

INCREASING NUMBER OF INVASIVE INFECTIONS WITH GROUP A STREPTOCOCCI (iGAS)

RAG 17/01/23 - validated on 19/01/2022 by the RMG, except the recommendation on a uniform case definition, which remains for regional health authorities to decide.

1. Context

On the 2nd of December 2022, the UK reported an increased number of scarlet fever and invasive GAS infections (including several deaths in children <10y of age), above expected levels for the time of year. Following this, several EU/EEA countries also confirmed an increase in GAS infections in 2022, especially in children <10y of age. WHO Europe sent out a press release on the 12th of December to raise awareness. Early data did not indicate a new circulating strain or increased antibiotic resistance, but rather pointed towards a combination of factors leading to the increase. Reduced exposure during the pandemic years, increased closed contacts after relaxation of NPIs and increased circulation of viral illnesses such as varicella, Influenza and RSV (which increase the risk of iGAS) probably all contribute.

In Belgium, a rapid signal assessment was conducted on 8th of December 2022. As in other countries, an increase in cases was indeed seen, with in particular an unusual spike in cases in June. The regional health authorities were informed and a communication to healthcare workers was sent out via the "flash infectious diseases" and through professional networks of pediatricians. However, as regional health authorities observed an unusually high peak of notifications of iGAS in December, a more elaborate Risk Assessment involving external experts is now conducted.

2. Recommendations

1. Increase awareness and reduce transmission by communication

- to the general public
 - o repeating the importance of basic prevention measures (hand & respiratory hygiene, ventilation) and staying home when sick, to reduce transmission
 - o use paracetamol as the drug of 1st choice in case of pain and fever and seek medical attention when worried or clinical worsening after 3 days
- to first line healthcare providers:
 - o to raise awareness to ensure timely diagnosis
 - o no changes required in treatment guidelines for pharyngitis and mild GAS infections
- to hospital-based healthcare providers:
 - o to raise awareness to ensure timely diagnosis
 - o to notify regional health authorities and send strains to the NRC
 - o to treat according to standards of practice and accepted guidelines (including potential use of IVIG for STSS/necrotizing fasciitis/ICU admission)

2. Prevent secondary cases

- by correctly informing close contacts about the increased risks and give antibiotic prophylaxis where appropriate
- to increase chances of correct notification to the health authorities and collect more information, a **common case definition for notification** should be used, including fasciitis necroticans, toxic shock syndrome, puerperal sepsis and ICU admission or death due to GAS infection.
- it is the responsibility of regional health authorities to decide when to give antibiotic prophylaxis, but they are encouraged to review the antibiotic regimen they propose, preferably choosing a narrow-spectrum type of antibiotics.

3. Further close monitoring of the situation, using all available surveillance networks

4. As Varicella increases the risk of iGAS infections, the NITAG and responsible authorities for vaccination programmes are asked to take iGAS epidemiology into account when decisions on (reimbursement of) **varicella vaccination** are made.

5. The RIZIV-INAMI is asked to consider **reimbursement of feniticilline syrup**, which is useful for correct treatment of GAS in children.

3. Current situation in Belgium

3.1. EPIDEMIOLOGY

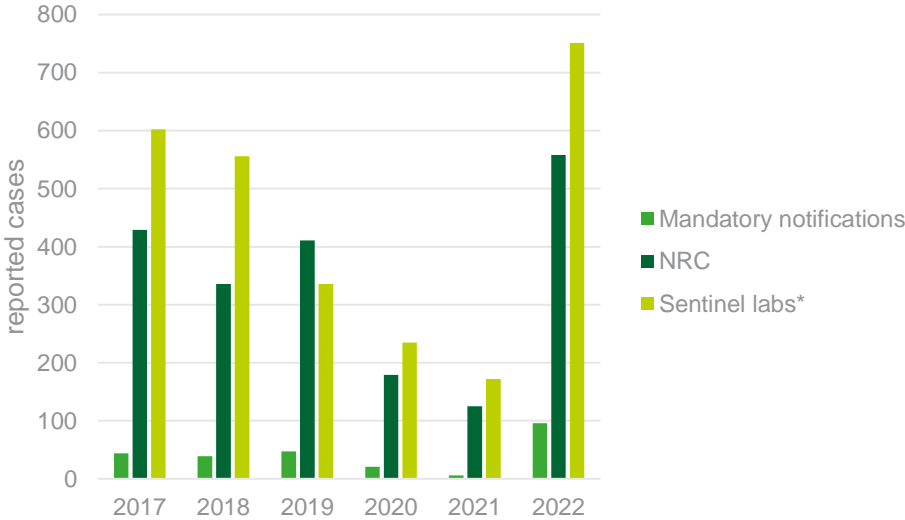
Three surveillance systems exist in Belgium to follow up iGAS: the National Reference Centre (UZA), mandatory notification to the regions, and the network of sentinel labs. Clinicians are asked (but not legally required) to send isolates of iGAS to the NRC for confirmation of diagnosis and genotyping. Notification of the regional health authorities is mandatory for all iGAS infections, but case definitions differ between regions (see below) and underreporting is likely. Finally, labs participating to the sentinel lab network (SL) are asked to monthly report samples from a normally sterile site where GAS is detected. However, not all sentinel labs follow the case definition. As information on sample type was missing for 79.4% of all reported samples by the SL, the data from SL are best interpreted to reflect general trends in circulation of GAS (both invasive and non-invasive).

In all three surveillance networks, there was a clear reduction in cases throughout the pandemic years 2020 and 2021 and a high total number of reported cases for 2022 (Table and Figure 1). Of note, reporting for December is still incomplete for SL.

Table 1-Fig1. Yearly reported number of (i)GAS cases through different surveillance networks, Belgium

	2017	2018	2019	2020	2021	2022
Mandatory notifications	44	39	47	21	6	96
NRC	429	336	411	179	125	558
Sentinel labs*	602	556	336	235	172	751

*mix of iGAS and GAS. Reporting for December is still incomplete



However, whereas the mandatory notifications show more than double the number of reported cases in 2022 compared to the average of 2017-2019 (+122%), the increase is less pronounced in the other surveillance systems (SL +51%, NRC +42%). **The number of mandatory notifications seems to have been unusually high in the month of December, with 53% of all cases for 2022 being reported in that single month** (n=51, FL=19 / BXL=6 / WAL=26). There might however be an influence of increased awareness and reporting, as in the NRC data only 21% of the yearly total was reported in December (n=116, FL=69 / BXL=20 / WAL=21 / UNK=6). In both surveillance systems levels for Oct-Dec were clearly higher than usual (Figure 2) Generally, cases of iGAS peak in early spring, but in the NRC data for 2022 there was a very unusual peak in June. Changed seasonality has also been observed for other

respiratory viruses, most likely as a result of non-pharmaceutical interventions during large parts of 2020 and 2021.

Fig.2. Monthly number of cases of iGAS by mandatory notification (above) or NRC (below), 2017-2022, Belgium

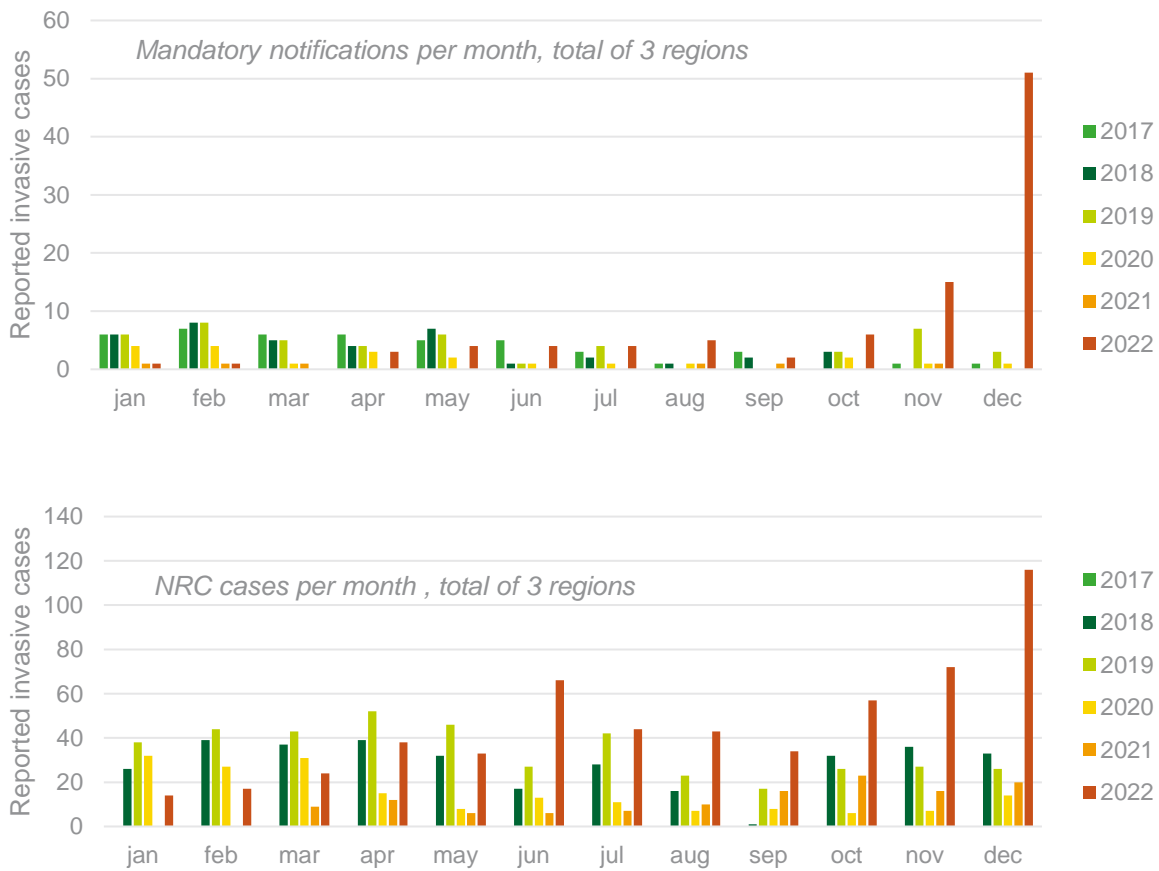


Figure 3 (next page) shows the number of cases reported to the NRC by month and age group, either as absolute numbers (above) or as a relative proportion of the total number of cases. Risk groups for iGAS are **young children and elderly**, and these groups did indeed see the **largest increase in absolute case numbers, particularly in June and December**. This peaks might be linked to peaks in circulation of other viral infections that predispose to iGAS, such as Varicella (peak in June), RSV (November) and Influenza (December). The relative importance of age groups seems broadly similar to pre-COVID years. From 2017-2019, on average 16.3% of all cases occurred in children <5y of age, compared to 22.6% in 2022.

Distribution of genotypes is different in <5y and 65+ (Figure 4). M1, M12 and M4 are dominant in the <5y, with a marked peak of M12 in June 2022 and a high proportion of M1 in November. Genotyping data for December is still largely unknown.

Fig. 4 Number of iGAS isolates by month and genotype, NRC, Belgium 2018-2022

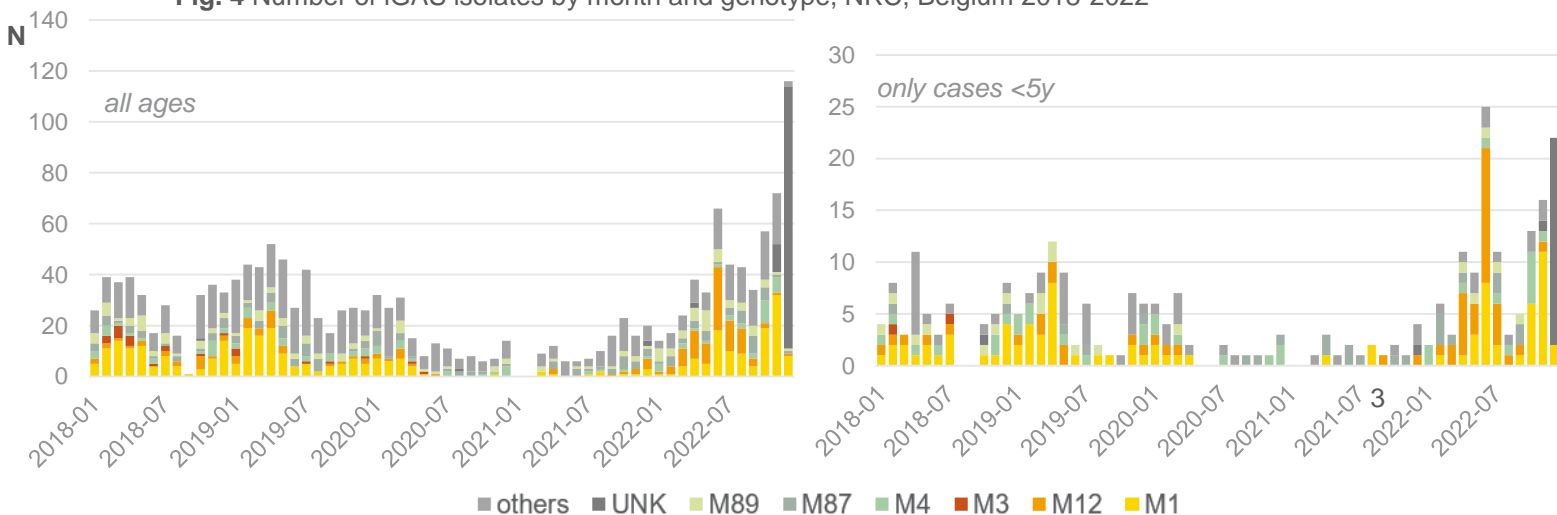
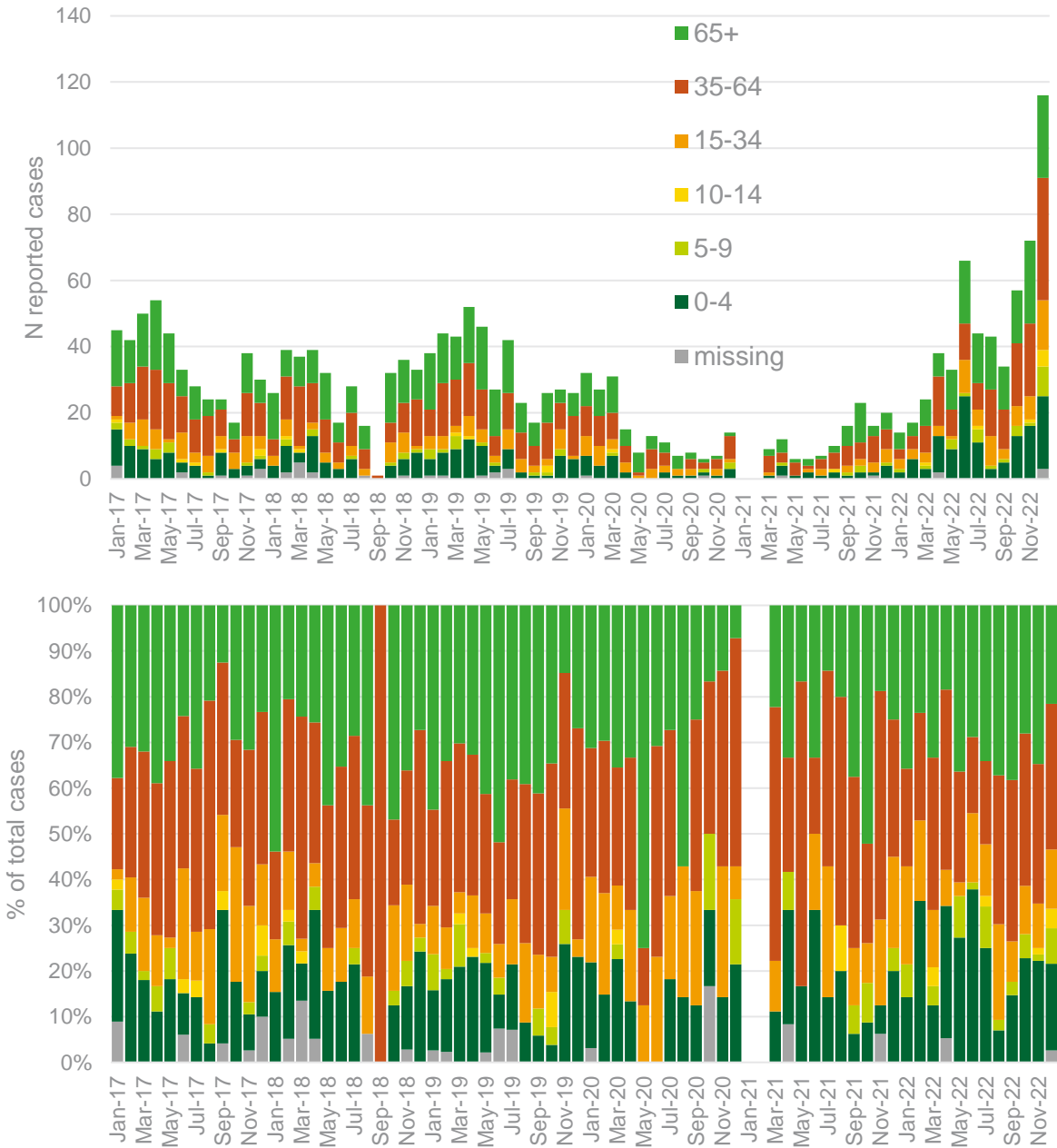


Fig. 3: Monthly number of iGAS cases reported to the NRC, by age group, Belgium 2017-2022



According to the NRC data, between 2017-2019 there were **16-36 deaths each year** due to iGAS (average 28/year). In 2022, a total of 33 deaths was reported. Of these deaths, 21 (64%) were in people aged 65 and older, compared to an average of 15 deaths (53%) in elderly people for the years 2017-2019 and 3 were in children <5 years (compared to 1-6 for 2017-2019). Of note, information on the outcome is mostly missing: in 2022, information was only available for 15% of cases.

Data on antibiotic resistance in the past years have been published by the NRC in their most recent report, from which an extract is pasted below.

2. ANTIBIOTIC SUSCEPTIBILITY

From 2012 – 2018, the sensitivity to tetracycline, erythromycin and clindamycin was determined for all submitted *S. pyogenes* strains. From 2019 onwards, a yearly selection of 50 strains (with wide geographical distribution) was made for which susceptibility testing was performed. The percentage of resistant strains per antibiotic is shown in Figure 5. The resistance of *S. pyogenes* to tetracyclines is increasing and up to 40% in 2021. In contrast, resistance to macrolides and clindamycin is lower and declining after a peak in 2019.

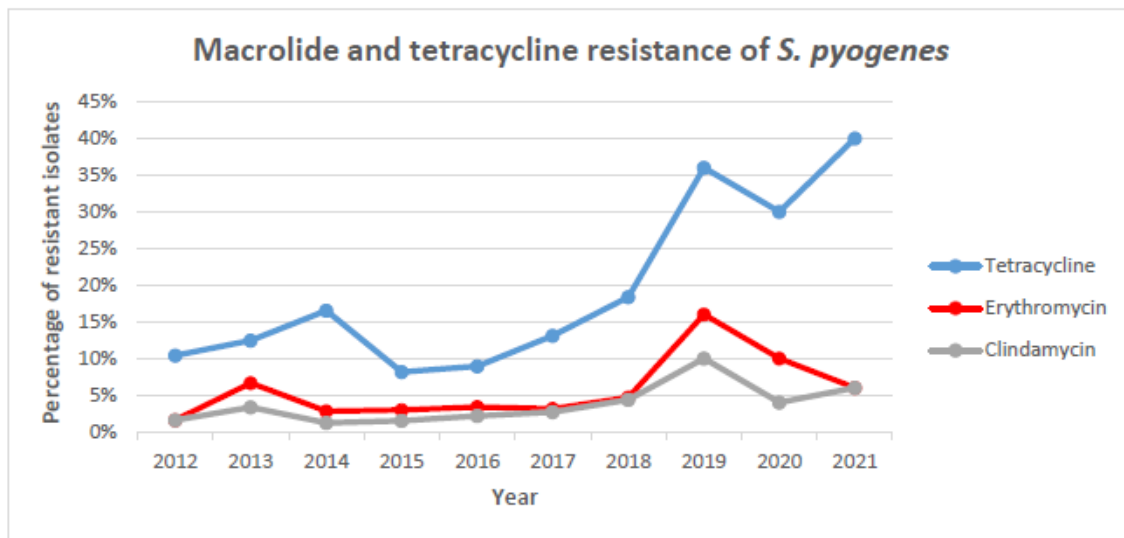


Figure 5: Percentage of macrolide and tetracycline resistance of *S. pyogenes* per year

Source: Report 2021 national reference centre for invasive β -hemolytic streptococci non group b. Antwerp University hospital. Available online: https://www.sciensano.be/sites/default/files/annual_report_2021_streptococci.pdf

3.2. GUIDELINES

3.2.1. Notification

Every case of 'invasive GAS infection' has to be notified, in the three regions.

- Flanders
<https://www.zorg-en-gezondheid.be/streptococcus-pyogenes-invasieve-infecties>
- Wallonia
<https://matra.sciensano.be/Fiches/sga.pdf>
- Brussels
<https://www.ccc-ggc.brussels/nl/voor-professionelen/aangifte-van-overdraagbare-ziekten>

3.2.2. Case definition invasive GAS infection

Broadly, iGAS infections are under mandatory notification to the regional health authorities in all three Belgian regions, but regions use different case definitions.

Zorg en Gezondheid	AVIQ	COCOM
<ul style="list-style-type: none"> ➤ Fasciitis necroticans ➤ Toxic shock syndrome 	<ul style="list-style-type: none"> ➤ Fasciitis necroticans ➤ Toxic shock syndrome ➤ Puerperal sepsis ➤ ICU admission or death due to GAS infection 	Cf. Aviq

CRITERIA
Klinische criteria
Eén van volgende klinische syndromen:
> fasciitis necroticans
> Streptococcal Toxic Shock Syndrome (STSS)
Criteria voor laboratoriumconfirmatie
> isolatie van groep A <i>Streptococcus</i> (<i>Streptococcus pyogenes</i>) door cultuur uit een anders steriele locatie
GEVALSDEFINITIE
Bevestigd
> patiënt met klinische criteria EN laboratoriumconfirmatie

Définition d'une infections invasives à SGA :

- Isolement bactériologique de SGA dans un site habituellement stérile (sang, céphalorachidien, autres sites profonds, lavage broncho-alvéolaire).
- Isolement bactériologique de SGA dans un site habituellement non-stérile (ex. peau respiratoires hautes, vagin), associé à une des formes cliniques suivantes :
 - Syndrome de choc toxique streptococcique (SCTS)
 - Nécrose des tissus mous, y compris la fasciite nécrosante, la myosite ou la gangrène
 - Fièvre puerpérale
 - Admission aux soins intensifs ou décès pour cette infection streptococcique

3.2.3. Chemoprophylaxis iGAS infections: indications and recommended AB

ZG/Brussels	Aviq
<ul style="list-style-type: none"> ➤ Household contacts 	<ul style="list-style-type: none"> ➤ Household contacts ➤ Close contacts (e.g. kissing contacts, repeated physical contacts, exchange of toothbrush etc.) ➤ Class of kindergarten or special education ➤ Crèche ➤ Medical staff after unprotected invasive actions
>24h, in period 1 week before start symptoms - 24 hours after start R/ case	>24h, in period 1 week before start symptoms - 24 hours after start R/ case
<ul style="list-style-type: none"> ➤ Azithromycine 5 days ➤ Clindamycine 10 days 	<ul style="list-style-type: none"> ➤ Céfadroxil 10 days = first choice ➤ Allergy beta lactams: azithromycine 3 days OR clindamycine 10 days (pregnant women or macrolide resistance)
Pregnant /breastfeeding women: case by case, if prophylaxis is given: clindamycine	

Plus increased vigilance 30 days

3.2.4. Treatment guidelines for mild GAS infections

Acute throat infections should generally not be treated by antibiotics according to the Belgian Antibiotic Policy Coordination Committee (BAPCOC)(1). Based on symptoms and clinical evaluation, the distinction between viral and bacterial infections cannot be made. Besides, most bacterial throat infections are self-limiting and the additional gain of antibiotic treatment is limited (2). Antibiotic treatment is only advised for risk patients (history of acute rheumatic fever, immunocompromised patients, oncological patients, patients with recent prosthetic surgery, patients with heart valve disease at risk of endocarditis) or in severely ill patients. If treatment is needed, feneticilline is first choice, alternatives are céfadroxil, cefalexin, amoxicillin or azithromycin (in case of IgE mediated penicillin allergy). Following the alerts on iGAS infection, the Belgian Collège de Médecine Générale Belge francophone reminded their members of these considerations in their December newsletter.

4. Topics and elements for discussion

4.1. IS A TEMPORARY CHANGE NEEDED IN THE GUIDELINES FOR USE OF ANTIBIOTICS IN MILD GAS INFECTIONS (SCARLET FEVER, STREPTOCOCCAL THROAT INFECTIONS) ?

The question has been raised if it would be useful to temporarily lower the threshold for use of antibiotics in mild GAS infections. Although invasive GAS infections are rarely a complication of throat infections, the measure could help slowing down transmission rates of GAS in the population and thus also the number of new invasive infections. Indeed, although the effect of antibiotic use on transmission has not been explicitly studied, GAS are eliminated from the oropharynx in 80-90% of cases after 24h of therapy (3,4). In contrast, studies from the 1950's showed that GAS can be isolated from the oropharynx for up to 3-4 weeks after symptom onset in approximately 50% of patients with streptococcal pharyngitis if left untreated (5,6). Thus, antibiotic treatment of cases and contacts has been used to stop outbreaks in closed communities, such as army training facilities or care homes (7,8). On the other hand, patients with streptococcal pharyngitis represent only a very small part of the human reservoir of GAS: prevalence of *S. pyogenes* carriage among school-aged children was estimated in multiple studies to be between 10-20% (9). Although sick persons seem more likely to spread GAS through respiratory droplets than asymptomatic carriers (10), the question remains whether treatment of streptococcal pharyngitis would significantly influence epidemiology of iGAS. Of note, the current increase of iGAS infections is also observed in countries that recommend antibiotic treatment of GAS pharyngitis (see [section 5.1](#) for an overview of guidelines in other countries).

Moreover, potential benefits of broadening antibiotic use need to be weighed against the risk of development of antimicrobial resistance. A study by Malhotra-Kumar and colleagues performed in 2007, showed that the use of macrolides (azithromycin and clarithromycin) in healthy volunteers significantly increased the proportion of macrolide-resistant streptococci compared to a placebo group (11). Also, a 'temporary' expansion of indications for antibiotic use may be difficult to reverse afterwards, with continued increased antibiotic use and thus risk for development of resistance.

The RAG therefore estimates that a revision of the current guidelines is not needed. To reduce transmission, it is useful to repeat the messages about basic hygienic measures, indoor ventilation and staying home from work, school and daycare when feeling sick. This will not only directly impact transmission of GAS but also of the viral infections that can be followed by invasive GAS infections.

4.2. PROPHYLAXIS IN CLOSE CONTACTS

There is no consensus, either in Belgium between different regions nor internationally, regarding the definition of 'close contacts', whether or not antibiotic prophylaxis is required and, if so, in which regimen. Several studies have shown a clear increased risk (up to 200-2000x higher) of invasive disease in close contacts (12) and **guidelines thus agree that it is paramount to have a high index of suspicion in close contacts and inform them to seek medical advice early in case of symptoms.**

On the other hand, as the absolute risk of invasive infection remains low, even in close contacts, the number needed to treat to prevent one secondary case is high. US data from 2013-2016 have estimated this NNT to prevent a secondary case to be 1329 in all household contacts and 303 in household contacts ≥ 65 years (13). For an overview of guidelines in other countries, see [section 5.2](#).

Of note is also that, as the case definition for 'invasive infection' used in Flanders is more restrictive than the one used in Brussels and Wallonia, less contacts will be traced.

The RAG highlights that it is paramount to correctly inform close contacts that they are at increased risk of infection and should seek early medical attention if symptoms develop. To increase chances of correct notification to the health authorities, a common and slightly broader case definition for notification should be used. It is the responsibility of regional health

authorities to decide when to give antibiotic prophylaxis, but they are encouraged to review the antibiotic regimen they propose, preferably choosing a narrow-spectrum type of antibiotics.

4.3. SHORTAGE OF CEFADROXIL

Several countries have indicated a shortage of beta-lactam antibiotics, in particular in pediatric formulations (see e.g. [alert from France](#)) In Belgium, the website of FAGG-AFMPS indicates that Cefadroxil is again available as of 2nd of January. Sciensano contacted the FAGG-AFMPS but there was no extra information available on this topic.

In general, pediatric options for treatment and prophylaxis are often lacking: Cefadroxil does not exist in syrup, and there is no reimbursement of feniticilline syrup. **The RAG requests to bring the issue of feniticilline reimbursement to the attention of RIZIV-INAMI.**

4.4. INTRAVENOUS IMMUNOGLOBULIN G THERAPY

Some studies indicate a benefit from adding intravenous immunoglobulin G (IVIG) to the treatment of patients with severe iGAS infections (14,15). However, IVIG has a high cost and is prone to problems in availability. Treating physicians should be aware of the possibility of adding IVIG to the treatment of severe iGAS (STSS / necrotizing fasciitis / ICU admission) and decide on a case by case basis, guided by the [IGGI guidelines](#) of the Belgian Society of Infectiology and Clinical Microbiology.

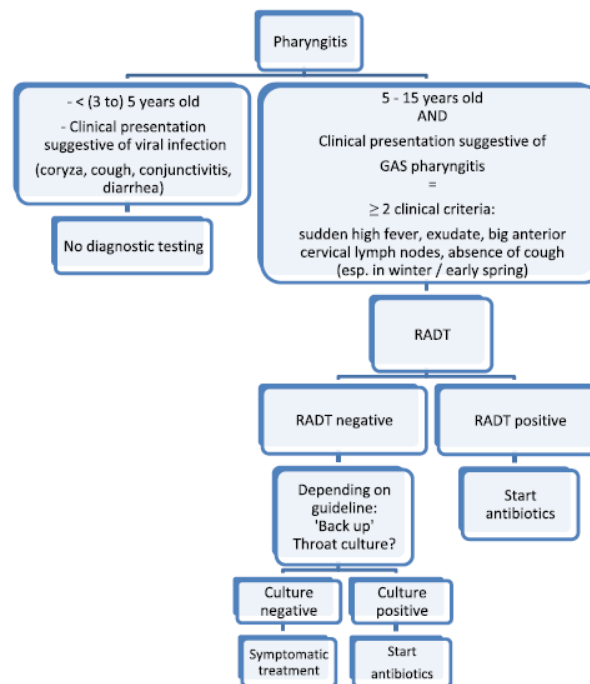
4.5. CONCERNS ABOUT USE OF IBUPROFEN

Clinicians have raised concern about the use of Ibuprofen in children. As symptoms are suppressed, this could delay seeking medical attention and worsen outcome. Moreover, the ability of NSAIDs to alter the host immune response could impact the course of the disease (16). These concerns about use of NSAIDs and iGAS have already been the topic of scientific research in the past, with studies showing mixed results (17,18). Experiments in mice have indeed shown that the use of nonselective NSAIDs for GAS soft tissue infection could contribute to worse outcomes (16).

Although it seems unpractical to ban the over-the-counter use of Ibuprofen in children during winter season, it might be useful to repeat to the general public that paracetamol is always the drug of first choice in case of pain and fever and that clinical worsening of a patient after 3 days (e.g. a child with varicella) is a reason to seek medical attention.

4.6. USE OF RAPID DIAGNOSTIC TEST

If guidelines would be in favor of treating streptococcal pharyngitis, it is important to adequately distinguish viral from bacterial pharyngitis. A review article from 2014 argues that clinical judgement has poor specificity and therefore, if it is felt important to treat 'strep throat', a rapid diagnostic test should be used to limit antibiotic overuse (19). The algorithm proposed by the authors is the following:



On the other hand, a [Belgian expert panel convened by INAMI-RIZIV in 2016](#) noted the following opinion:

NL

“De jury is zich bewust van de wens van sommige eerstelijnsartsen om over klinische (zoals de Centor-criteria) en technologische (zoals testen voor de opsporing of de kweek van antigenen) diagnostische hulpmiddelen te kunnen beschikken. De klinische scores zijn weinig gevoelig en specifiek, de sneltesten daarentegen worden gebruikt in meerdere landen zoals Frankrijk, de VS of Zwitserland. De jury herinnert er echter aan dat een etiologische diagnose niet nodig is voor de behandeling en dat er dus geen indicatie is om een keeluitstrijkje te nemen om te beslissen of men al dan niet met antibiotica zal behandelen. Hoewel de sneltesten betrouwbaar zijn voor het opsporen van bèta-hemolytische streptokokken van groep A, kan tot 30% van alle kinderen en adolescenten gezonde dragers zijn van deze streptokokken in de keel. Daardoor kan men dus niet met zekerheid bepalen of de aangetroffen bèta-hemolytische groep A-streptokok wel degelijk de ziekteverwekker is die verantwoordelijk is voor de infectie. (Expert opinion, sterke aanbeveling)”

FR

“Le jury est conscient des souhaits de certains médecins de première ligne de disposer d'outils diagnostiques cliniques (comme les critères de Centor par exemple) et ou biologiques (comme les tests de détection antigénique ou la culture). Si les scores cliniques sont peu sensibles et spécifiques, les tests biologiques sont eux utilisés dans plusieurs pays comme la France, les USA ou la Suisse. Cependant, le jury rappelle que le diagnostic étiologique n'est pas nécessaire pour la prise en charge et qu'il n'y a donc pas d'indication de faire un frottis de gorge pour décider éventuellement de traiter ou non par antibiotiques. Même si les tests rapides sont fiables pour détecter un Streptocoque bêta-hémolytique du groupe A, jusqu'à 30% d'enfants et d'adolescents en sont porteurs sains dans le pharynx, ce qui ne permet pas de déterminer si le streptocoque bêta-hémolytique du groupe A retrouvé est bien l'agent responsable de l'infection. (avis d'expert, forte recommandation)”

5. International situation and guidelines

5.1. TESTING AND TREATMENT FOR THROAT INFECTIONS

The below table gives an overview of official guidelines in several countries.

	TESTING	ANTIBIOTICS	COMMENTS
UK (source)	Yes	If test+	Throat swabs recommended in initial cases but not necessary during outbreak. 5-days antibiotics with clarithromycin where sore throat presents with pain and fever. Clinical guidance has been adjusted as a result of the current high prevalence of GAS.
US (source)	Yes	If test+	Testing in children older than 3 years of age, RADT (Rapid Antigen Detection Test). Antibiotics in all patients, regardless of age, who have positive RADT or throat culture. Penicillin or amoxicillin are the antibiotic of choice
FR (source)	+-	If test+	RADT if modified Centor score ≥ 2 (can also be done by pharmacist) Amoxicillin 1 g 2x daily for 6 days; if allergies cefuroxime or josamycin
NL (source)	No	No	
DE (source)	+-	+-	GAS rapid test optional if patients ≤ 15 y and Centor score ≥ 3 . Antibiotic therapy to consider if score ≥ 3 or GAS test positive On 19/12/22 the German Association of Pediatric Infectiology stated that, despite the increase in iGAS, a change in AB prescribing practice was not warranted and 'watchful waiting' continued to be an acceptable approach in many cases.

5.2. PROPHYLAXIS OF CONTACTS:

The below table gives an overview of official guidelines in several countries.

	DEFINITION	ANTIBIOTICS	TYPE OF AB
UK (source)	prolonged contact in a household-type setting during	If risk factors or ≥ 2 cases	Penicillin V if allergy: macrolides
US (source)	≥ 24 h in the same household	If risk factors	-
FR (source)	- household contacts - intimate physical contact - crèche, nursing homes, contact sports	If risk factors	Cephalexine Macrolides
NL (source)	≥ 24 h in the same household	Only if index STSS/necrotic fasciitis	Azithromycin 500mg 1dd 3d Penicillin V + Rifampicine Clindamycine
DE (source)	household contacts	Consider if index sepsis/STSS/necrotic fasciitis	-

6. Literature

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