others are slow growing (e.g. M. avium).[1,2,5] The mode of **transmission** is inhalation (causing pulmonary infection and possibly lymphadenitis), ingestion (possibly causing lymphadenitis) or direct inoculation to the skin or subcutaneous tissue as a result of trauma.[5,7] It was previously thought that human-to-human transmission of NTM infections does not occur. However, this has been observed in patients with cystic fibrosis (CF).[5,7] Except for reciprocal separation of patients with CF, isolation of an NTM-infected child and contact tracing is unnecessary.[1]

On the contrary, **contamination** of **TB** occurs mostly by inhalation of aerosolized drops produced by someone with pulmonary (open) TB, usually an adult who lives in close contact with the child.[8,13] Therefore contact investigation of close-contacts and households of the child and the primary source are important to avoid further spread of the disease.[13,14] TB infection occurs in phases. After contamination, a symptom-free period will occur in which the **primary complex** (or Ghon focus) will form at the entrance and the proximal lymph node. Haematogenic and lymphogenic spread will lead to secondary foci. In immunocompetent adults, the response of the innate immune system will be strong enough to resolve the primary complex and/or secondary foci. A small number of mycobacteria will slumber and can become **reactivated**, after a variable period (**latent period**), and cause disease.[8,13] In infants, children younger than 5 years of age and immunocompromised patients, rapid progressive primary disease may occur. These patients often have paucibacillary disease and a limited ability to cough. This makes them little contagious and complicates microbiological confirmation of disease. Reactivation disease ("adult-type" or open pulmonary TB) occurs more often in adolescents and adults, with multibacillary disease and development of caverns in the lungs.[8,13]

### Clinical manifestations of mycobacterial infections.

**Latent TB** is defined as tuberculous contamination without clinical or radiological signs of the disease. In this phase treatment is important to avoid progression to active disease.[8,13] In **active TB**, the child will have clinical signs and symptoms and/or radiographic changes. The most common symptoms are unspecific: fever, malaise, weight loss or poor weight gain, loss of appetite, chronic cough, and sometimes night sweats. Slow growing lymphadenitis can also be a first sign of disease.[8,9,13] **Different organs can be affected in active TB** and more than one organ can be involved: pulmonary disease, extra-pulmonary disease (which can present in any organ) including tuberculous meningitis, and miliary TB (when haematogenic spread occurs). Pulmonary disease is the most common form. Based on radiographic and bronchoscopic findings this form is further differentiated in gangliopulmonary TB, endobronchial TB (with visualization of granuloma's or caseum on bronchoscopy), fibrotic lesions, pleural effusion, and adult-type or open pulmonary TB.[8]

As in TB, **NTM infections** can occur in any organ.[1] Isolated lymphadenitis is the most common form of NTM disease in children, followed by skin and soft tissue infections and pulmonary NTM disease.[7] The majority of children with NTM lymphadenitis are previously healthy children without underlying immunodeficiency and are typically under five years of age.[1,5,7] This in contrast to TB lymphadenitis, which most commonly affects teenagers and young adults.[7] Contrary, the majority

of children and adolescents with pulmonary NTM disease have underlying lung disease, such as CF, bronchopulmonary dysplasia or primary ciliary dyskinesia.[1,5,7] Disseminated NTM disease occurs almost exclusively in immunocompromised children, and can be rapidly progressing and fatal.[1,5,7] Therefore, disseminated disease warrants detailed immunological investigations.[1,7]

### Diagnosing mycobacterial infections

Diagnosis of mycobacterial disease in children is **challenging**, especially in infants and young children (<5 years), who are at particular risk for disease and adverse outcomes.[17] Gold standard for diagnostic confirmation is culture (on a mycobacteria-specific medium). Due to the paucibacillary nature of mycobacterial infections in children, diagnosis is often made based on clinical suspicion, combined with results of immunologic testing, radiologic findings, possible exposure history and culture confirmation.[4,18] Difficulties arise in every step of this diagnostic process. The aim of this study is to illustrate the challenges in diagnosing mycobacterial infections in children, by a series of recent cases from a single centre.

**Tuberculin skin testing (TST)** is an intradermal injection of purified protein derivative (PPD), a heterogeneous mixture of more than 200 mycobacterial peptides, some of which are expressed by both M. tuberculosis and NTM. This test is used to show immunologic response of the body to mycobacteria. A positive TST result can occur in both TB and NTM disease. The incubation period from infection to skin test conversion by the TST is usually two to twelve weeks after infection with a mycobacterium.[7,8,13,15,16]

Another immunologic test is the interferon-gamma release assay (IGRA) which is a blood test measuring in vitro interferon-gamma release after stimulation of lymphocytes with different antigens specific to Mycobacterium tuberculosis. This could also differentiate between TB and NTM. There is limited experience in children and this test is not yet used in routine daily practice in paediatrics in Brussels.[18]

### Treatment of mycobacterial infections.

Treatment of **active TB** is based on a combination of **tuberculostatic agents**, usually tri- or quadritherapy for two months, followed by several months of bitherapy. Children with **latent TB** are treated with bi- or monotherapy. Young children (<5 years) or immunocompromised patients who are a **close-contact** of a contagious patient, who do not have any symptoms and who have a negative TST should receive **prophylaxis**.[13,14] **NTM infections** can be treated with anti-mycobacterial agents, but in case of isolated NTM lymphadenitis surgical excision or watchful waiting (i.e. no intervention since these infections are often self-limiting) are other treatment options. Drug regimens should be adjusted to the results of susceptibility testing. Mycobacterial infections universally respond slowly to antibiotic treatment.[7]

## Material and Methods.

The clinic of Paediatric Pulmonology and Infectiology at the Universitair Ziekenhuis Brussel (UZ Brussel) is a reference centre for TB, situated in the European capital city. We reviewed retrospectively a series of eight cases diagnosed with a mycobacterial infection between March 2016 and April 2018, and in whom challenges were found in differential diagnosis and in finding the causative pathogen.

Selection criteria :

- Paediatric patients (0-16 years of age) followed at the department of paediatric pulmonology and infectiology of the UZ Brussel in the study period (March 2016 – April 2018)

  AND
- Proven diagnosis of mycobacterial infection: M. tuberculosis complex or non-tuberculous mycobacteriae.

  AND
- In whom diagnosis was made late (not at first clinical signs).

  OR
- In whom no typical respiratory signs were present.

  OR
- In whom difficulties arose in interpretation of TST or other diagnostic tests.

TST is performed by intradermal injection according to the Mantoux method of 0,1 ml or 2 IU of tuberculin RT 23 from the Statens Serum Institut Kopenhagen purified protein derivate (PPD). Inoculation is performed by an experienced nurse. 72 hours after inoculation interpretation is performed by one of the paediatric pulmonologists. Size of induration is measured with a ruler and type of induration is described according to criteria from the Vlaamse Vereniging voor Respiratoire Gezondheidszorg en Tuberculosebestrijding (VRGT) (table 1).[16]

**Table 1:** Interpretation of TST

| TST induration | Interpretation |
|---|---|
| <5mm | Negative |
| 5-10mm<br>a) Type I-II<br>b) Type III-IV | a) Suggestive of TB if risk factors for TB (<5 years old, close contacts, clinical symptoms) or immunodeficiency present<br>b) Suggestive of NTM |
| >10mm | Positive (suggesting TB) |

Legend: TST = tuberculin skin testing. Level of induration can be subclassified in types : Type I = induration with phlycten, often painful. Type II = very hard, sometimes painful induration. Type III = soft induration. Type IV= minimal, hardly tangible induration.[15,16]

Diagnostic flexible fiberoptic bronchoscopy (Olympus) is performed under sedation with midazolam and atropine. If needed therapeutic rigid bronchoscopy is performed with a Storz bronchoscope, under general anaesthesia by an anaesthesiologist.
Culture samples are obtained in various ways, according to the clinical picture: lymph node biopsy or excision, gastric aspiration, bronchoalveolar lavage (BAL) and/or cerebrospinal fluid (CSF). Cultures are analysed in the microbiology lab using mycobacterium-specific culture media.
The study was approved by the Ethics Committee of the Universitair Ziekenhuis Brussels.

## Case series (table 2)

**Patient 1** – A 14-year-old boy of Belgian origin with rectocolitis ulcerohaemorraghica (RCUH) treated since 2013 with different immunosuppressive therapies, presented in 2016 with **persisting fever** since 10 days not improving with broad-spectrum antibiotics. At that time, he was treated with infliximab, a tumour necrosis factor alpha (TNF-alpha) blocker. **Radiology** was performed: computed tomography (CT) of the abdomen showed multiple lymph nodes and lung infiltrates in inferior lung fields, not visible on a previous chest X-ray. A CT of the lungs (figure 1) showed diffuse nodules. Positron emission tomography-CT (PET-CT) showed hypermetabolic nodules in lungs, abdominal and mediastinal lymph nodes and a liver nodule. **Differential diagnosis** included lymphoma, aspergillosis and TB. **TST** was initially thought to be negative, but careful examination by a paediatric pulmonologist revealed a 10 mm type IV reaction after 72 hours, and was considered as positive since the patient was under immunosuppression (infliximab). Multiple cultures were taken, with suspicion of aspergillosis and TB, before **treatment** initiation of antifungal therapy and tuberculostatics (quadritherapy - see table 2), together with broad-spectrum antibiotics. Fever ceased. One week after start of treatment the patient had a generalized tonic-clonic convulsion. Imaging of the brain (figure 2) revealed two intracranial nodular lesions, again most suggestive of aspergillomas, possibly tuberculomas. After 2 weeks culture of gastric aspiration, BAL and biopsy of an abdominal lymph node confirmed ***M. tuberculosis*** infection, consistent with **miliary TB**. Cultures of cerebrospinal fluid and brain biopsy remained negative for both fungi and TB. **Contact investigation** eventually showed open TB in the father.

**Figure 1:** CT scan of the lungs of patient 1 showing a lung nodule on the right with surrounding halo, suggestive of lymphoma.

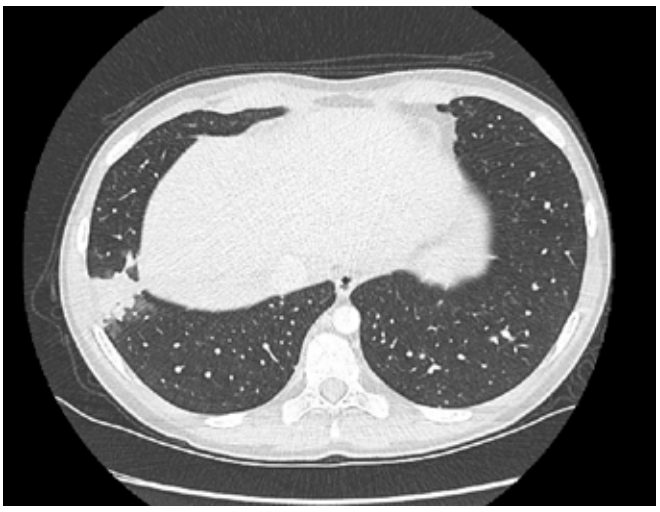
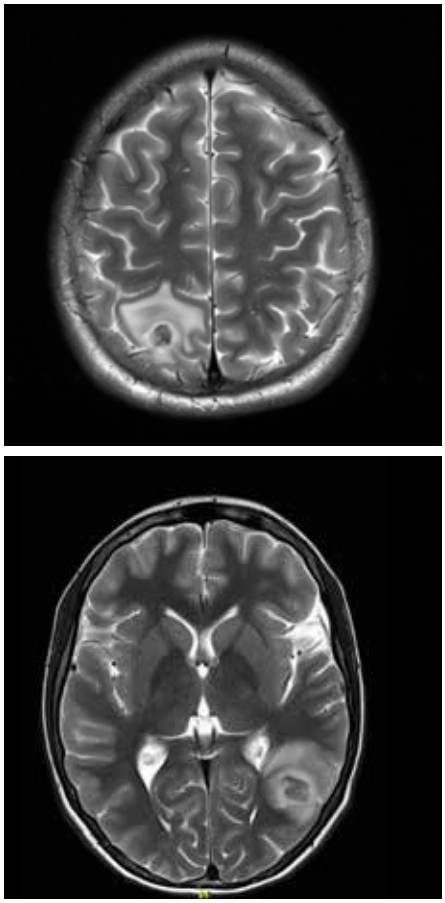


**Table 2:** Case series overview

| Patient nr<br>Age<br>Sex | Symptoms | Initial attempted diagnosis | TST | ESR (mm/h) | Culture/ source detection | positive sites | diagnosis | treatment |
|---|---|---|---|---|---|---|---|---|
| Patient 1<br>14y<br>M | Fever >10 days in patient with immunosuppression (TNF alpha blocker) | Lymphoma, aspergillosis | 10mm, type IV, after 72h | 76 | *M. tuberculosis/ father* | Lung lesions, abdominal adenitis, and tuberculomas in brain | Miliary TB | Quadritherapy (RFD, INH, PZA, EMB) |
| Patient 2<br>4y<br>F | Cervical + inguinal lymph nodes<br>Fever<br>Cough | Lymphoma | 12mm, type I, after 72h | >120 | *M. tuberculosis/ mother* | Cervical, inguinal and abdominal adenitis, endobronchial TB | Miliary TB | Quadritherapy (RFD, INH, PZA, EMB) |
| Patient 3<br>2y<br>F | Cervical lymph node | Bartonellosis | 15mm, type II-III | normal | *M. avium* | Cervical adenitis | NTM adenitis | RFD + Clarithromycin |
| Patient 4<br>2y<br>F | Cervical lymph node | TB | 15mm, type II, after 48h | 93 | *M. avium* | Cervical adenitis, mediastinal adenitis, lung infection | Disseminated MAC infection | RFD + Clarithromycin |
| Patient 5<br>3y<br>F | Abdominal pain and constipation >1 month<br>Fever 5 days<br>Cough | Lymphoma | 30mm, type I, after 48h | 79 | *M. tuberculosis/ father* | Abdominal adenitis | Abdominal TB | Quadritherapy (RFD, INH, PZA, EMB) |
| Patient 6<br>1y<br>M | Cervical mass, fever, cough, diarrhea and rhinitis | GE + tuberculous adenitis | 11mm, type II, after 48h | 118 | *M. bovis* | Cervical adenitis, gangliopulmonary TB, abdominal TB | Miliary TB | Tritherapie (RFD, INH, PZA) |
| Patient 7<br>8y<br>F | Spontaneous wound left arm<br>Adenopathies left elbow | Cellulitis | 11mm, type IV, after 48h | normal | *M. heamophilum* | Skin wound and adenitis of the elbow | NTM adenitis | RFD + Clarithromycin |
| Patient 8<br>11m<br>F | Pneumonia | Simple pneumonia | 11mm, Type III, after 48h | 45 | *M. tuberculosis/ unknown* | Lung infection | Endobronchial TB | Tritherapy (RFD, INH, PZA), EMB was added after 2 months. |

Legend: Y = years. M = male. F= female. ESR = erythrocyte sedimentation rate. TB = tuberculosis. GE = gastro-enteritis. NTM = non-tuberculous mycobacteria. MAC = M. avium complex. RFD = rifampicin. INH = isoniazid. PZA = pyrazinamide. EMB = ethambutol.

**Figure 2:** MRI of the brain of patient 1: round contrast-captating lesion left temperoparietal (on the left image) and right parietal (on the right image) with maximal diameter of 1,5cm and hypo-intens on this T2 weighed acquisition, with perilesional oedema.



**Patient 2** – a 4-year-old girl of African origin, but born in Belgium, was taken to the doctor because of **a fast growing cervical mass**. On physical examination, the mass seemed to be a group of enlarged lymph nodes, with also enlarged and painful inguinal lymph nodes. On suspicion of lymphoma, she was referred to the paediatric oncologist, where she presented with intermittent fever since three weeks, night sweats, fatigue and loss of appetite. Repeated **ultrasound** was performed, which showed necrotizing lymph nodes in the neck, and also enlarged abdominal lymph nodes. Blood analysis showed a high erythrocyte sedimentation rate (ESR). Because of high suspicion of malignancy, an excision of a cervical lymph node was performed, before performing a **TST** several days after surgery. 72 hours later this TST was clearly positive with an induration of 12 mm of type I. On chest **X-ray** a broadened mediastinum with hilar lymph nodes was seen. **Bronchoscopy** (figure 3) showed granulomas with a suspicion of an endobronchial TB, which is a contagious form of TB. Unfortunately, a TST was placed only late in the work-up, and preventive isolation measures were initially not taken, with possible contamination of multiple health care workers taking care of this child during initial work-up (including removal of a lymph node under general anaesthesia). With multiple sites involved, the diagnosis of **miliary TB** was made for which she was started on quadritherapy once all cultures were taken (table 2). BAL and gastric aspiration confirmed the presence of ***M. tuberculosis*** two weeks later. CSF and urine cultures were negative. **Contact investigation** revealed open TB in the mother, and the 6-year old sister also being contaminated by the mother. None of the three had ever been outside of Belgium since the birth of the oldest sister.

**Patient 3** – A 2-year-old girl of Belgian origin presents with **a large cervical lymph node** since three months with initially fever for a few days and purple colouration. Fever ceased without treatment but the cervical mass did not decrease in size. **Ultrasound** was performed, showing a lymph node of 3,5 cm diameter, suggestive of bartonellosis. **TST** was strongly positive (15 mm induration) with a strong suspicion of M. tuberculosis infection. The lymph node was partially resected, and Ziehl-Neelsen stain showed acid-fast bacilli on direct examination. Tritherapy was started (table 2). Culture was positive after two weeks for ***M. avium***. Therefore, treatment was changed to rifampicin and clarithromycin, which was sustained for one year resulting in recovery on clinical basis as well as on ultrasound findings.

**Patient 4** – A 2-year-old girl of Belgian origin presented with a **fast growing cervical mass**, with intermittent fever. Initially, she was treated with antibiotics but the cervical mass did not improve. A **CT** of the neck was performed, which showed multiple lymph nodes in the neck with central necrosis and by coincidence also an upper mediastinal enlarged lymph node. She was referred to the tertiary centre with **differential diagnosis** of malignancy versus TB. A **TST** was strongly positive with an induration of 15 mm of type II after 48 hours. **Chest X-ray** showed enlarged hilar lymph nodes. **Bronchoscopy** was performed, which did not show any signs of compression or granulomas. Gastric aspiration and BAL were performed and an excision of a cervical lymph node was done. Because of strong suspicion of TB, she was started on tritherapy (table 2). Cultures of the biopsy and the gastric aspiration were positive for ***M. avium***, a NTM. By that time, she already had signs of peripheral neuropathy, a known side effect of isoniazid. Isoniazid and pyrazinamide could be stopped, and treatment was changed to rifampicin and clarithromycin. Because of diagnosis of disseminated NTM infection with NTM lung infection, the patient was screened for immunodeficiency and CFTR-defects (cystic fibrosis transmembrane conductance regulator defects). Results of these screenings are ongoing.

**Patient 5** – A 3-year-old girl of Moroccan origin but born in Belgium, presented with **abdominal pain and constipation** since one month; fever since five days and a cough. **Radiologic** testing was performed: an ultrasound of the abdomen showed multiple large mesenteric lymph nodes (suspicion of lymphoma), chest X-ray was normal and a PET-CT scan (figure 4) showed hypermetabolic action in these lymph nodes. A **TST** was performed, which was strongly positive (induration of 30 mm type I after 48 hours). Diagnosis of lymphoma was abandoned. Gastric aspirations were performed. There was a strong **suspicion** of M. bovis infection because of abdominal lymph nodes, and because she recently went on a vacation to Morocco were she consumed unpasteurized milk products. Because there were also lesions above the diaphragm, quadritherapy was started (table 2). Cultures of a biopsied abdominal lymph node grew ***M. tuberculosis***. Culture of gastric aspirations were negative. On **contact investigation** her father, who is a CF patient, had an open TB.

**Patient 6** – A 1-year-old boy of Algerian origin, born in Belgium, presented with f**ever, diarrhoea, cough and rhinitis** since four days. On physical examination he had an **important swelling in the neck**. He was admitted to the hospital because of dehydration due to gastroenteritis. His mother was hospitalized one week earlier because of fever and lymphadenitis in the neck. She had a very mildly positive TST (>5 mm induration type 1). **TST** was performed in her son, which was positive with an induration of type II of 11 mm after 48 hours. A work-up with chest **X-ray** and **bronchoscopy** was suspicious of a gangliopulmonary TB, together with cervical adenitis (figure 5). He was treated with tuberculostatics (tritherapy) (table 2). After 5 weeks culture of the gastric aspirate was positive for ***M. bovis***, for which tritherapy was continued. BAL remained negative, but showed a concomitant CMV infection. CSF and urine cultures were negative. Culture of a puncture biopsy of a lymph node remained negative. His twin brother had the same kind of symptoms. Their symptoms started one month after travelling to Algeria, where they consumed non-pasteurised fresh milk products.

**Patient 7** - An 8-year-old girl of Belgian origin presented with a **spontaneous wound on the left arm**, with initially a cellulitis for which she received flucloxacillin orally for ten days. The cellulitis improved but the wound did not heal. She developed **big, hard but painless lymph nodes** in the left elbow. She did not have fever or cough. A **TST** showed a very soft (type IV) induration of 11 mm after 48 hours. **Ultrasound** of the elbow showed a central necrosis in the lymph nodes. A chest **X-ray** was normal. Excision of the lymph node was performed and tuberculostatics (rifampicin + clarithromycin) were started, with suspicion of an atypical mycobacterial infection. Culture was positive after 7 weeks for ***M. haemophilum*** (table 2).

**Patient 8** – An 11-month-old girl of Turkish origin, born in Belgium, was sent to our reference centre because of a **non-resolving pneumonia despite antibiotherapy**. History revealed cough since three weeks and fever since two weeks. Chest **X-ray** (figure 6) taken in the initial hospital showed a pneumonia in the upper right lobe, with a broadened mediastinum. We considered this as suspicious for TB, although initially the picture was not protocolled as such. A **TST** was performed, which showed an induration of 11 mm of type III after 48 hours. Bronchoscopic findings showed granulomas with caseum. Tritherapy was started (table 2). BAL and gastric aspirations were positive for **M. tuberculosis**. CSF was negative. **Contact investigation** could not reveal an active TB in her surroundings. She visited Turkey a few months before symptoms occurred. She needed multiple rigid bronchoscopies for evacuation of caseum obstructing the bronchi.

**Figure 3:** Bronchoscopy of patient 2 showing a granuloma with caseum in the right main bronchus.

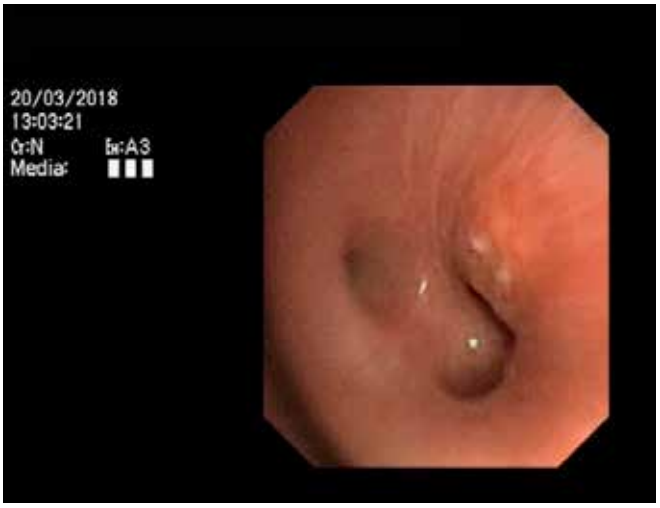



**Figure 4:** PET-CT scan of patient 5 showing hypermetabolic abdominal lymph nodes.

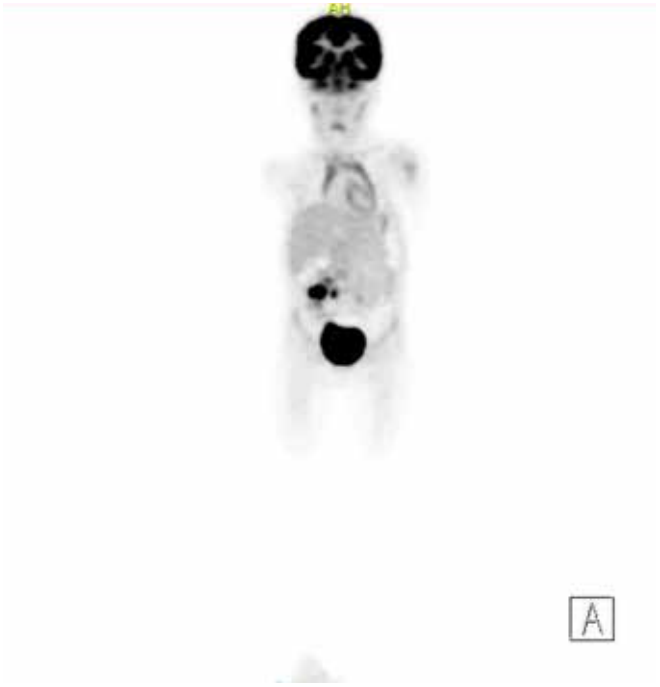



**Figure 5:** CT of the neck of patient 6 showing left cervical adenitis with central necrosis and a parapharyngeal collection.

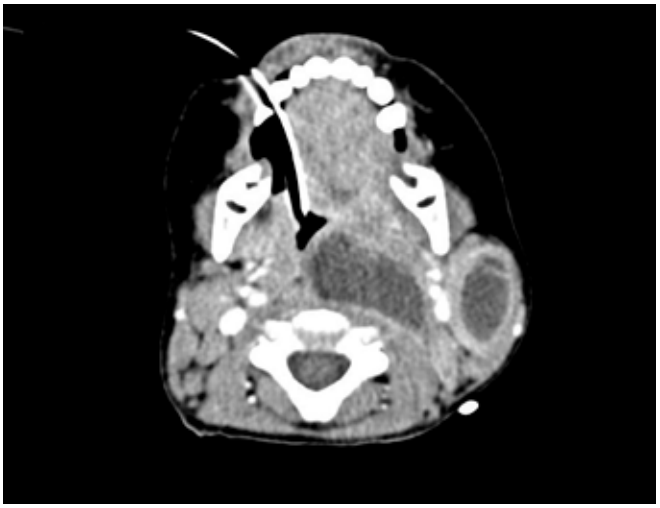
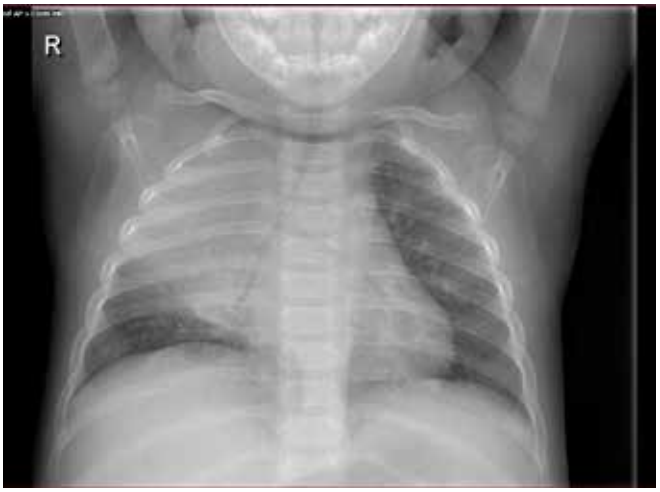


**Figure 6:** Chest X-ray of patient 8 showing an opacity in the right upper lobe, with shift of the trachea to the right, suggestive of partial atelectasis.




## Discussion.

### Difficulties in differential diagnosis

Although it is known that TB is transmitted from adults to children, the child often presents as the first index patient and the infected adult is only discovered thereafter by contact screening, as proven by these case series. In NTM infections contact screening is unnecessary.

As illustrated by these cases, the spectrum of mycobacterial infections in children is broad and can be confused with a myriad of common childhood infections and non-infectious diseases.[4,7-9] TB is therefore also called "the great imitator", and this is also true for NTM infections.4 The most common mimicking disease in these cases was **lymphoma**, as illustrated in patient 1, 2 and 5. The unspecific and common symptoms of fever, weight loss and fatigue combined with multiple enlarged lymph nodes is very suspicious for malignancy, but these are also the most common symptoms of pulmonary and extrapulmonary mycobacterial infection.[4,8] Especially in low incidence countries, TB or NTM are often not immediately suspected. Although lymphoma is the third most common childhood cancer with an incidence of around 50 new paediatric cases per year in Belgium, the incidence of TB in Belgium is the double of that (100 new paediatric cases/year).[11,19] Thus mycobacterial infections should be suspected, especially in immunocompromised patients like patient 1, and migrant children, even of second generation (like patient 6 and 8) who regularly travel to their parents' home country. But even without travel, as illustrated by patient 2, contamination could possibly occur via visitors from high-incidence TB countries. Patient 5 recently travelled to her parents' home country, and also had a parent with CF, the latter being at higher risk to acquire a mycobacterial lung infection.

Mycobacterial infections can also mimic **other common childhood infections**, like pneumonia, as illustrated in patient 8.[4] Also in patient 7 a "simple" cellulitis was the first diagnosis. A high suspicion of mycobacterial infection should be considered in every persisting lesion not resolving with classical antibiotics, or in atypical presentations of common diseases.[1] Moreover, if there is discrepancy between relatively mild clinical signs and severe radiologic findings, think of TB.[9]

### Difficulties in interpreting diagnostic tests

It is thus important to think of mycobacterial infection, because this has implementations for work-up, preventive isolation measures, contact investigation and therapy. In the case of patient 2 the diagnosis of TB was considered late and isolation measures were not taken initially. Interpretation of TST can only be done minimum 48 hours after injection, so early implementation in work-up is important to minimise risks of contamination and for initiation of the correct treatment.[1,16]

If a TST is placed, correct interpretation can also be challenging, especially in young children or in the immunocompromised. It must be underlined that TST has different cut-offs for a positive test result based on age, and immune status (table 1).[16] Patient 1 only had a type IV reaction which was initially interpreted as negative based on the cut-off of the VRGT. Taking into account the immunosuppressive status of the patient, any minimal reaction must be considered and if in doubt, a TB-expert should interpret the TST result. Although a small or weak TST reaction can sometimes be more suggestive for NTM versus TB infection, the cases 3 and 4 show that discrimination between typical and atypical mycobacterial infection based on TST is not reliable in children.

Radiology could sometimes give clues of mycobacterial infection. However, pulmonary TB in children does not show typical "adult-like" features like caverns. A broadened hilar region is the main feature, but chest radiographic findings of TB are very diverse.[9,20] These radiologic features of childhood TB are not broadly known, as illustrated in the case of patient 8, where the radiologist did not recognize a possible pulmonary TB. Also with chest X-ray, mycobacterial infections can mimic other diseases, as shown in patient 1, in whom imaging of lung nodule and brain lesions radiologically corresponded best with aspergillomas but appeared to be tuberculomas at the end. Ultrasound of lymph nodes can also suggest mycobacterial infection if central necrosis is present, which is not present in a suppurative lymphadenitis, like in the cases of patient 3 and 4.[7] But these two cases illustrate that imaging also cannot discriminate between TB and NTM infection.

Since discrimination between typical and atypical mycobacteria has implementations in work-up, it is important to obtain cultures for definitive diagnosis, to minimise the burden of treatment and unnecessary examinations of the patient (in search of other infection sites) or close contacts.[17]

### Difficulties in confirming diagnosis of mycobacterial infections.

Obtaining cultures in children can be difficult. To obtain respiratory specimens expectorated sputum, gastric aspiration or BAL can be used.[9] Young children can't expectorate sputum, so invasive procedures are often needed. In lymphadenitis thinking of mycobacterial infection is also important for the choice of biopsy technique. Needle biopsy could be done for diagnosis of lymphoma, but in case of mycobacterial infection this holds the risk of fistulisation, and full excision is the first choice.[1,7] This also allows histopathological assessment for detection of granulomas.[7,9] PCR is another diagnostic method that can be used on specimens obtained for culture, but sensitivity is only 50% in children.[4] Culture remains the gold standard for diagnostic confirmation.

Direct investigation with Ziehl-Neelsen staining can show the presence of acid-fast bacilli in a timely manner, but can't discriminate between TB or NTM. Unfortunately, due to the paucibacillary nature of mycobacterial infections in children, direct investigation is often negative, and culture confirmation occurs only in 15-50% of paediatric TB cases.[17,20] Therefore, it is important to take multiple high-quality specimens for culture to maximise the yield. Nevertheless, since most mycobacteria are slow-growing, culture confirmation can take weeks.[9]

If mycobacterial disease is suspected, treatment initiation should be done as soon as possible to improve clinical outcome and relieve morbidity, preferably after collecting appropriate specimens for microbiological evaluation.[4,9] Unfortunately treatment burden is high, with bad taste of medication and common side effects like nausea, but also liver failure and peripheral neuropathy. As illustrated in patients 1 and 4, unnecessary treatments (for Aspergillus and TB, respectively) were given the first weeks before culture confirmation, with even the appearance of side effects in patient 4. Culture also allows for susceptibility testing.

Alternative new reliable diagnostic tools are needed to determine whether a patient has a mycobacterial infection, and to differentiate between TB and NTM infection, preferably in a fast and minimal invasive manner. This could avoid unnecessary work-up with invasive procedures or exposure to radiation, and avoid unnecessary treatment. Upcoming diagnostic tools like the IGRA could possibly become daily clinical routine with promising improvement of diagnosis, and replacing TST by a blood test.[18]

## Conclusion.

Mycobacterial infection should also be suspected in low-incidence countries, especially in immunocompromised or migrant children (even of second generation), even when clinical presentation or localisation of the infection is atypical. Therefore, basic knowledge of the variety of presentations of mycobacterial infections is important as it is very diverse.

This study demonstrates that challenges arise in every aspect of the clinical diagnostic work-up. Culture remains gold standard, and can discriminate TB from NTM, but requires invasive procedures and is time consuming. There is a need for new, reliable and in particular fast diagnostic tools.

## Conflicts of Interest

No author has any competing interests (financial or non-financial).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# Risk assessment drives the treatment of pulmonary hypertension in childhood

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## Key words

pulmonary hypertension-treatment-children-risk assessment-combination therapy

## Abstract

Pulmonary arterial hypertension (PAH) is a rare disease. Treatment of adults and children with the disease consists mainly of selective pulmonary vasodilators. The majority of symptomatic patients need a combination of 2 or 3 of these drugs. In adult patients, risk assessment is important for the initiation and adjustment of treatment. This policy has shown to have an impact on prognosis.

Unfortunately, risk assessment-based treatment has not been studied in children with PAH yet, but nevertheless risk assessment has been advocated to guide treatment in pediatric PAH also. The risk assessment for children is somewhat simplified compared to adult tools. We propose the use of a leaflet that summarizes the most important risk factors for children. This leaflet can be used during follow-up by patients/parents and general physicians/pediatricians and help them to understand changes in treatment.

## Introduction

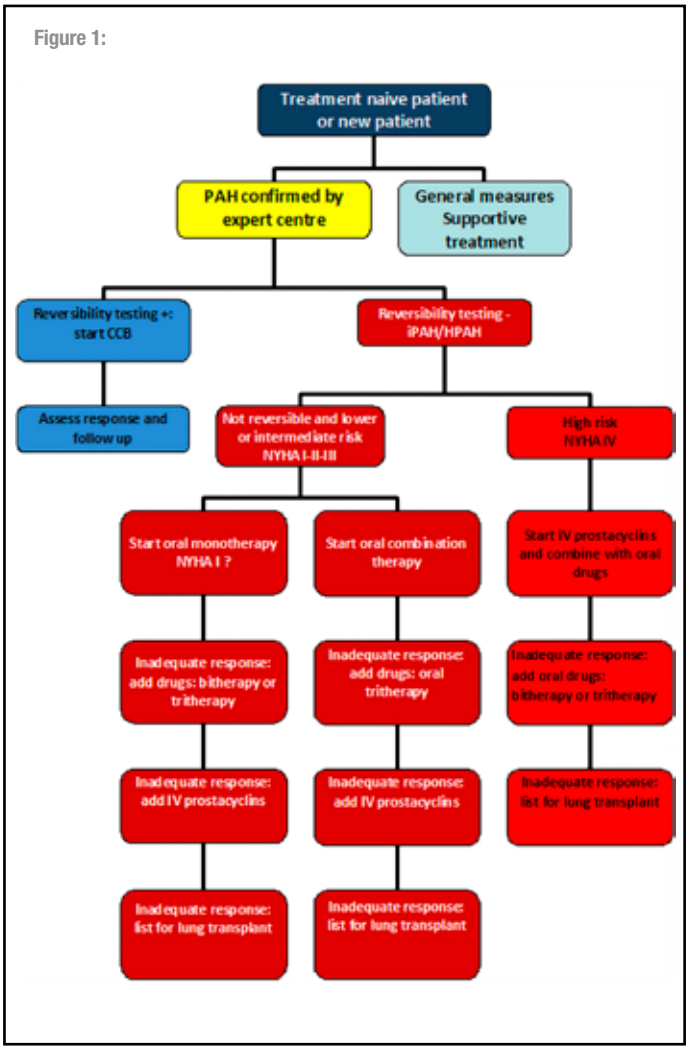
Pulmonary hypertension is a rare disease. The prevalence and incidence are variable in the literature. Not many data are available for children, but the prevalence of idiopathic pulmonary hypertension ranges between 2.07 and 4.4 per million and the incidence between 0.48 and 0.7 new children per million per year [1-3].

Pulmonary arterial hypertension (PAH) is usually defined as a mean pulmonary artery pressure ≥ 25 mmHg at rest, measured by cardiac catheterization. The term PAH describes a group of pulmonary hypertension patients characterized hemodynamically by the presence of pre-capillary PH, defined by a pulmonary artery wedge pressure (PAWP) ≤15 mmHg and a pulmonary vascular resistance (PVR) >3 Wood units (WU) in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic pulmonary hypertension or other rare diseases.

The results of the first randomized control study (RCT) that clearly demonstrated clinical improvement and better survival in patients with "primary" pulmonary hypertension on treatment with intravenous epoprostenol (prostacyclin) were published in 1996 [4]. In 2001, a limited RCT showed improved hemodynamics and clinical function after treatment with an oral endothelin-receptor antagonist (ERA) [5]. Since then several new drugs were designed, mostly oral: other ERA's, phosphodiesterase-5 inhibitors (PDE5), guanylate cyclase stimulators (GCS),prostacyclin analogues and prostacyclin receptor agonists. Like in most other rare diseases, guidelines for treatment of children with pulmonary hypertension are essentially extrapolated from studies and guidelines for adults [6-9]. In Belgium, sildenafil (PDE5 inhibitor), bosentan (ERA) and intravenous epoprostenol are the drugs most commonly used for the treatment of irreversible pediatric pulmonary arterial hypertension (PAH) [10].

These specific treatments allowed to improve the functional capacity, quality of life and life expectancy of children with PAH, but unfortunately PAH remains a progressive disease without cure [11]. Nevertheless, our experience and knowledge about the disease grew. Initially patients were treated with one single drug (monotherapy) until their clinical condition deteriorated whereupon treatment was switched to IV prostacyclin. Later on, we learned that a combination of 2 drugs (bitherapy, combination therapy) improved the short- and long-term clinical outcome and prognosis. The initial hesitation to combine several drugs was due to the high costs, the increased importance of the side effects and the possible mutual interference of the drugs. More recently, it became clear that combination therapy from the start improved the clinical outcome and prognosis of the patients compared to a treatment policy in which a second drug was only added if treatment goals were not met or the clinical condition of the patient worsened [12]. Nowadays even patients (children also) presenting with a less severe disease are treated with combination therapy (usually oral bitherapy) from the start, whether upfront (both drugs immediately) or fast sequential (one after the other on a short notice) (figure 1).

Figure 1:



As discussed before, in earlier days the initial treatment was more or less the same for every patient presenting with PAH, except for the sickest patients, for whom IV therapy was chosen. Treatment was adjusted merely on the "clinical gut feeling" of the physician, which did not always prove correct. Next targeted therapy was advocated in which improvement of functional class or the achievement of a minimal distance of 380 m during the 6-minute walk test (6MWD) were the goals. Eventually, patients were classified conform a certain risk score at baseline (diagnosis or presentation) and treated accordingly and recently it became evident that not only the risk score at baseline was important for an optimal treatment but that also the evolution of that risk score during follow up affected prognosis and should be taken into consideration when adjusting treatment.

## Risk assessment and treatment of PAH in adults

The Guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) were published in 2015 [8]. In these guidelines patients of group 1 (patients with pulmonary arterial hypertension (table1)) were classified in low, intermediate and high-risk groups. (table2)

The annual mortality of each of these groups is predictable: less than 5% in the low risk group, between 5 and 10% in the intermediate risk group and more than 10% in the high-risk group. The variables used for the risk assessment are clinical (signs of right heart failure and syncope, the rate of disease progression), functional (functional New York Heart Association (NYHA) class, the 6MWD and the results of a cardiopulmonary exercise test (CPET)), imaging (right atrium (RA) area and any sign of pericardial effusion), invasive measurements during right heart catheterization (RHC) (RA pressure, cardiac index (CI) and mixed venous saturation) and biomarker assessment of cardiac function: BNP (Brain Natriuretic peptide) and NT-proBNP (N-terminal-proBNP)). However, some important issues remain: most of these variables and cut-off values are based on "expert-opinion" and hardly evaluated nor confirmed by prospective research and clinical trials. Moreover, the guidelines do not only recommend risk assessment at baseline, but also at regular intervals during follow up. None of the variables carries any weight: the value of each of them seems equal, hemodynamic variables or functional class are as important as the 6MWD, which may be questionable? And the score is only valid for adults with idiopathic or hereditary types of PAH in group 1 and not for children nor adults with other types of PH in other subgroups. Mortality and morbidity are also affected by other parameters as age, gender, co-morbidities, complications of the disease and treatment and none is accounted for. And last but not least, till now any evidence is lacking that the relationship between risk score and prognosis which applies to the population of adults with idiopathic PAH or hereditary PAH in group 1 is also valid for the assessment and follow up of the individual group 1 PAH patient.

Meanwhile a few retrospective studies evaluated and validated this and other scores. The most interesting studies used the ESC/ERS tables or a simplified version, the REVEAL score (mainly USA) or the French Registry score. A few findings seem to be rather consistent over the different studies.

The risk score at baseline is important for the prognosis, particularly for the annual mortality, but the evolution of the risk score during follow up (especially the first 3 to 6 months) is even more important. Practically this means that patients who belong to the intermediate or high risk group at baseline and achieve a low risk score during follow up, have the same prognosis (better than at baseline) as those in the low risk group at baseline with a stable evolution at follow up. Vice versa those classified in the low risk group at baseline and deteriorating to intermediate or high risk during follow up worsened their prognosis [13-19]. Unfortunately, only a small number of patients belongs to the low risk group 12-23% at baseline increasing to 24-41% during follow up [15, 17, 18]. This confirms that PAH is still a disease with a bad prognosis and that even the newest treatments do not cure the disease [11]. Moreover, changes in risk category, regardless of the direction, seem to be an accurate predictor of mortality and long-term survival and could be a candidate as surrogate end-point in clinical trials.

The first study to confirm the benefit of regular assessment of the variables on which the risk scores depend [13], showed that a shorter 6MWD, a high RA pressure (RAP), low cardiac index (CI), low mixed venous saturation (SvO2) and high NT pro-BNP were independent predictors of survival at baseline and during follow up. Changes in functional class, changes of CI and SvO2 were also independent predictors of survival. In other studies as in the French study using the more simplified French Registry score, especially a baseline 6MWD > 440 m seemed to predict better survival and 6MWD > 440 m, NYHA I-II, RA pressure below 8 mmHg and CI ≥ 2.5 L/min/m²at follow up were independent predictors of survival [15]. The authors proposed a simplified score composed of 4 criteria for follow up: NYHA I-II, 6MWD > 440 m, RAP < 8 mmHg and CI ≥ 2.5 L/min/m². Those with 3 or more of these

**Table 1:** Updated classification of PH (Nice, 2013)

**1. PAH**
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
  - 1.2.1 BMPR2
  - 1.2.2 ALK-1, ENG, SMAD9, CAV-1, KCNK3
  - 1.2.3 Unknown
- 1.3 Drugs or toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
- 1". Persistent pulmonary hypertension of the newborn

**2. Pulmonary hypertension due to left heart disease**
- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired left heart inflow/outflow obstruction and congenital cardiomyopathies

**3. Pulmonary hypertension due to lung disease and/or hypoxia**
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary disease with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung disease

**4. Chronic thromboembolic pulmonary hypertension**

**5. Pulmonary hypertension with unclear multifactorial mechanisms**
- 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disease, splenectomy
- 5.2 Systemic disorders: sarcoid, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

**Table 2:** Risk assessment in Pulmonary Arterial Hypertension

| Determinants of prognosisa (estimated 1-year mortality) | Low risk <5% | Intermediate risk 5-10% | High risk >10% |
|---|---|---|---|
| Clinical signs of right heart failure | Absent | Absent | Present |
| Progression of symptoms | No | Slow | Rapid |
| Syncope | No | Occasional syncopeb | Repeated syncopec |
| WHO-FC | I, II | III | IV |
| 6MWD | > 440 m | 165-440 m | < 165 m |
| CPET | Peak $VO_2$ > 15 ml/min/kg (>65% pred.) | Peak $VO_2$ 11-15 ml/min/kg (35-65% pred.) | Peak $VO_2$ < 11 ml/min/kg (<35% pred.) |
| | $VE/VCO_2$ slope <36 | $VE/VCO_2$ slope 36-44,9 | $VE/VCO_2$ slope ≥45 |
| NT-proBNP plasma levels | BNP <50 ng/l | BNP 50-300 ng/l | BNP >300 ng/l |
| | NT-proBNP < 300 ng/l | NT-proBNP 300-1400 ng/l | NT-proBNP >1400 ng/l |
| Imaging (echo, CMR imaging) | RA area < 18 $cm^2$ | RA area 18-26 $cm^2$ | RA area >26 $cm^2$ |
| | No pericardial effusion | No or minimal pericardial effusion | Pericardial effusion |
| Hemodynamics | RAP < 8 mmHg | RAP 8-14 mmHg | RAP >14 mmHg |
| | CI ≥ 2,5 l/min/$m^2$ | CI 2,0-2,4 l/min/$m^2$ | CI <2,0 l/min/$m^2$ |
| | $SvO_2$ > 65% | $SvO_2$ 60-65% | $SvO_2$ <60% |

low risk variables had a lower mortality than the others. A Swedish study using the ESC/ERS score tables found that 6MWD > 440 m, NYHA I-II and at least 1 favorable parameter that assessed the function of the right heart (NT-proBNP, echo measurements or of measurements during RHC) after 4 months follow up were signs of a better prognosis [17].

The problem with all these scores is that all variables have the same weight, and that there is no discrimination between the relative importance of these variables in the ultimate risk score. One example: how many low risk parameters does one need to achieve before belonging to the low risk group? For instance, is the 6MWD as important as the measurements during invasive measurements (RHC). What about missing data [18,19]? The only score that tries to answer these issues is the REVEAL score [14] (link: https://www.mdcalc.com/reveal-registry-risk-score-pulmonary-arterial-hypertension-pah) The REVEAL score is validated in a larger population compared to the other scores, doesn't need invasive measurements (RHC), can be used for all groups of patients with PAH, is as valid in incident patients as in prevalent patients, adds a certain weight to the measurements and is useful in the individual patient. It has not been proven yet whether REVEAL is superior to the other risk scores. One study compared the French Registry score and the REVEAL score and found comparable results [20].

The ideal score is a score which is easy to use and is as valid for new patients (incident) as well as patients that are already treated at any time during follow up (prevalent). This will allow to identify changes of the risk profile at follow-up and adjust treatment accordingly. The score has to remain valid in case of missing data too. Moreover PAH-related morbidity and hospitalizations within the month after initiation or changes of treatment should be considered in order to adjust the treatment installed. These are also important independent negative predictors of prognosis [16]. None of these risk scores has been validated yet in prospective studies.

## Pediatric Risk score

In contrast with the adult guidelines, which are often based on the results of at least one RCT or validated by a retrospective study, guidelines for children are mostly based on studies with a limited number of patients or limited clinical experience, the so-called expert level of evidence (level C). The American Heart Association and the American Thoracic Society recommend targeted therapy as well, promoting a risk score table with only a low and high-risk group (table 3) [9]. Combination therapy is recommended without addressing the issue of upfront initiation of both drugs or sequential initiation of the drugs. European experts prefer a targeted treatment as well, based on comparable risk score table (table 4) that have been established after an extensive review of the available pediatric data in the literature [6,7].

A careful glance at the tables reveals some important issues: like in adults, growth is important for the risk assessment in children, syncopes are more frequent in childhood and have important clinical and psychological repercussions, absolute cut off values are rare and routine serial monitoring with invasive measurements (RHC) is rarely done in children without signs of clinical deterioration.

The Belgian pediatric cardiologists who treat children with PAH and are part of the Pediatric PH network are encouraged to use these risk assessment tables as a tool at baseline and during follow up. The risk stratification allows a more accurate and objective follow up of our patients and avoids relying too much on our "clinical gut feeling". We developed a simplified leaflet that can be used during the serial follow up of our patients and is a tool that facilitates counselling of patients and parents and clarifies changes of treatment (figure 2). We do not discuss numbers and cut-off values, but rather discuss the low or high-risk classification of several important issues that can affect prognosis and treatment. The features are kept up to date on the leaflets during every visit and the patients and parents will be able to assess and discuss their global evolution and hopefully better understand adjustments of treatment. The features are signs of right heart failure, clinical deterioration (symptoms, NYHA class, but also hospitalizations), syncope (fainting or near-fainting), growth (percentile curves), exercise tolerance (NYHA class, 6 MWD, exercise test), lab results (essentially NT-proBNP), echocardiography (signs of increased RA pressure and ventricular function) and if relevant results of heart catheterization. Of course, not all features will be examined during each outpatient visit, but even despite some missing data, the patient, parents and general physician or pediatrician will be able to assess and understand the global evolution over a longer period of follow up. We are convinced that this tool could increase the confidence of our patients and their families in our objective and evidence-based approach of their disease and will avoid misinterpretation if the patient or the parents would find these risk scores on the internet without adequate counselling. The patient's general physician or pediatrician can use the information in the continuously updated leaflet in order to follow their patients with PAH with a more accurate background and more direct involvement. Indeed, most of the general practitioners and pediatricians have only limited experience and knowledge of PAH, which remains a rare disease. They will only be too happy to get relevant information on their patient's disease and prognosis.

**Table 3:** AHA/ATS Consensus Pediatric PAH: Disease Severity

| LOWER RISK | DETERMINANTS OF RISK | HIGHER RISK |
|---|---|---|
| No | Clinical evidence of RV failure | Yes |
| I, II | WHO class | III, IV |
| None | Syncope | Recurrent syncope |
| Minimal PVR<br>Enlargement/dysfunction | Echocardiography | Significant RV<br>enlargement/dysfunction<br>Pericardial effusion |
| PVRI < 10 WU*$m^2$ | Hemodynamics | PVRI>20 WU*$m^2$<br>CI <2.0 L/min/$m^2$<br>PVR/SVR >1.0 |
| Minimally elevated | BNP / NTproBNP | Significantly elevated |
| Longer (>500 m) | 6MWD | Shorter (<300 m) |
| Peak $VO_2$ >25 mL/kg/min | CPET | Peak $VO_2$ <15 mL/kg/min |

**Table 4:** Determinants of Risk in Pediatric Pulmonary Vascular Disease (PHVD)

| LOWER RISK | DETERMINANTS OF RISK | HIGHER RISK |
|---|---|---|
| No | Clinical evidence of RV failure | Yes |
| No | Progression of symptoms | Yes |
| No | Syncope | Yes |
| | Growth | Failure to thrive |
| I/II | WHO functional class | III, IV |
| Minimally elevated | Serum BNP / NTproBNP | Significantly elevated |
| | Echocardiography | Severe RV enlargement/<br>RV dysfunction<br>Pericardial effusion |
| CI >2.0 L/min/$m^2$<br>mPAP/mSAP <0.5<br>Acute vasoreactivity | Hemodynamics | CI >2.0 L/min/$m^2$<br>mPAP/mSAP <0.75<br>mRAP >15 mmHg<br>PVRi > WU x $m^2$ |

## Conclusion:

risk-assessment drives the initial therapy and therapy adjustments in adults with PAH. Although not proven by randomized control trials, this approach is also advocated for the treatment of children with PAH. Leaflets to help patients, parents and referring physicians understand treatment goals will be provided for the treatment of these patients in Belgium.

Figure 2:



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# Wart remover instead of Vitamin D drops: a dangerous mistake

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## Key words

chemical burns, caustic esophagitis, home accidents, wart remover, child

## Abstract

Aporil® is a commonly used keratolytic topical wart remover. This product has a local caustic effect on mucosae and can, when ingested, cause damage to the upper airways and esophagus. A bottle of Aporil® looks similar to a bottle of Vitamin D drops.
This article describes five cases where a bottle of Aporil® was mistaken for a bottle of Vitamin D drops by either a young child or a parent. The consequences of accidental Aporil® ingestion are severe. Securing the bottle with a safety cap would in our opinion be a first step in avoiding similar cases.

## Introduction

Aporil® is a commonly used topical wart remover, applied locally to the skin. The solution contains thuyatincture 45 mg/1 g, Chelidonium majus tincture 45 mg/1 g, salicylic acid 135 mg/1 g, lactic acid 20 mg/1 g and acetic acid 80 mg/1 g. It is commercially available in a brown glass bottle containing 10 ml of liquid. A bottle of Aporil® looks very similar to a bottle of Vitamin D drops. By this, it can be easily mistaken not only by children, but also by parents. Accidental ingestion of Aporil® is potentially fatal due to the local caustic effect on mucosae. To illustrate this health issue, we present five cases that occurred at the Antwerp University Hospital.

## Cases

From January 2014 until December 2018 five children were presented to the emergency room with an accidental ingestion of Aporil®. Three children aged 2.2 to 3.7 years accidentally drank the solution themselves. Two children aged 7 and 10 months had the solution unintentionally administered by a parent because of confusion with vitamin D drops.

Four children were admitted to the intensive care unit for observation. Two children, aged 7 months and 2.2 years, had a threatened airway and were intubated. All children had ulcerative lesions in and/or around the mouth. Esophagogastroduodenoscopy was performed in four children. One child had no apparent lesions at thorough inspection of the mouth. One child had superficial ulcerations in the proximal esophagus (grade 2A caustic injury). Two children had circumferential ulcerations of the esophagus (grade 2B caustic injury). None of the children had gastric lesions.

The children with grade 2B caustic injury received nasogastric feeding during 24 and 96 hours after which a control endoscopy was done. Control endoscopies showed a normal esophageal mucosa in both patients after which normal feeding was reintroduced. All children recovered completely and were able to leave the hospital in good clinical condition. The mean duration of stay at the intensive care unit was 2,2 days, the mean duration of hospitalization was 3,6 days.

## Discussion

The acids in Aporil® can cause caustic lesions in the esophagus after ingestion. Breathing support can be necessary in case of laryngeal injury and upper airway edema. Although all our cases had a good clinical outcome, they do illustrate the potential danger of ingestion of this product. Four out of five children required observation in the intensive care unit and 2 required airway intubation. Three children had extensive esophageal caustic lesions.

The Health Council recommends giving vitamin D to children up to the age of 6 years. The use of vitamin D is thereby widely spread. However; because the packaging of Aporil® is similar to that of vitamin D drops, it is easily confused by children, but also by parents. Moreover, the Aporil® bottle is not secured with a safety cap that could protect young children.

In PubMed, only two reports are published concerning accidental ingestion of wart remover, one in 2014 and one in 1986 [1,2].

## Conclusion

We would like to draw attention to the potentially life-threatening consequences of accidental Aporil® ingestion. Hereby we would encourage the pharmaceutical company to secure the bottle with a safety cap. Pediatricians should alert parents to this danger and create awareness to keep cosmetics, medications, and other healthcare products out of reach of children in child-proof containers.

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**Table 1:** patient characteristics

| | Age | Sex | Mode of ingestion | Respiratory support | Endoscopy | Days of intensive care | Days of hospitalisation |
|---|---|---|---|---|---|---|---|
| 1 | 2J6M | M | Self-ingestion | None | None performed | 1 | 2 |
| 2 | 0J7M | M | Administered by parent | Intubation | Grade 2B caustic injury | 4 | 6 |
| 3 | 0J1M | F | Administered by parent | None | Grade 2A caustic injury | 1 | 2 |
| 4 | 2J2M | M | Self-ingestion | Intubation | Grade 2B caustic injury | 5 | 7 |
| 5 | 3J7M | M | Self-ingestion | None | No lesions | 0 | 1 |

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**Erratum :**

*"This version of Short Communication replaces previous one: BJP 2018; 20(3): 180. Results about Offset weeks are corrected."*

## Short Communication

# Seasonality of respiratory syncytial virus (RSV) in Belgium

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## Abstract

The timing and duration of the respiratory syncytial virus (RSV) season is crucial for efficient administration of immunopropfylaxis to prevent infection in vulnerable infants. We describe a retrospective study of the seasonal RSV pattern in Belgium over a 13-year period, from July 2004 till June 2017. The RSV season begins mostly at the beginning of October. The end of the season is less clearly definable with a range between mid-February to the end of March.

## Introduction

Respiratory syncytial virus is the most frequent cause of bronchiolitis and pneumonia in infants and young children and an important source of morbidity, mortality and financial burden worldwide[1]. Immunoprophylaxis to prevent RSV infection with neutralizing monoclonal antibodies, palivizumab, is available for monthly administration during the season to high-risk infants: preterm birth, cyanotic or complicated heart disease and chronic lung disease[2]. In Belgium only 5 injections are reimbursed annually. The exact timing and duration of the RSV season is crucial for efficient administration

## Objectives.

To guide the timing of RSV prophylaxis, we investigated the seasonal pattern of RSV in Belgium over a 13-year period: July 2004 – June 2017.

## Methods.

Data collection was retrospective. Nine hospitals throughout Belgium (16 % of pediatric beds) participated. All RSV detection test from out- and inpatients performed in children < 3 years old from July 1st 2004 until May 31th 2017 were eligible for the study.

Onset and offset of the RSV season was defined as the first respectively the last 2 consecutive weeks with at least 10% positive tests and a minimum of 10 samples tested that week[3]. Peak week was defined as the highest percentage of positive tests.

## Results. (Table, Figure)

Over the study period, 87.574 were retained for analysis from which 22.239 (25.4 %) tested positive (56.3 % boys) (and 97 % within the identified epidemics (green area in figure). Most often season starts around week 41 (second week of October) or 42. The onset was remarkably early in 2008-2009 (week 30) and 2015-2016 (week 37). In 2016-2017, after an early start (week 30), two times there was a switch-off for 3 to 4 weeks in between. Offset ranged from week 7 to week 10, except for 2007-2008 (week 17), 2008-2009 (week 3), 2009-2010 (week 10), 2010-2011 (week 13), 2014-2015 (week 10) and. 2016-2017 (week 4). Median peak week was week 49 (range: 47 – 52). Season duration ranged from 13 to 28 weeks (mean: 20.9 weeks), except for the longest epidemics in 2007-2008 (28 weeks), 2008-2009 (26 weeks) and 2010-2011 (25 weeks)

## Conclusion

Although the start of the RSV season was relatively consistent (at the beginning of October), the end of the season is more difficult to define. Our data are in line with the findings of the WIV/ISP[4]. Prophylaxis should start "before" the season taking into account a mean season duration of 20.9 weeks and knowing that 5 monthly doses give sustained exposure to a therapeutic level of antibodies for more than 150 days after the 1st dose[5].

**Table :** Number of (positive) RSV tests and epidemic characteristics among children <3 years in 9 hospitals in Belgium, July 2004 – June 2017.

| Season | N tests | N positive tests | Onset (week) | Offset (week) | Peak (week) | Duration (N weeks) |
|---|---|---|---|---|---|---|
| 2004-2005 | 2533 | 752 | 44 | 7 | 52 | 17 |
| 2005-2006 | 4255 | 1339 | 40 | 8 | 48 | 21 |
| 2006-2007 | 5017 | 1391 | 42 | 9 | 49 | 20 |
| 2007-2008 | 4684 | 1159 | 42 | 17 | 52 | 28 |
| 2008-2009 | 6813 | 1751 | 30 | 3 | 47 | 26 |
| 2009-2010 | 6485 | 1814 | 43 | 10 | 50 | 21 |
| 2010-2011 | 7307 | 1751 | 41 | 13 | 50 | 25 |
| 2011-2012 | 7405 | 1753 | 41 | 8 | 49 | 20 |
| 2012-2013 | 7496 | 2177 | 39 | 6 | 48 | 20 |
| 2013-2014 | 8691 | 2154 | 43 | 8 | 50 | 18 |
| 2014-2015 | 9298 | 2144 | 43 | 10 | 50 | 20 |
| 2015-2016 | 8900 | 1991 | 37 | 6 | 48 | 23 |
| 2016-2017 | 8690 | 2063 | 40 | 4 | 48 | 13 |

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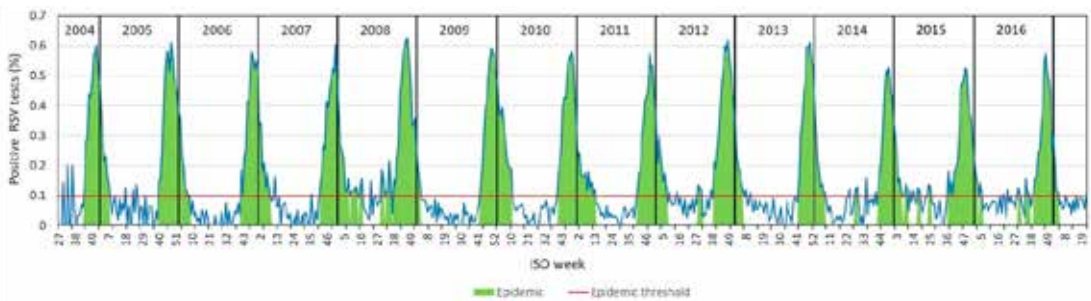
**Figure:** Weekly percentage of positive RSV tests (inpatient + ambulatory) among children <3 years in 9 hospitals in Belgium, July 2004 – June 2017.



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# Family-centred care: partnering with families in the care of small and sick newborns

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## Key words

Family-centred care, developmental care, neonatology, kangaroo care

## Abstract

Premature or sick newborns are at risk of developing important long-term morbidities. Developmental care practices are used to diminish stress and to promote brain development in these newborns. Families have a prominent role in these practices, with parents as primary caregiver for their sick or preterm infant. Family-centred care has a positive effect on the outcome of these newborns. It also has a positive effect on the mental status of the parents and on the parent-infant bonding. Family-centred care has different aspects and the implementation demands a mind-shift in all caregivers involved in the care of preterm and sick newborns.

## Introduction

On the 17th November we 'celebrate' world prematurity day. The motto this year was 'Working together: Partnering with families in the care of small and sick newborns'.

In Belgium about 7% of all babies are born too soon, at less than 37 weeks gestational age. Recent advances in neonatal care led to increased survival of more immature babies. Despite this positive evolution, these babies are at risk of developing important long-term morbidities such as complex cognitive dysfunctions, socio-emotional problems and learning and behavioural disabilities. But not only the most immature babies develop these problems, also moderately and late preterm babies who are born between 32 and 37 weeks gestational age (GA), are at increased risk of developing behavioural disorders and learning disabilities[1].

At present, developmental care practices, such as NIDCAP® (Newborn Individualised Developmental Care and Assessment Program), are widely used for the care of preterm or sick newborns in order to diminish stress and to promote brain growth and development. With these interventions we hope to diminish the long-term morbidities and to ameliorate the quality of life of the former 'preemies'.

One of the most important features of most developmental care strategies is parental involvement and participation in the care of their newborn. Different aspects of family-centred care have shown to have positive short and long term effects on the infant as well as on the family of these infants.

## Aspects and effects of family-centred care

We know from animal and clinical studies that mother-child separation causes stress in the newborn and that early life stress alters brain development and structure[2]. The Stockholm neonatal family centred care study was one of the first and most important clinical studies showing that family presence in the neonatal intensive care unit (NICU) has an impact on neonatal morbidity of babies born preterm (GA 27-37 weeks). Örtenstrand et al showed that in a setting where parents could stay with their babies 24/7 in family rooms, there was a significant reduction of hospital stay with 5 days as compared to standard NICU care. Also, the risk of pulmonary morbidity (moderate to severe bronchopulmonary dysplasia) was significantly reduced in the family care group[3].

Kangaroo care is the aspect of family centred care that has the strongest evidence for a positive impact on the infant's health both through direct as well as indirect effects[4]. Kangaroo care promotes cardiorespiratory stability, improves sleep and reduces infections. It also has important maternal effects such as enhancement of breastfeeding and improved parent-infant bonding, which affects the infant's health and long-term outcome favourably. With this evidence in mind, kangaroo care should be considered as a therapy in premature and sick infants. Therefore, we have to strive for kangaroo care for every infant in the neonatal ward as early as possible and as long as possible.

Fortunately, parental presence in neonatal units has made a tremendous evolution in the last decades. In the past, parents were seen as visitors having to respect strict visiting hours and having no function in the care of their babies. Today, an increasing number of neonatal units adopt the principles of family-centred care, such as unrestricted parental access, kangaroo care and active parental participation in the care for their baby.

At the same time, however, family-centred care remains one of the biggest challenges of neonatal care because it requires a fundamental change in mentality of all neonatal caregivers. Parents should be considered as the primary caregivers for their infant, whereas nurses should focus on coaching the parents. Medical staff should involve the parents as a partner in clinical decision making.

To guide neonatal caregivers in this process, Roué et al published in 2017 'Eight principles for patient-centred and family centred care for newborns in the NICU[5]. The first principle states that there should be free parental access to the unit 24 hours a day, without limitations due to staff shift or medical rounds. This is of course a basic and primary requirement of family-centred care. The second principle, which is less obvious, states that psychological support for parents should be provided. Parents of children admitted to a neonatal ward often have psychological problems, such as depressive symptoms, anxiety and posttraumatic stress[6]. These psychological problems can impair bonding with their child and lead to insecure attachment, which in turn, has been associated with poor neurodevelopmental outcome and emotional problems in their offspring[6,7]. Therefore, psychological support for parents of a prematurely born or sick newborn is absolutely required and can have a positive effect on the neurodevelopment of the infant. In addition, family-centred care, and especially kangaroo care, reduces depressive and anxious symptoms in parents of preterm babies[9].

Family centred care also implies that parents are involved in all medical or non-medical decisions about their child. As such parents should take part in medical rounds and (multidisciplinary) patient discussions. This involvement goes beyond informing parents, it assumes a shared decision making. Of course, if parents do not wish to take part in clinical decision making for their child, this should be respected as well. Ideally, informing parents and involving them in care and decision making for their baby begins even before birth. Pregnant women at risk for preterm birth or with a known fetal anomaly should be counselled by a neonatal team before birth. When available, they should receive written information about the care their baby will receive[9].

The family of a newborn is often more than just his or her parents. Siblings, who often feel neglected by their parents who spend so much time with their sick newborn in the NICU, should not be forgotten. We should try to involve siblings as much as possible by letting them visit and participate in care, and by informing them appropriately. Parents can guide us in our approach of these children depending on their age and personality. Grandparents, other family members or close friends probably require a more individualised approach in terms of visiting

moments, participation in care and perhaps even the possibility of "kangarooing" the infant.

Working together with families on a NICU is not an obvious thing to do. Different barriers can be perceived. First, every family has a different background or socio-economic status and has different preferences, which all have to be respected if we want to collaborate closely with them. The approach to the family should be as individualised as possible. This can sometimes be achieved by small but important details, such as personalizing the babies space with a family picture, a sibling's drawing or milestone cards. In our hospital we recently introduced a multidisciplinary round in which we discuss the strengths and challenges of each child and family with the aim of individualising the infant-family care as much as possible. Discussions and decisions are based on detailed patient observations (according to NIDCAP® principles), psychologic evaluations and our daily practice with the parents and the child. In the near future, we are planning to ask parents to participate in these multidisciplinary rounds. Second, infrastructure is often perceived as an important barrier to implement family centred care (too little space, too little privacy), we believe that this barrier can be overcome if we think creatively. It is our conviction that the mind-shift is the biggest challenge of all.

Official programs have even been developed to teach and guide caregivers and neonatal units about this collaboration ('Close Collaboration with Parents Training Program®'). Likewise the EFCNI (European Foundation for the Care of Newborn Infants) recently published standards of care for newborn health. The EFCNI incorporates family centred care in their work as they have a parent advisory board who contribute in the development of these standards. One topic is infant- and family-centred developmental care in which they emphasize that parents have a primary role in the provision of care for their infant. They also state that their should be unrestricted access, 'continuous' skin-to-skin contact and that the needs of the families in the NICU should be supported[10].

## Conclusion

Neonatal family centred care is becoming increasingly important in the daily care of the preterm and sick newborn. It is not only a changing atmosphere, but it is about improving outcome of these children and their families on the long term. Adjusting our work to the principles of family-centred care requires a mind-shift in all neonatal caregivers and eventually also in hospital administrations.

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# Study of the role of the X chromosome in sex differences in pediatric inflammatory diseases

PhD thesis presented on 30th of October 2017 at Université Libre de Bruxelles, Brussels, Belgium.

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## Relevance of the study

Sex differences in inflammatory diseases are largely reported in the literature. Until recently, it was commonly admitted that the clinical differences observed between men and women in terms of inflammatory response may be explained by the different levels of sex steroids, mainly testosterone and estradiol. However, recent findings have revealed significant differences in inflammatory markers between prepubertal boys and girls and in immune processes involving X-linked genes.[1,2] The sex hormones levels are highly variable along life and most likely insufficient to account for the differences observed during inflammatory conditions between sexes from neonates to the elderly, thus suggesting another origin. Many X-linked genes are involved in the immune response and the mechanism underlying these sex-dependent differences are multiple and probably involve both hormonal and genetic factors.

In this work, we sought to evaluate the sex differences in the immune response in children and the role of the X chromosome, relatively to the sex hormones.

## Sex differences in prepubertal children

In order to minimize the multiple and complex effects of the sex hormones on the immune system, we first decided to study prepubertal subjects, whose levels of sex steroids are very low and probably insufficient to influence the inflammatory processes. We analyzed clinical and biological inflammatory parameters in prepubertal children with severe sepsis as a model of acute inflammatory disease, and *in vitro* innate immune response in prepubertal boys and girls, and in children with Turner syndrome.[3,4]

We observed higher neutrophilic inflammation in prepubertal girls with severe sepsis, associated with longer fever duration. We also recorded lower pH recorded in girls on admission. This increased acidosis in girls could also have influenced immune response by stimulating neutrophil recruitment and pro-inflammatory cytokine secretion, as well as outcome of sepsis, illustrated by a tendency to higher survival in girls compared to boys.

As we previously reported in prepubertal children suffering from acute and chronic inflammatory diseases, an increased inflammatory response in girls compared to boys, could contribute to better pathogen clearance in case of acute disease, but also to enhanced tissue damage in case of chronic process, explaining the worse prognosis in case of persistent inflammatory response.[5]

*in vitro*, we found an increased inflammatory cytokine (interleukin (IL) -1β, IL- 6, and tumor necrosis factor (TNF)-α) and prostaglandin (PG)-E2 production in prepubertal boys in comparison with girls, in response to lipopolysaccharide (LPS) and pokeweed mitogen (PWM). Children with Turner syndrome, carrying only X chromosome, followed the male pattern of reactivity, with increased sensitivity to low levels of stimulation by LPS for IL-1 response and a dose response relationship equivalent to that of males for IL-6. The similarities between boys and children with Turner syndrome are in favor of a specific gene expression between monosomy and disomy for the X chromosome, and a role for X-linked genes. The general observation of a higher inflammatory cytokine production in males, in spite of lower inflammatory markers, is in favor of differences in the kinetic of secretion of these cytokines and/or, of possible differences in the sensitivity of the cell receptors for these cytokines in various organs as liver (proteins of acute inflammatory phase) and bone marrow (neutrophils). However, higher neutrophil count in females could also be influenced by higher level of IL-8 in females as discussed lower.

## Sex differences in X-linked genes

Based on our observations in prepubertal children, we focused our work on X-linked genes involved in the innate immune response such as: the Toll-like receptor (TLR) 4, which activation leads to the secretion of the main inflammatory cytokines of the innate immune response; the transmembrane glycoprotein (gp)91phox of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, responsible for the respiratory burst of the monocytes and neutrophils; and the diapedesis molecule cluster of differentiation (CD) 99 located on the pseudo-autosomal region of the X chromosome.[6] Given the significant amount of blood needed to perform these experiments, we chose first to study adults of both sexes.

The percentage of monocytes expressing CD99 was higher in men than in women. CD99 is encoded by a gene, which lies on the boundary between the pseudo-autosomal region (PAR) 1 and X-linked regions. As the pseudo-autosomal regions of the sex chromosomes are equivalent, genes of this regions are supposed to be equally expressed in males and females. However, spreading the methylation process which inactivates the X-linked regions in females, across this boundary, could result in silencing some genes such as the CD99 gene, explaining the higher percentage of monocytes expressing the CD99 in males compared to females. Indeed, a higher CD99 expression in men compared to women was already reported using reverse transcription polymerase chain reaction (RT-PCR). On the contrary, CD11b, another surface marker involved in the leucocyte migration, but encoded on the chromosome 7, did not display any sex-difference, confirming the specificity of this random inactivation event to the X chromosome. As the CD99 plays a major role in leucocyte diapedesis, a higher CD99 expression in male monocytes could affect monocyte recruitment to injured tissues and participate to the sex differences in clinical studies. Production of TNF-α was also higher in males compared to females after LPS stimulation, indicating, once more, an increased *in vitro* innate immune response in males compared to females. TNF-α production also significantly correlated with monocyte count, with men having a higher monocyte count than women. This difference in monocyte count was previously described in a larger study including 200 Caucasian subjects and was confirmed in our second study, in addition to a higher monocyte count in patients with Klinefelter syndrome.[7] However, comparison of the blood cell count in more than 80 prepubertal children admitted for surgery, revealed no difference in leucocyte populations between boys and girls, indicating the possibility that the difference observed in adults in monocyte count, might be related to sex hormones. After normalization of cytokine levels to monocyte count, a higher IL-8 secretion was found in women, which may explain the higher neutrophil count we observed in girls suffering from acute inflammatory process such as sepsis, pneumonia, bronchiolitis or pyelonephritis but also from chronic inflammatory process such as asthma or cystic fibrosis, since IL-8 is a major chemoattractant.

## Sex differences in the activation of TLRs

To evaluate more precisely the respective contribution of the X chromosome and sex hormones, we measured the activation of some TLRs in subjects with different X/Y sex chromosome ratios. We used whole blood as well as purified neutrophils and monocytes to identify which phagocyte population was playing a predominant role in the sex-specific response to early inflammation. We observed significant differences between the innate immune response of men and women, and some, independently from the level of estradiol or testosterone. We confirmed that men produced higher levels of inflammatory

**Figure 1:** Physiological and pathological inflammatory responses

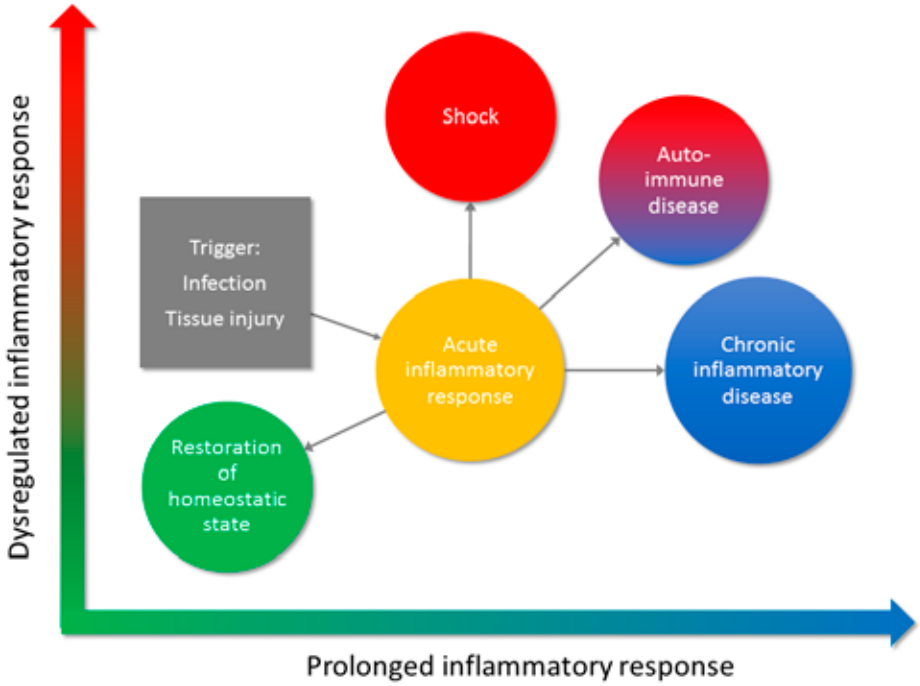
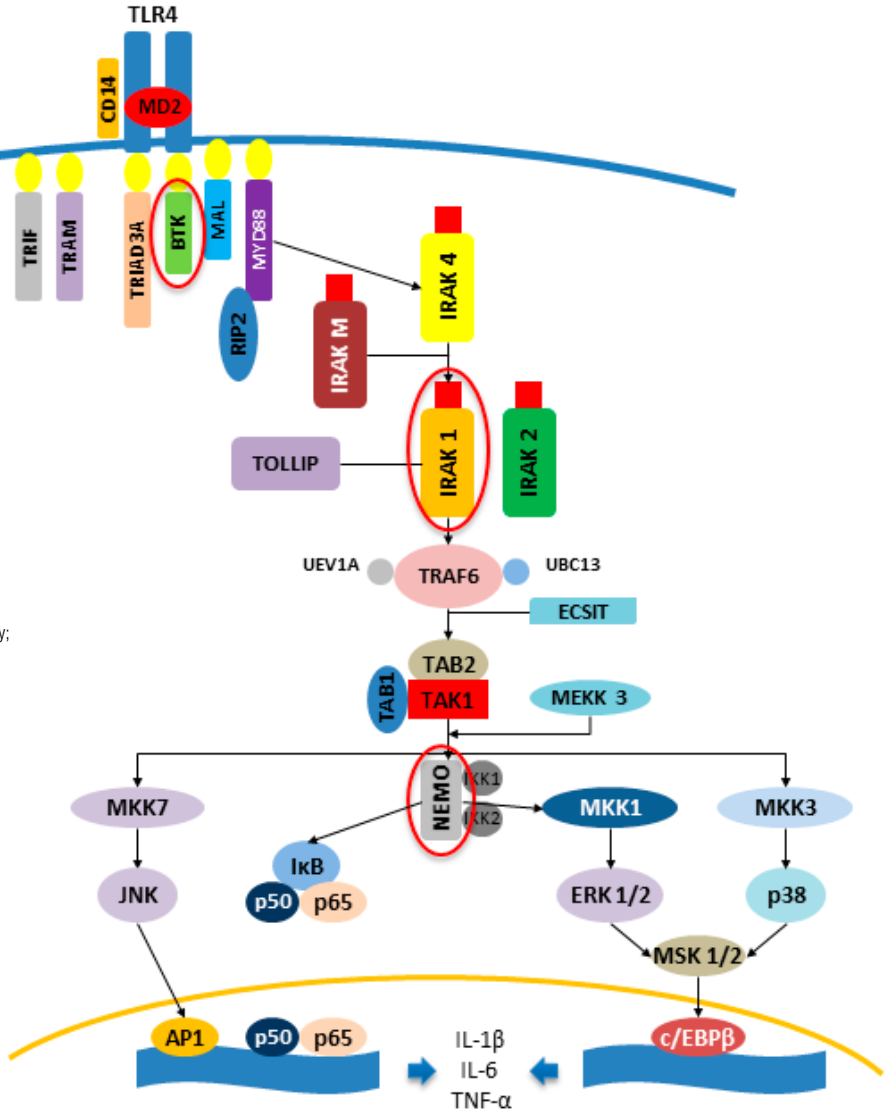



**Figure 2:** Protein kinases encoded by X-linked genes and involved in the TLR4 signaling pathway.




**MD2:** lymphocyte 96 antigen;
**TIR:** Toll/interleukin-1 receptor;
**TRIF:** TIR-domain-containing adapter-inducing interferon-β;
**TRAM:** translocating chain-associating membrane;
**TRIAD3/RNF216 :** ring finger protein 216;
**BTK:** Bruton's tyrosine kinase;
**MAL:** myelin and lymphocyte;
**MYD88:** myeloid differentiation primary response 88;
**RIP2:** receptor interacting protein-2;
**IRAK:** interleukin-1 receptor-associated kinase;
**TOLLIP:** Toll interacting protein;
**UEV1A:** ubiquitin-conjugating enzyme variant 1A;
**UBC13:** ubiquitin-conjugating enzyme 13;
**TRAF:** tumor necrosis factor receptor associated factor;
**ECSIT:** evolutionary-conserved signaling intermediate in Toll pathway;
**TAB:** TAK1-binding protein;
**TAK:** TGF-β activated kinase;
**MEKK:** MAP/ERK kinase kinase;
**NEMO:** NFκB essential modulator;
**IKK:** IκB kinase;
**IκB:** inhibitor kappa B;
**MAP:** mitogen-activated protein;
**MKK:** MAP kinase kinase;
**JNK:** c-Jun N-terminal kinase;
**p50:** NFκB subunit 1;
**p65:** NFκB subunit 3 or RELA: v-rel avian reticuloendotheliosis viral oncogene homolog A;
**ERK:** extracellular regulated MAP kinase;
**p38:** p38 MAP kinase;
**MSK:** mitogen- and stress-activated kinase;
**AP1**: activator protein 1;
**c/EBPβ:** CCAAT/enhancer-binding protein β

cytokines compared to women after stimulating whole blood with various TLR ligands, reflecting the activation of the immune system by fungal (TLR2), bacterial (TLR4), and viral (TLR7/8) products.

## Role of the X chromosome

Klinefelter patients showed a cytokine profile more similar to that of women, although their level of testosterone was much higher than women and their level of estradiol not significantly different from the women. These results observed in Klinefelter patients, who are phenotypically male but carry an extra X chromosome like women, suggest that sex chromosomes are more influential than sex steroids. Production of inflammatory cytokines in response to TLR ligands did not differ significantly according to the level of 17β-estradiol, supporting a less important role of estrogens.

In purified monocytes, activation of TLRs produced as well lower levels of inflammatory cytokines in women compared to men. Yet, in contrast with whole blood analyses, the purified monocytes of Klinefelter subjects expressed the same pattern of cytokine production as that found in males. These contrasting results might result from the absence of other immune cells in comparison with whole blood and might indicate that monocytes are probably not the cells responsible for the differences observed in whole blood or in vivo.

## Role of the sex hormones

In order to distinguish more precisely the influence of the hormones from the chromosomes, we corrected our results according to the levels of estradiol and testosterone. In whole blood, this correction revealed higher levels of IL-1β and TNF-α in women compared to subjects with Klinefelter syndrome, in response to TLR4 stimulation. In monocytes, most of the differences remained after correcting for the levels of sex hormones, indicating there to be no priming or persistent effect from the sex steroids, given that the culture medium of the purified monocytes was free of hormones. These results support that the X chromosome contributes to sex-related differences in cytokine secretion, independently of levels of the two main sex hormones. Although the sex-specific response of the TLRs seems to be based on gene expression, it is probably regulated by the hormonal environment, hence the discrepancies after adjusting for estradiol and testosterone levels. In this context, it is important to remember that hormonal levels are determined by karyotype. Therefore, statistical correction of estradiol and testosterone as covariates could have artificially modified the results, assuming both hormone levels and immune parameters are equally modulated by sex chromosome balance.

Likewise, estradiol levels did not seem to influence inflammatory cytokine production or TLR4 expression in women in reproductive age between the beginning and the end of the follicular phase characterized by low and high level of estradiol, respectively.

## Limitations of the *in vitro* model

Our *in vitro* studies revealed higher inflammatory cytokine production in response to various TLRs ligands, in males compared to females, either children or adults. However, these results contrast with some observations obtained in vivo about increased inflammatory markers in females. This paradox might be explained by other cells not included in the ex vivo experiments, such as endothelial cells. Endothelial cells play a major role in inflammation by regulating activation and migration of the immune cells through expression of adhesion molecules and liberation of numerous inflammatory mediators.[8,9] Besides, numerous innate and adaptive immune cells reside in non-lymphoid tissues, participating to tissue function and homeostasis in the skin, the lungs, the intestines and the liver.[10–12] Hepatocytes perform multiple immunological roles by producing proteins of the acute phase response, the complement or anti-microbial proteins but also play a role in antigen presentation, endotoxin removal or detoxification.[13,14] Another important factor is the timing and/or the kinetic of the response, far more controlled in an *in vitro* stimulation than a clinical observation.

## Perspectives

Despite major differences between male and females in immunological processes, most of the studies either do not take into account sex in their data analysis, or do not report the sex of their subjects.[15] These sexual bias and the under-representation of females in animal and clinical studies leaded to uncomplete understanding of certain sex-specific processes in diseases and poorly female adapted treatments.[16] Sex differences in pharmacokinetics and pharmacodynamics are found in numerous classes of drugs and contribute to the variations in drug efficacy and toxicity. Anti-inflammatory drugs exert sexually dimorphic effects on both animals and humans and sex may, among others, influence the potency of anti-inflammatory drugs, such as steroids.[17-18]

The comprehension of the inherent biological advantages of either sex may lead to new therapeutic strategies aimed to improve responses against infections and traumas in males and reduce the risk of auto-immune diseases and tissue damage in chronic inflammatory disease in females.[5]

## Conclusion

The results presented in this dissertation have contributed to the understanding of the potential role of the X chromosome relatively to the sex hormones in the sex-specific innate immune response. In prepubertal children, whose levels of sex hormones are very low and probably insufficient to influence the immune response, we observed, in vivo, higher inflammatory response in girls compared to boys. Meanwhile, inflammatory cytokine production after TLR *in vitro* stimulation was higher in males and subjects carrying only one X chromosome, compared to females and subjects carrying two copies of the X chromosome, independently from the sex steroids levels. These sex chromosomes-related differences between subjects carrying only one X chromosome and those with two X chromosomes, who potentially benefit of a cellular mosaicism for the X-linked genes, may be related to polymorphisms of X-linked genes. This mechanism could give females an advantage in case of acute inflammatory process but would lead to increased inflammatory damages in case of chronic inflammatory response with a worse prognosis, and this from early in life.

Although our work does not have the pretention to have elucidated the complex and multiple mechanisms responsible for the numerous specificities observed between the males and the females in various diseases, it highlighted important sex differences in terms of in vivo acute inflammatory response and *in vitro* activation of certain X-linked genes, which cannot be explained by the sex steroid levels, thus supporting the role of sex chromosomes in inflammatory response.

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# Bexsero: het eerste vaccin tegen meningokokken van serogroep B.

## Het enige geïndiceerd vanaf 2 maanden.[1,2]

**BEXSERO**

**Vaccin tegen meningokokken van groep B (rDNA, component, geadsorbeerd)**

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN Gelieve de Samenvatting van de Produktkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. ▼ 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 "Bijwerkingen" voor het rapporteren van bijwerkingen. NAAM VAN HET GENEESMIDDEL Bexsero suspensie voor injectie in voorgevulde spuit. Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd) EU/1/12/812/001. Farmacotherapeutische categorie: meningokokkenvaccins, ATCcode: J07AH09 KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Een dosis (0,5 ml) bevat: Recombinant *Neisseria meningitidis* groep B NHBAfusieeiwit [1, 2, 3] : 50 microgram Recombinant *Neisseria meningitidis* groep B NadAeiwit [1, 2, 3] : 50 microgram Recombinant *Neisseria meningitidis* groep B fHbpfusieeiwit [1, 2, 3] : 50 microgram Buitenmembraanvesikels (BMV) van *Neisseria meningitidis* groep Bstam NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat [2] : 25 microgram [1] Geproduceerd in *E. coli*cellen door recombinantDNAtechnologie [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg $Al^{3+}$) [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit) THERAPEUTISCHE INDICATIES Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. DOSERING EN WIJZE VAN TOEDIENING Dosering

**Tabel 1. Samenvatting van de dosering**

| Leeftijd bij eerste dosis | Primaire immunisatie | Intervallen tussen primaire doses | Booster |
|---|---|---|---|
| **Zuigelingen van 2 tot en met 5 maanden** [a] | Drie doses, elk van 0,5 ml | Niet minder dan 1 maand | Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis [b,c] |
| **Zuigelingen van 3 tot en met 5 maanden** | Twee doses, elk van 0,5 ml | Niet minder dan 2 maanden | |
| **Zuigelingen van 6 tot en met 11 maanden** | Twee doses, elk van 0,5 ml | Niet minder dan 2 maanden | Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis [c] |
| **Kinderen van 12 tot en met 23 maanden** | Twee doses, elk van 0,5 ml | Niet minder dan 2 maanden | Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis [c] |
| **Kinderen van 2 tot en met 10 jaar** | Twee doses, elk van 0,5 ml | Niet minder dan 1 maand | Noodzaak niet vastgesteld [d] |
| **Adolescenten (11 jaar of ouder)en volwassenen*** | Twee doses, elk van 0,5 ml | Niet minder dan 1 maand | Noodzaak niet vastgesteld [d] |

[a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor een boosterdosis na dit vaccinatieschema is niet vastgesteld [d] Zie rubriek 5.1 van de volledige SPK. * Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. CONTRAINDICATIES Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). BIJZONDERE WAARSCHUWINGEN EN VOORZORGEN BIJ GEBRUIK Zoals dat voor alle vaccins geldt, dient ook toediening van Bexsero te worden uitgesteld bij personen die lijden aan een acute, ernstige, met koorts gepaard gaande ziekte. De aanwezigheid van een lichte infectie, zoals verkoudheid, mag echter niet leiden tot uitstel van vaccinatie. Niet intravasculair injecteren. Zoals dat voor alle injecteerbare vaccins geldt, dienen passende medische behandeling en toezicht altijd direct beschikbaar te zijn voor het geval zich na toediening van het vaccin een anafylactische reactie voordoet. Reacties die verband houden met angst, waaronder vasovagale reacties (syncope), hyperventilatie of stressgerelateerde reacties, kunnen in relatie met vaccinatie voorkomen als psychogene reactie op de naaldinjectie (zie rubriek "Bijwerkingen"). Het is belangrijk dat er passende procedures zijn om letsel als gevolg van flauwvallen te voorkomen. Dit vaccin mag niet worden toegediend aan personen met trombocytopenie of een bloedstollingsstoornis die een contraindicatie voor intramusculaire injectie vormt, tenzij het mogelijke voordeel duidelijk opweegt tegen het risico van toediening. Zoals dat voor alle vaccins geldt, beschermt vaccinatie met Bexsero mogelijk niet alle gevaccineerden. Bexsero wordt niet geacht bescherming te bieden tegen alle circulerende meningokokken Bstammen. Zoals dat voor veel vaccins geldt, moet het medisch personeel zich ervan bewust zijn dat een temperatuursstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Individuen met een immunodeficiëntie, door het gebruik van immunosupressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van individuen met complement deficiëntie, asplenie of miltdisfuncties. Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. BIJWERKINGEN Overzicht van het veiligheidsprofiel De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38**°C**) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥1/10) Vaak: (≥1/100, <1/10) Soms: (≥1/1.000, <1/100) Zelden: (≥1/10.000, <1/1.000) Zeer zelden: (<1/10.000) Niet bekend: (kan met de beschikbare gegevens niet worden bepaald) De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar)** Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Voedings en stofwisselingsstoornissen Zeer vaak: eetstoornissen Zenuwstelselaandoeningen Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn Soms: insulten (inclusief febriele insulten) Niet bekend: hypotoon – hyporesponsieve episode Bloedvataandoeningen Soms: bleekheid (zelden na booster) Zelden: ziekte van Kawasaki Maagdarmstelselaandoeningen Zeer vaak: diarree, braken (soms na booster) Huid en onderhuidaandoeningen Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster) Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar) Soms: eczeem Zelden: urticaria Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: koorts (≥38°C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid Soms: koorts (≥40°C) Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) **Adolescenten (van 11 jaar en ouder) en volwassenen** Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Zenuwstelselaandoeningen Zeer vaak: hoofdpijn Niet bekend: syncope of vasovagale reacties op injectie Maagdarmstelselaandoeningen Zeer vaak: misselijkheid Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: myalgie, artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) **Melding van vermoedelijke bijwerkingen** Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België** Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie EUROSTATION II Victor Hortaplein, 40/40 B-1060 Brussel Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be **Luxemburg** Direction de la Santé – Division de la Pharmacie et des Médicaments Villa Louvigny – Allée Marconi L-2120 Luxembourg Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië DATUM VAN DE GOEDKEURING VAN DE TEKST 06/2018(v05) **AFLEVERINGSWIJZE** Op medisch voorschrift.

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# Haematuria in children : a pragmatic approach

An Bael

ZNA Koningin Paola Hospital Antwerp

## 1/ How to test?

*Urinary dipstick :*
Positive = blood, free haemoglobin or myoglobin
Negative = pigments from food or drugs (red beets / rifampicin), metabolites (e.g. porphyria)

*Urine centrifugation :*
- Sediment red/brown: most likely blood
- Supernatant red/brown: haemoglobin or myoglobin

*Microscopic examination of the sediment :*
Confirmation red blood cells (RBC) (dysmorphic? normal?)

## 2/ What to ask for? History

- Recent vigorous exercise
- Trauma
- Incontinence / dysuria / frequency / urgency / fever / flank pain: urinary tract infection (UTI)?
- Flank pain with radiation to groin: stone/blood clot/ obstruction
- Colour: brownish / pink/red
- Timing: onset of micturition = urethral / end of micturition = bladder
- Upper respiratory tract infection / pharyngitis/impetigo: post-streptococcal glomerulonephritis
- Predisposing condition: sickle cell disease
- Medication: NSAID, Cyclophosphamide

## 3/ What to look for? Physical examination

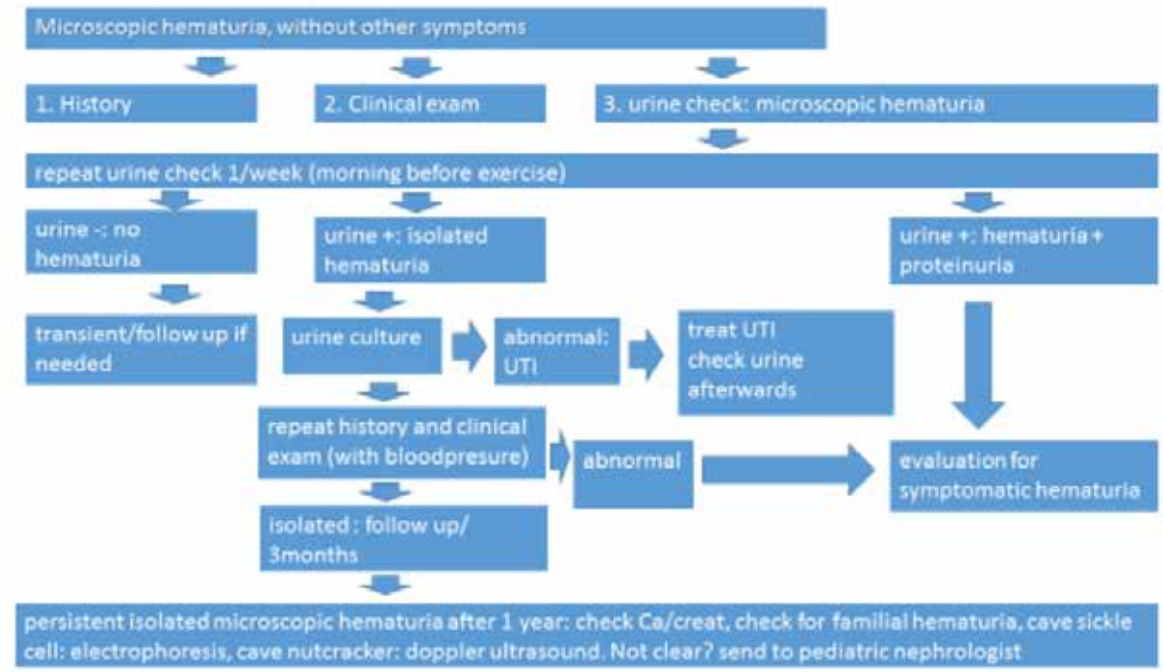
- Blood pressure: high = glomerular disease? / low = bleeding?
- Weight (weight gain) / oedema
- Skin examination: rash? purpura? possible systemic disease
- Evaluation of genitals
- Abdominal masses?

## 4/ Further evaluation:

### *A. If microscopic / asymptomatic: KEEP CALM*

Transient : UTI / trauma / fever / exercise / urethritis / irritation of meatus or perineum

Persistent: glomerulonephritis- glomerulopathies (post infectious, IgA, Alport, Thin Basement membrane nephropathy), nephrolithiasis / hypercalciuria / nutcracker syndrome)

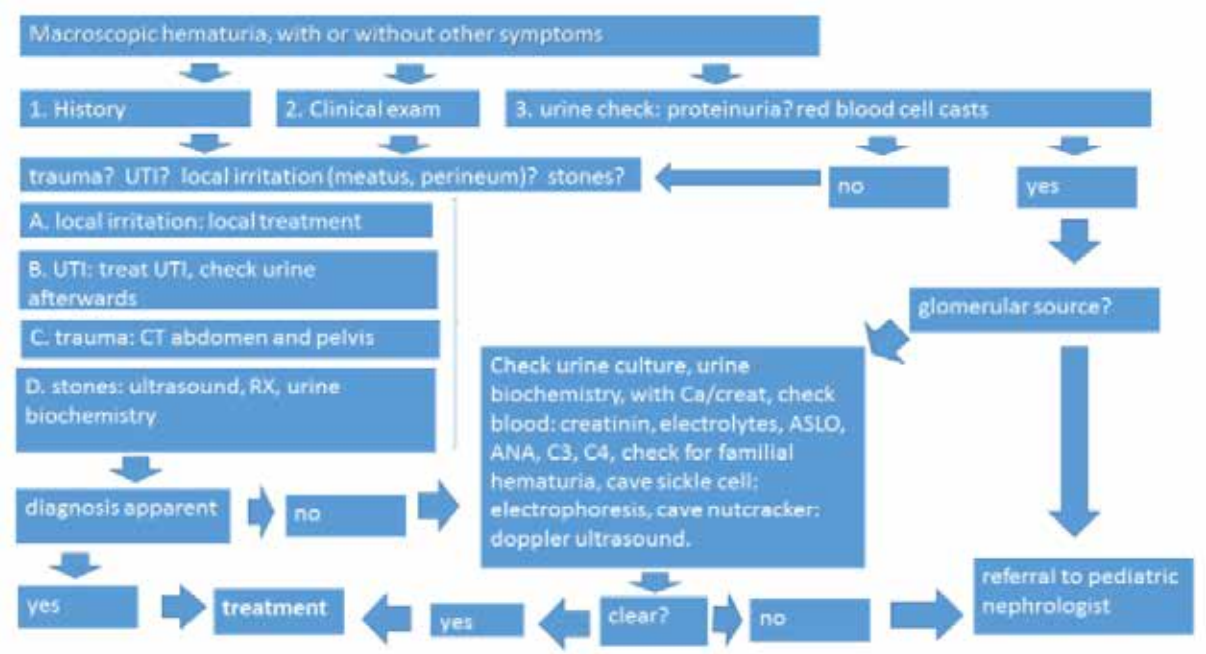



Modified from: Patel HP, Bissler JJ. Hematuria in children. Pediatr Clin North Am 2001; 48:1519

### *B. if Macroscopic (visible to the naked eye)/ symptomatic: DON'T WASTE TIME*

Most frequent : UTI / irritation of meatus or perineum / trauma

Less common : nephrolithiasis / sickle cell disease / coagulopathy / glomerular disease (postinfectious glomerulonephritis, Ig A nephropathy, Alport, Henoch-Schönlein, SLE) / malignancies (Wilms) / drug induced / interstitial or tubular disease: e.g. interstitial nephritis)




Modified from: Patel HP, Bissler JJ. Hematuria in children. Pediatr Clin North Am 2001; 48:1519.

### *C. How to make the distinction between glomerular/non-glomerular haematuria?*

*Glomerular:*

- Red cell casts
- Protein excretion greater than 100 mg/m2 (at a time when there is no gross bleeding). First morning sample to exclude orthostatic proteinuria
- Dysmorphic RBCs .

*Non-glomerular:*

- urinary RBCs with normal size and shape.
  (Exception: hypercalciuria can be associated with dysmorphic RBCs, but not red cell casts.)

### *D. Kidney biopsy: when?*

- To be performed only if there are signs suggestive of more severe or progressive disease: urine protein excretion of at least 500 mg/day, elevated serum creatinine, hypertension.

### *E. Genetic testing:*

- Alport/TBS (Thin Basement Syndrome): Genetic testing for mutations in COL4A3, COL4A4, and COL4A5 is commercially available in the United States and Europe.

### *F. REMEMBER: There is always a kind paediatric nephrologist nearby to talk to and change ideas!*

In collaboration with Cebam, Cochrane Belgium
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# Glucocorticoids may reduce symptoms of croup within two and up to 24 hours

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## Clinical question

Are glucocorticoids effective to treat croup in children?

## Context

Croup, pseudo croup or laryngotracheobronchitis is a frequent cause of upper airway obstruction in young children, usually caused by a viral infection. The main symptoms include hoarseness, a barking cough and inspiratory stridor probably due to oedema of the larynx and trachea. Glucocorticoids could reduce this swelling and, hence, make it easier to breathe again. The first Cochrane review regarding glucocorticoids for croup was published in 1999 and this update integrates the latest randomized controlled trials (RCTs) with the existing evidence. The review included RCTs that compared glucocorticoids (any type, dose or mode of administration), alone or in combination, to placebo or any other pharmacological intervention. These studies included children aged 0 to 18 years old who were diagnosed with croup, pseudo croup or laryngotracheitis. The main outcomes of interest were (1) changes in clinical croup score from baseline to 2, 6, 12 and/or 24 hours of treatment and (2) return visits or (re)admissions to the hospital or both.

## Summary of the results

The authors included five new trials with 330 children in this update and the review now contains 43 studies with a total of 4565 children.

Half of the studies (22, 49%) described outpatient children presenting at an emergency department (21 RCTs) or a physician office (1 RCT) and the other half (21 RCTs) assessed hospitalised children.

The investigated glucocorticoids included beclomethasone, betamethasone, budesonide, dexamethasone, fluticasone and prednisolone. Most studies (26, 60%) compared any glucocorticoid to placebo. Of those, 15 (58%) tested dexamethasone compared to placebo. Eleven studies (26%) compared one glucocorticoid to another and three (7%) compared one glucocorticoid to a combination of glucocorticoids. Five studies (12%) compared glucocorticoids given in different ways. Four studies (9%) compared glucocorticoids given in different amounts.

Compared to placebo, glucocorticoids resulted in a greater reduction of croup scores at two hours (SMD*: -0.65, 95% CI^ from -1.13 to -0.18, 7 studies, 426 children). This effect lasted for at least 24 hours after the start of treatment (SMD: -0.86, 95% CI from -1.40 to -0.31, 8 studies, 351 children). Furthermore, the risk for a return visits and/or (re)admission to the hospital was reduced by almost 50% in children treated with glucocorticoids compared to those given placebo (RR‡: 0.52, 95% CI from 0.36 to 0.75, 10 studies, 1679 children). Additionally, glucocorticoids reduced length of stay in the hospital or emergency department by 15 hours (MD¤, 95% CI from -23.58 to -6.22, 8 studies, 476 children). Only half of the studies collected data on adverse events, but serious adverse events such as secondary infections (e.g. pneumonia, ear infection) were rare.

Data from head-to-head trials show that dexamethasone is more effective than budesonide at reducing the symptoms of croup after six (SMD -0.46, 95% CI -0.79 to -0.13, 4 studies, 326 children) and 12 hours (SMD -0.75, 95% CI -1.19 to -0.30, 2 studies, 84 children). There was no difference between dexamethasone and budesonide in rates of return visits and/or (re)admissions (RR 0.69, 95% CI 0.40 to 1.22, 5 studies, 374 children). Combined dexamethasone and budesonide in comparison to using either treatment alone did not reduce croup symptoms or rate of return visits and/or hospital (re)admissions.

The other comparisons in this review often contained one or two small studies so it is not possible to draw any strong conclusions from them.

## Remarks

The evidence presented in this review is of moderate to low quality. The reason for lowering our confidence is the risk of bias in the studies and large heterogeneity between the studies. Some of the heterogeneity can be explained by the need to combine studies on outpatients with studies on hospitalised patients into one analysis. In other comparisons, studies using different doses, modes of administration or types of corticosteroids had to be combined to answer the research question.

## Conclusion

Glucocorticoids seem to reduce the symptoms of croup after two hours of treatment and the effects lasts for 24 hours. It also seems to result in fewer return visits or hospital (re)admissions. Dexamethasone seems to be more effective than budesonide. There were insufficient data to draw conclusions about the role of other glucocorticoids (e.g. fluticasone, prednisolone). It remains uncertain which type of corticosteroid, dose or mode of administration is the best.

## Implications for practice

Glucocorticoids should be considered to reduce symptoms of croup in children. Some data favour the use of dexamethasone over budenoside or a combination of dexamethasone and budenoside. However, dose, mode of administration and choice of type are largely still up to the preference of the treating physician and the treated children.

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* **SMD:** standardised mean difference
^ **CI:** confidence interval
‡ **RR:** risk ratio
¤ **MD:** mean difference

# Asymmetric crying facies and pulmonary agenesis

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I read with interest the review article on congenital pulmonary malformations published in BJP[1]. Pulmonary agenesis is a rare congenital malformation of lung development. In 1976, we reported the association of peripheral facial paralysis (asymmetric crying facies), malformation of the homolateral ear, and contralateral pulmonary agenesis[2]. At the same time, three well documented observations of patients with lung aplasia and asymmetric crying facies were published[3]. Reviewing the literature, we found another interesting case described in an old French publication of 1924, which associates left facial paralysis, hypoplasia of the auricle of the left ear with absence of the external auditory meatus, and agenesis of the right lung[4]. The resemblance of these five cases with asymmetric crying facies and pulmonary agenesis allowed us to evoke a new entity[5,6]. In 2006, Nazir et al reported a similar case to ours[7].

Practically, the existence of facial asymmetry in the newborn during crying or screaming should instigate a search for associated visceral malformations, namely cervico-facial, urogenital, musculoskeletal, neurological, but also respiratory malformations.

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

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**Tableau 1. Résumé de la posologie**

| Age lors de la première dose | Primovaccination | Intervalles entre les doses de primovaccination | Rappel |
|---|---|---|---|
| **Nourrissons de 2 à 5 mois** | Trois doses de 0,5 ml chacune, | 1 mois minimum | Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel [b,c] |
| **Nourrissons de 3 à 5 mois** | Deux doses de 0,5 ml chacune | 2 mois minimum | |
| **Nourrissons de 6 à 11 mois** | Deux doses de 0,5 ml chacune | 2 mois minimum | Oui, une dose au cours de la deuxième année avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel [c] |
| **Enfants de 12 à 23 mois** | Deux doses de 0,5 ml chacune | 2 mois minimum | Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel [c] |
| **Enfants de 2 à 10 ans** | Deux doses de 0,5 ml chacune | 1 mois minimum | Besoin non établi [d] |
| **Adolescents (à partir de 11 ans)et adultes*** | Deux doses de 0,5 ml chacune | 1 mois minimum | Besoin non établi [d] |

[a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b] En cas de retard, la dose de rappel ne doit pas être administrée au-delà de l'âge de 24 mois. [c] Voir rubrique 5.1 du RCP complet. La nécessité et le moment d'administration d'une dose de rappel n'ont pas encore été déterminés. [d] Voir rubrique 5.1 du RCP complet. * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, sous-cutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **CONTRE-INDICATIONS** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **MISES EN GARDE SPÉCIALES ET PRÉCAUTIONS D'EMPLOI** Comme pour les autres vaccins l'administration de Bexsero doit être reportée chez des sujets souffrant de maladie fébrile sévère aiguë. Toutefois, la présence d'une infection mineure, telle qu'un rhume, ne doit pas entraîner le report de la vaccination. Ne pas injecter par voie intravasculaire. Comme pour tout vaccin injectable, un traitement médical approprié et une surveillance adéquate doivent toujours être disponibles en cas de réaction anaphylactique consécutive à l'administration du vaccin. Des réactions en rapport avec l'anxiété, y compris des réactions vaso-vagales (syncope), de l'hyperventilation ou des réactions en rapport avec le stress peuvent survenir lors de la vaccination comme réaction psychogène à l'injection avec une aiguille (voir rubrique « Effets indésirables »). Il est important que des mesures soient mises en place afin d'éviter toute blessure en cas d'évanouissement. Ce vaccin ne doit pas être administré aux patients ayant une thrombocytopénie ou tout autre trouble de la coagulation qui serait une contre-indication à une injection par voie intramusculaire, à moins que le bénéfice potentiel ne soit clairement supérieur aux risques inhérents à l'administration. Comme tout vaccin, la vaccination avec Bexsero peut ne pas protéger tous les sujets vaccinés. Il n'est pas attendu que Bexsero assure une protection contre la totalité des souches de méningocoque B en circulation. Comme pour de nombreux vaccins, les professionnels de santé doivent savoir qu'une élévation de la température corporelle peut survenir suite à la vaccination des nourrissons et des enfants (de moins de 2 ans). L'administration d'antipyrétiques à titre prophylactique pendant et juste après la vaccination peut réduire l'incidence et la sévérité des réactions fébriles post-vaccinales. Un traitement antipyrétique doit être mis en place conformément aux recommandations locales chez les nourrissons et les enfants (de moins de 2 ans). Les personnes dont la réponse immunitaire est altérée soit par la prise d'un traitement immunosuppresseur, une anomalie génétique ou par d'autres causes, peuvent avoir une réponse en anticorps réduite après vaccination. Des données d'immunogénicité sont disponibles chez les patients présentant un déficit en complément, une asplénie ou une dysfonction splénique. Il n'existe aucune donnée sur l'utilisation de Bexsero chez les sujets de plus de 50 ans et il existe des données limitées chez les patients atteints de maladies chroniques. Le risque potentiel d'apnée et la nécessité d'une surveillance respiratoire pendant 48 à 72 heures doivent soigneusement être pris en compte lors de l'administration des doses de primovaccination chez des grands prématurés (nés à 28 semaines de grossesse ou moins), en particulier chez ceux ayant des antécédents d'immaturité respiratoire. En raison du bénéfice élevé de la vaccination chez ces nourrissons, l'administration ne doit pas être suspendue ou reportée. Le capuchon de la seringue peut contenir du latex de caoutchouc naturel. Bien que le risque de développer des réactions allergiques soit très faible, les professionnels de santé doivent évaluer le rapport bénéfices/risques avant d'administrer ce vaccin à des sujets présentant des antécédents connus d'hypersensibilité au latex. La kanamycine est utilisée au début du procédé de fabrication et est éliminée au cours des étapes ultérieures de la fabrication. Les taux de kanamycine éventuellement détectables dans le vaccin final sont inférieurs à 0,01 microgramme par dose. L'innocuité de Bexsero chez les sujets sensibles à la kanamycine n'a pas été établie. **EFFETS INDÉSIRABLES** Résumé du profil de sécurité La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6837 étaient des nourrissons et des enfants (de moins de 2 ans), 1051 étaient des enfants (entre 2 et 10 ans) et 2677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3285 ont reçu une dose de rappel au cours de leur deuxième année de vie.. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69% à 79 % des sujets lorsque Bexsero était co-administré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et ***Haemophilus influenzae*** de type b), contre 44% à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés avec Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) Fréquent : (≥ 1/100 à < 1/10) Peu fréquent : (≥ 1/1 000 à < 1/100) Rare : (≥ 1/10 000 à < 1/1 000) Très rare : (< 1/10 000) Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles) Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans)** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Troubles du métabolisme et de la nutrition Très fréquent : troubles alimentaires Affections du système nerveux Très fréquent : somnolence, pleurs inhabituels, céphalée Peu fréquent : convulsions (y compris convulsions fébriles) Fréquence indéterminée : épisode d'hypotonie-hyporéactivité Affections vasculaires Peu fréquent : pâleur (rare après le rappel) Rare : syndrome de Kawasaki Affections gastro-intestinales Très fréquent : diarrhée, vomissements (peu fréquents après le rappel) Affections de la peau et du tissu sous-cutané Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel) Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans) Peu fréquent : eczéma Rare : urticaire Affections musculo-squelettiques et systémiques Très fréquent : arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité Peu fréquent : fièvre (≥ 40 °C) Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois) **Adolescents (à partir de 11 ans) et adultes** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Affections du système nerveux Très fréquent : céphalée Fréquence indéterminée : syncope ou réaction vaso-vagale à l'injection Affections gastro-intestinales Très fréquent : nausées Affections musculo-squelettiques et systémiques Très fréquent : myalgies, arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois) **Déclaration des effets indésirables suspectés** La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique** Agence fédérale des médicaments et des produits de santé Division Vigilance EUROSTATION II Place Victor Horta, 40/40 B-1060 Bruxelles Site internet: www.afmps.be e-mail: adversedrugreactions@fagg-afmps.be **Luxembourg** Direction de la Santé – Division de la Pharmacie et des Médicaments Villa Louvigny – Allée Marconi L-2120 Luxembourg Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ** GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Sienne, Italie **DATE D'APPROBATION DU TEXTE** 06/2018(v05) **MODE DE DELIVRANCE** Sur prescription médicale.

1. Bexsero SMPC 2. Medini D, Stella M, Wassil J, Vaccine 2015; 33; 2629-2636

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