

RAG

Risk Assessment Group

PRIMARY RISK ASSESSMENT

Cluster Fusidic acid-resistant *Staphylococcus aureus* in Flanders (Turnhout)

| Date of the signal | Date of the RA | Signal provider | Experts consultation | Method |
|--|---------------------|-----------------|---|--------------------|
| August 2018 | 24/09/2018 | AZG | Permanent experts: Dr Valeska Laisnez (AZG), Dr Romain Mahieu (COCOM-GGC), Dr Paul Pardon (FOD), Dr Sophie Quoilin (Sciensano), Dr Carole Schirvel (AViQ) Specific experts : Dr Joke De Backer (AZG), Wouter Dhaeze (AZG), Dr Marie Hallin (NRC Erasme), Maria A. Argudín (NRC Erasme), Ariane Deplano (NRC Erasme), Natalia Bustos (Sciensano). | eMail consultation |
| Date of update | Closing date | | | |
| 19 oct 2018 | | | | |
| 09 nov 2018 18 march 2019 5 April 2019 | | | | |

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UPDATE 10 APRIL 2019

The PRA has been discussed during the RMG on 21 March 2019.

Clarifications have been asked on the following:

Flyer: it should be ready to be distributed when clusters are notified to regional authorities. Sciensano can help drawing a proposition (for Wallonia and Brussels as Flanders already prepared one during cluster management), the spread remains under the responsibility of the regional authorities (when, to whom).

Based on the results of the study (to be performed between May 2019 – May 2020), in the context of antibiotic resistance, we agree that additional action will have to be taken:

To inform pharmacists of the Staph. aureus FUS-R problem in order to invite them to advise the patient to consult a doctor in case of treatment failure.

Or

To put such treatment under medical prescription.

PRIMARY RISK ASSESSMENT OF POTENTIAL PUBLIC HEALTH EVENT

| | |
|---------------|---|
| Signal | <p>Around 20 August 2018, a signal was sent to AZG by Dr Dana Van Kerkhoven, biologist at the AZ Turnhout. Since July 2018, three families have had children with impetigo with lesions that are difficult to treat. There was a recurrence in one of the children after treatment with Bactrim and isobetadine gel. Two families are in contact; the 2 mothers are laboratory assistants at the AZ in Turnhout. The Turnhout cluster contains 10 people with 9 children and 1 adult. The lesions are extensive and severe with a high risk of scarring.</p> <p>At the end of August 2018, there were 23 cases of impetigo reported in the Kempen with extensive lesions and yellow crust, but without general complications. The AZG sent a letter to general practitioners, paediatricians, school-doctors and Kind en Gezin in Kempen, to draw their attention upon the disease and remind them of the measures to be taken. A smear must be taken before oral antibiotic treatment (flucloxacilline during 7 days). In case of resistance to fusidic acid and recurrence or intra-family dissemination, the treatment will be followed, when the wounds are healed, by a decontamination of 5 days.</p> <p>According to the NRC, in 2018 there have been 64 isolates of fusidic acid-resistant <i>Staphylococcus aureus</i> (FRSA), belonging to the so-called clone 'EEFIC' (<i>Epidemic European fusidic acid-resistant impetigo clone</i>) sent to them for toxin gene detection. Among the 64 EEFIC isolates, 50 cases were clearly identified as coming from skin lesion smears. Majority of EEFIC cases were reported in August (n=16, 25%) and September (n=18, 28,1%). Children between 3 and 12 years of age are the most affected (53% male).</p> <p>The highest number of EEFIC isolates sent was from Flanders (n=51). The number of EEFIC isolates sent from Wallonia is low (n= 3). One case was reported in September. In Brussels, the number of EEFIC isolates sent is low (n=10) but higher than in Wallonia with 5, 1 and 2 cases in June, August and September 2018 respectively. There are 4 clusters detected (Flanders=3, Brussels=1).</p> <p>The number of cases is most certainly underestimated as smears are rarely indicated for simple wounds, and that sending isolates to the NRC is voluntary-based.</p> |
|---------------|---|

| Description | Score | Description / arguments |
|-------------|--------------------|--|
| 1 | Cause known? | <p data-bbox="639 289 1385 401"><i>Staphylococcus aureus</i> is the causative agent. The first choice treatment for impetigo caused by CA-MSSA ("community acquired methicillin-sensitive <i>Staphylococcus aureus</i>") is a local treatment with fusidic acid.</p> <p data-bbox="639 422 1385 562">Fusidic acid-resistant <i>S. aureus</i> (FRSA) are harboring either genetic mutations in <i>fusA</i> or the acquisition of the <i>fusB</i> gene. In other words, it is caused by a genetic mutation causing alteration of the EF-G protein (FusA class) or by expression of a protein that protects the drug target on the EF-G (FusB and FusC classes).</p> <p data-bbox="639 583 1385 814">Between 2002 and 2004, Norwegian, Swedish and UK studies reported genetic analysis showing that the great majority of isolates concerning impetigo-associated fusidic acid-resistant <i>S. aureus</i> during the outbreak of 2003 belonged to a single clone, the so-called <i>Epidemic European Fusidic acid-resistant Impetigo Clone (EEFIC)</i>. Later, the presence of the clone was also confirmed in France and the Netherlands. At present, most <i>S. aureus</i> isolates resistant to fusidic acid causing impetigo are belonging to the EEFIC.</p> <p data-bbox="639 835 1385 947">The clone is further characterized by the presence of exfoliative toxin A (<i>eta</i>), toxin B (<i>etb</i>) and EDIN-C. It belongs to the genetic type ST123 [clonal complex (CC) 121], <i>spa</i> type t171 (or single-repeat variants t408, t659, t874 and t875) and <i>agr</i> allelic group IV.</p> |
| 2 | Unexpected/unusual | <p data-bbox="639 968 1385 1079">FRSA clusters have been appearing since 2000 in Northern Europe (Norway, Sweden, UK, Ireland, France, Netherlands). Since 2004, the proportion of <i>S. aureus</i> isolates resistant to fusidic acid has decreased.</p> <p data-bbox="639 1100 1385 1297">In Belgium, between 2008 and 2014, the NRC did not observe any raise in the fusidic acid resistance among the MSSA sent to the national (hospital-based) epidemiological and antimicrobial susceptibility surveys. In fact, 96.2%, 90% and 87.5% of the MSSA isolates tested in 2008 (n=212), 2011 (n=210) and 2013-14 (one year of data overlapping 2013 and 2014) (n=288), respectively, were susceptible to fusidic acid.</p> <p data-bbox="639 1318 1385 1402">NRC reports are available here: https://nrchm.wiv-isp.be/fr/centres_ref_lab/staphylococcus_aureus/Rapports/Forms/AllItems.aspx</p> <p data-bbox="639 1423 1385 1528">Here are other results from the NRC based on <u>spontaneous declarations</u>, thus this information is not an exhaustive surveillance among EEFIC and cannot lead to the conclusion that EEFIC is increasing.</p> |

| | | | <p>Summary Results Impetigo Clone</p> <table border="1"> <thead> <tr> <th>Year</th> <th>N° strains Toxin Typed</th> <th>N° strains Impetigo clone (MSSA + FUS-R + <i>etazetb</i>)</th> </tr> </thead> <tbody> <tr> <td>2015</td> <td>555 (MRSA: 294, MSSA: 257, BORSA: 4)</td> <td>4 (0.7%)</td> </tr> <tr> <td>2016</td> <td>507 (MRSA: 270, MSSA: 237)</td> <td>6 (1.2%)</td> </tr> <tr> <td>2017</td> <td>451 (MRSA: 222; MSSA: 229)</td> <td>16 (3.55%)</td> </tr> <tr> <td>2018 until July*</td> <td>337 (MRSA: 122; MSSA: 215)</td> <td>18 (5.3%)</td> </tr> <tr> <td>2018 until August*</td> <td>391 (MRSA: 139; MSSA: 252)</td> <td>34 (8.7%)</td> </tr> <tr> <td>2018 only August-Sep</td> <td>115 (MRSA: 29; MSSA: 85)</td> <td>31 (26.9%)</td> </tr> </tbody> </table> <p>*Information letter sent by zorg-en-gezondheid the 31/08.</p> <p>In August, in the Netherlands (Den Haag region), there has also been an increase in the number of cases of impetigo in children¹.</p> | Year | N° strains Toxin Typed | N° strains Impetigo clone (MSSA + FUS-R + <i>etazetb</i>) | 2015 | 555 (MRSA: 294, MSSA: 257, BORSA: 4) | 4 (0.7%) | 2016 | 507 (MRSA: 270, MSSA: 237) | 6 (1.2%) | 2017 | 451 (MRSA: 222; MSSA: 229) | 16 (3.55%) | 2018 until July* | 337 (MRSA: 122; MSSA: 215) | 18 (5.3%) | 2018 until August* | 391 (MRSA: 139; MSSA: 252) | 34 (8.7%) | 2018 only August-Sep | 115 (MRSA: 29; MSSA: 85) | 31 (26.9%) |
|----------------------------------|--------------------------------------|--|---|------|------------------------|--|------|--------------------------------------|----------|------|----------------------------|----------|------|----------------------------|------------|------------------|----------------------------|-----------|--------------------|----------------------------|-----------|----------------------|--------------------------|------------|
| Year | N° strains Toxin Typed | N° strains Impetigo clone (MSSA + FUS-R + <i>etazetb</i>) | | | | | | | | | | | | | | | | | | | | | | |
| 2015 | 555 (MRSA: 294, MSSA: 257, BORSA: 4) | 4 (0.7%) | | | | | | | | | | | | | | | | | | | | | | |
| 2016 | 507 (MRSA: 270, MSSA: 237) | 6 (1.2%) | | | | | | | | | | | | | | | | | | | | | | |
| 2017 | 451 (MRSA: 222; MSSA: 229) | 16 (3.55%) | | | | | | | | | | | | | | | | | | | | | | |
| 2018 until July* | 337 (MRSA: 122; MSSA: 215) | 18 (5.3%) | | | | | | | | | | | | | | | | | | | | | | |
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| 2018 only August-Sep | 115 (MRSA: 29; MSSA: 85) | 31 (26.9%) | | | | | | | | | | | | | | | | | | | | | | |
| 3 | Severity | Medium | <p>There is an overrepresentation of younger patients because of the higher prevalence of impetigo among this age group.</p> <p>The significant differences in carriage of fusidic acid-resistant isolates among children compared with adults suggest that children are more prone to carrying these resistant isolates.</p> <p>The lesions can be extensive, painful, disabling with long-term scars. In very rare cases, the bacteria can cause very serious lung damage (necrotizing pneumonia).</p> <p>The increasing use of other antibiotics and decontamination could contribute to the development of new resistance in the long term.</p> | | | | | | | | | | | | | | | | | | | | | |
| 4 | Dissemination (Low/Medium/High) | Medium | <p>Transmission requires close contact or sharing of personal belongings (hygiene).</p> <p>In case of resistance to fusidic acid, the transmission may be higher due to the presence of more extensive and recurrent lesions.</p> <p>Children or persons, for whom hand and wound hygiene can be guaranteed, or for whom injuries can be completely covered or completely dried, may participate in all activities except swimming, wellness and showering in common shower rooms.</p> <p>Children or persons for whom hand and wound hygiene cannot be guaranteed, or for whom injuries cannot be completely covered, may not attend childcare, school, institution, work, sports activities until 48 hours after the start of the antibiotics treatment.</p> | | | | | | | | | | | | | | | | | | | | | |
| 5 | Risk of (inter)national spread | High/Low | <p>The risk of clustering within a family or communities is high.</p> <p>The communal/provincial level spread is medium.</p> <p>The regional/national and international spread is low.</p> <p>The risk of impetigo will probably decrease during the winter and reappear in the spring with heat (shorter clothing for skin-to-skin contact and more perspiration).</p> | | | | | | | | | | | | | | | | | | | | | |
| Preparedness and response | | | | | | | | | | | | | | | | | | | | | | | | |
| 6 | Preparedness | Good | <p>In Belgium, the NRC is the microbiology laboratory at Erasme Hospital/LHUB-Site Anderlecht (Brussels). Analysis were made to verify the belonging to the <i>EEFIC</i>. All laboratories can send their strains to verify if the strains causing outbreaks do belong or not to the <i>EEFIC</i>.</p> <p>Belgium has experienced some problems with the delivery of</p> | | | | | | | | | | | | | | | | | | | | | |

¹ <https://www.nivel.nl/nl/nieuws/meer-kinderen-met-krentenbaard-dit-najaar-oorzaak-onbekend>

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| | | | Mupirocin (Bactroban®), but the situation has been normalized since October 2018. |
| 7 | Specific control measures (surveillance, control, communication) | | <ul style="list-style-type: none"> • The 30 and 31 August 2018, AZG sent a letter to the GPs, paediatricians, dermatologists, hospitals, school doctors, Kind&Gezin in the region of Kempen to inform them of the following procedures: Swabbing +oral antibiotic treatment (Flucloxacilline for 7 days, 3 to 4 times daily) is advised and in case of resistance to fusidic acid and recurrence or intra-family dissemination, the treatment will be followed, when the wounds are healed, by a decontamination of 5 days with: (1) Mupirocin (3 times a day) and (2) daily complete body washing with disinfectant soap on days 1 and 4. In case of recurrent skin lesions or expansion within the family: decolonize all family members without checking for carriage. In addition to antibiotic treatment, the treatment will include adequate wound care for the patient, hygiene measures for the patient and his family, treatment of linen and clothing, and non-shared personal belongings and dishes. • On 8 October 2018, AZG sent a second letter to the same recipients to say that the situation was not yet under control and that the advices given in the first letter are still valid. Another letter will be sent to them to inform when they can return to the usual advice. • In case of resistance to mupirocin, no justified guidelines were found and actually there is no generic advice we can give on what to do about the joint resistance to AF and mupirocin. However according to the NRC Erasme, two different cases exists : 1) In case of high-<i>mupA</i> mediated resistance, some institutions use isobetadine gel. But isobetadine gel cannot be administered to children. 2) In case the resistance is low or at intermediate level (absence of <i>mupA</i> or <i>mupB</i>), mupirocin can still be used. Nevertheless, for intermediate level of resistance, failure can be observed in some cases. • On 21 December 2018, AZG sent a letter to the same recipients : the problem has decreased; follow the general recommendations in case of impetigo. Physicians no longer have to report resistance to AF to AZG, but laboratories are asked to provide AZG with data to monitor the situation. |
| Public health impact | | | |
| A | Public health impact in Belgium (Low/Medium/high) | Low/Medium | <p>The increasing prevalence of fusidic acid-resistant isolates from wound infections is of concern because the fusidic acid cream is still the empirical choice for treatment of impetigo in Belgium.</p> <p>Fusidic acid cream is obtained at the pharmacy without a prescription.</p> <p>The number of cases is underestimated at this time because a smear</p> |

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| | | | <p>is not usually indicated before treatment.</p> <p>Without awareness of the problem, there is a risk that oral treatment will not be followed by decontamination, which can lead to a recurrence of infections. Nevertheless, recurrences are observed in the case of oral treatment followed by decontamination.</p> <p>The consequences on a family are important: the care of long and painful wounds for the child, the risk of scars, the reduction of activities, the impact of decontamination on the family. The decontamination starts only when the wound is healed, but wounds do not heal quickly, which increases the risk of transmission to close contacts persons.</p> <p>The increasing use of other antibiotics and decontamination could contribute to the development of new resistance in the long term.</p> <p>Obstacles:</p> <ul style="list-style-type: none"> - Mupirocin nasal ointment is not intended for children under 6 years of age due to the lack of clinical data on this age group to date. - The use of mupirocin for pregnant women is not clear but it could be used because systemic absorption would be very low. |
| B | Recommendations (surveillance, control, communication) | | <p>Every case or suspected cases of impetigo does not require a mandatory notification to federated entities. But any infectious diseases must be reported in case of a particular or unusual presentation (epidemic).</p> <p>In Flanders, school doctors must contact the AZG if there are more than 3 cases in a class.</p> <p>The resistance of <i>S. aureus</i> to AF is known and common, but its exact prevalence in the community is unknown.</p> <p>In view of the data provided by the NRC, there has been more EEFIC cases in Flanders compared to Brussels and Wallonia, but it is difficult to assess the evolution on the basis of samples sent voluntarily, probably either from complicated cases or following the AZG recommendation letter.</p> <p>On 12 October 2018, AZG, Sciensano and NRC Erasme met to discuss the situation. The lack of quality data to assess the situation leads us to reflect on monitoring proposals.</p> <p>In March 2019, the NRC Erasme and Sciensano will submit an extraordinary funding proposal to the MTAO/OCMT meeting to perform a survey on the fusidic acid-resistant European Impetigo clone prevalence among <i>S. aureus</i> causing skin and soft tissues infections (SSTI) in the community in Belgium.</p> <p>Federated entities:</p> <ul style="list-style-type: none"> • To discuss about the EEFIC survey proposition. • Since the Fucidin is available without a prescription, pharmacists should be made informed of the <i>Staph. aureus</i> FUS-R problem to advise the patient to consult a doctor in case of treatment failure (a letter has already been sent to the pharmacist by AZG in late August). • To share what are the regional guidelines for impetigo, to see if there are any differences between regions. |

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| | | | <ul style="list-style-type: none">• Other : A general surveillance plan for the <i>Staph. aureus</i> (CA and HA- MRSA, MSSA) is being developed by Sciensano and NRC Erasme. Consider developing a flyer on the fusidic acid-resistant in case of impetigo (different from the existing CA-MRSA one). |
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Results based on the last analysed received in April 2019 (NRC data, hospital-based):

Table 1. Number of EEFIC isolates sent to the NRC from Flanders, 2018

| Flanders in 2018 | All ages | Age (years) | | | | | | | | | |
|------------------|------------|-------------|------------|------------|------------|------------|-----------|-----------|----------|----------|-----------|
| | | 0 | 1-2 | 3-6 | 7-12 | 13-18 | 19-35 | 36-45 | 46-55 | 56-65 | 65+ |
| Jan | - | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Feb | - | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mar | - | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Apr | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| May | 2 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Jun | 2 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Jul | 5 | 0 | 0 | 1 | 3 | 1 | 0 | 0 | 0 | 0 | 0 |
| Aug | 15 | 0 | 2 | 3 | 6 | 2 | 0 | 2 | 0 | 0 | 0 |
| Sep | 15 | 0 | 1 | 6 | 6 | 1 | 0 | 0 | 0 | 0 | 1 |
| Oct | 4 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nov | 4 | 0 | 0 | 0 | 2 | 0 | 1 | 1 | 0 | 0 | 0 |
| Dec | 3 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 51 | 2 | 5 | 13 | 21 | 5 | 1 | 3 | - | - | 1 |
| % | 100 | 4% | 10% | 25% | 41% | 10% | 2% | 6% | - | - | 2% |

Table 2. Number of EEFIC isolates sent to the NRC from Wallonia, 2018

| Wallonia in 2018 | All ages | Age (years) | | | | | | | | | |
|------------------|------------|-------------|------------|------------|------------|----------|----------|----------|----------|----------|----------|
| | | 0 | 1-2 | 3-6 | 7-12 | 13-18 | 19-35 | 36-45 | 46-55 | 56-65 | 65+ |
| Jan | 1 | - | 1 | - | - | - | - | - | - | - | - |
| Feb | - | - | - | - | - | - | - | - | - | - | - |
| Mar | - | - | - | - | - | - | - | - | - | - | - |
| Apr | - | - | - | - | - | - | - | - | - | - | - |
| May | - | - | - | - | - | - | - | - | - | - | - |
| Jun | - | - | - | - | - | - | - | - | - | - | - |
| Jul | 1 | - | - | 1 | - | - | - | - | - | - | - |
| Aug | - | - | - | - | - | - | - | - | - | - | - |
| Sep | 1 | - | - | - | 1 | - | - | - | - | - | - |
| Oct | - | - | - | - | - | - | - | - | - | - | - |
| Nov | - | - | - | - | - | - | - | - | - | - | - |
| Dec | - | - | - | - | - | - | - | - | - | - | - |
| Total | 3 | - | 1 | 1 | 1 | - | - | - | - | - | - |
| % | 100 | - | 33% | 33% | 33% | - | - | - | - | - | - |

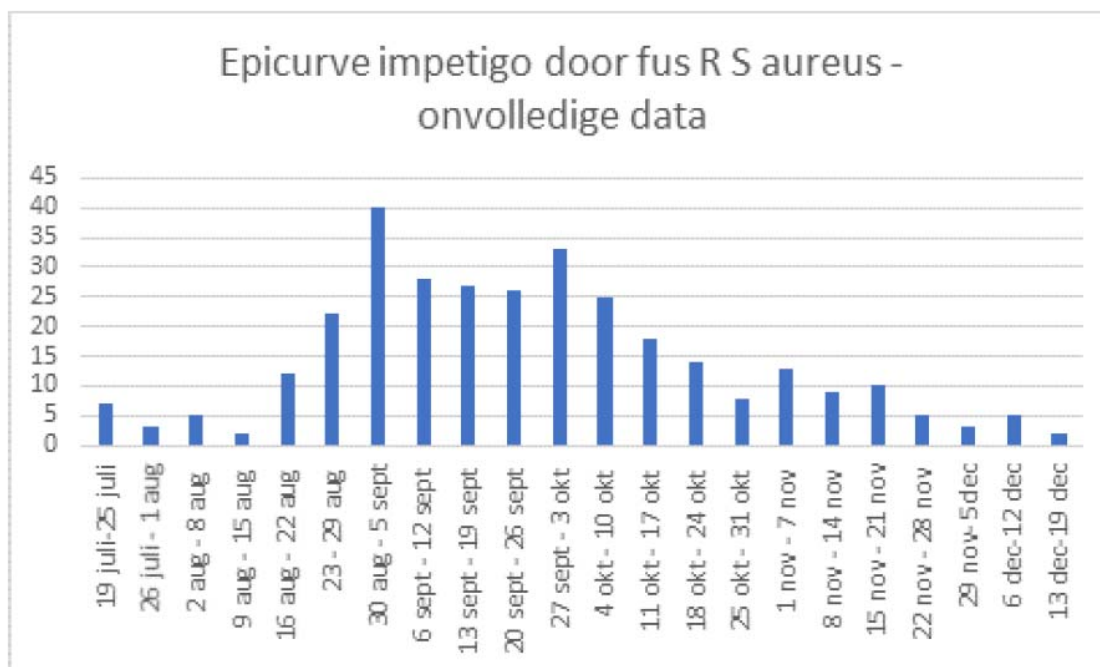
Table 3. Number of EEFIC isolates sent to the NRC from Brussels, 2018

| Brussels in 2018 | All ages | Age (years) | | | | | | | | | |
|------------------|------------|-------------|------------|------------|------------|----------|------------|------------|------------|----------|----------|
| | | 0 | 1-2 | 3-6 | 7-12 | 13-18 | 19-35 | 36-45 | 46-55 | 56-65 | 65+ |
| Jan | - | - | - | - | - | - | - | - | - | - | - |
| Feb | - | - | - | - | - | - | - | - | - | - | - |
| Mar | - | - | - | - | - | - | - | - | - | - | - |
| Apr | - | - | - | - | - | - | - | - | - | - | - |
| May | 1 | - | - | - | 1 | - | - | - | - | - | - |
| Jun | 5 | 2 | - | - | 1 | - | - | 1 | 1 | - | - |
| Jul | - | - | - | - | - | - | - | - | - | - | - |
| Aug | 1 | - | 1 | - | - | - | - | - | - | - | - |
| Sep | 2 | - | - | 1 | - | - | - | 1 | - | - | - |
| Oct | 1 | - | - | - | - | - | 1 | - | - | - | - |
| Nov | - | - | - | - | - | - | - | - | - | - | - |
| Dec | - | - | - | - | - | - | - | - | - | - | - |
| Total | 10 | 2 | 1 | 1 | 2 | - | 1 | 2 | 1 | - | - |
| % | 100 | 20% | 10% | 10% | 20% | - | 10% | 20% | 10% | - | - |

Table 4. Number of EEFIC isolates sent to the NRC from Belgium, 2018

| Belgium in 2018 | All ages | Age (years) | | | | | | | | | |
|-----------------|------------|-------------|------------|------------|------------|-----------|-----------|-----------|-----------|----------|-----------|
| | | 0 | 1-2 | 3-6 | 7-12 | 13-18 | 19-35 | 36-45 | 46-55 | 56-65 | 65+ |
| Jan | 1 | - | 1 | - | - | - | - | - | - | - | - |
| Feb | - | - | - | - | - | - | - | - | - | - | - |
| Mar | - | - | - | - | - | - | - | - | - | - | - |
| Apr | 1 | - | - | - | - | 1 | - | - | - | - | |
| May | 3 | - | - | 1 | 2 | - | - | - | - | - | |
| Jun | 7 | 2 | 1 | - | 2 | - | - | 1 | 1 | - | |
| Jul | 6 | - | - | 2 | 3 | 1 | - | - | - | - | |
| Aug | 16 | - | 3 | 3 | 6 | 2 | - | 2 | - | - | |
| Sep | 18 | - | 1 | 7 | 7 | 1 | - | 1 | - | 1 | |
| Oct | 5 | 1 | 1 | 1 | 1 | - | 1 | - | - | - | |
| Nov | 4 | - | - | - | 2 | - | 1 | 1 | - | - | |
| Dec | 3 | 1 | - | 1 | 1 | - | - | - | - | - | |
| Total | 64 | 4 | 7 | 15 | 24 | 5 | 2 | 5 | 1 | - | 1 |
| % | 100 | 6% | 11% | 23% | 38% | 8% | 3% | 8% | 2% | - | 2% |

Cases reported to AZG by doctors (AZG data):



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