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Dienst Epidemiologie van Infectieziekten

Service Epidemiologie Maladies Infectieuses

Risk Assessment Group

RISK ASSESSMENT

Continuing increase in pertussis cases in Belgium

Date of the signal	Date of the meeting	Signal provider	Present	Method
2012-2015			**Permanent experts:** W. Dhaeze, V. Laisnez, S. Quoilin, D. Reynders, C. Schirvel, J-M. Trémérie.	**Consensus document**
Date of update	**Closing date**			
			Specific experts invited: S. Blumenthal, B. Brasseur, O. Chatzis, I. de Schutter, J. Frère, T. Goetghebuer, M. Hainaut, K. Huygen, S. Jourdain, P. Lepage, E. Leuridan, D. Pierard, M. Sabbe, O. Stévart, B. Swennen, G. Top, D. Tuerlinckx, D. Van der Linden.	

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RATIONALE FOR RA

Description of the signal under assessment

! Important note: Data were extracted on 22/09/2015, since this is close to the end of the first semester of 2015, numbers may not be definitive for this period. Therefore, the number of pertussis cases for the first semester of 2015 may be underestimated in the figures and numbers presented in this document.

An overall and continuing increase in the number of reported cases of pertussis, caused by the bacteria *Bordetella pertussis* has been observed in Belgium since 2012, despite a high vaccination coverage (see paragraph Prevention: vaccination).

Pertussis tends to occur in cycles of about 3-5 years. The peak that is observed in 2014-2015 is however more than twice as high as the previous peak in cases, registered in 2007. The increase is detected through all Belgian surveillance networks.

Sources of information

Belgian surveillance for pertussis occurs through 3 different systems:

- a network of sentinel laboratories (included in 1996-1998 and from 2005 onwards) (SNL)
- mandatory notification in the three communities
- the national reference centre (NRC) for *Bordetella pertussis*, based on a collaboration between UZBrussel en WIV-ISP, from 2012 onwards. Before that, the UZ Brussel acted as reference laboratory (RL).

In addition, data on hospital admissions for pertussis (based on the Minimal Clinical Dataset) have been analysed for the period 2000-2012 (most recent available year).

For the analysis of longer time trends, the network of sentinel laboratories is preferably used. The NRC-RL data became more exhaustive in recent years, especially after the inclusion of serology testing in 2012 and are used for description of cases characteristics, jointly with data from the mandatory notification.

Summary of the epidemiological trends from 2011 to 2015 (first semester):

- Since 2011, the network of sentinel laboratories has reported an increase in pertussis cases. From 2011 till 2015 the number of cases reported yearly were respectively 102, 324, 447, 658 and 473 (1e semester 2015). (Figure 1).
- Data obtained from the mandatory notification and the national reference centre confirm this trend (Figure 1).
- There is no specific geographical distribution of pertussis cases; the density of pertussis cases is closely related to the population density.
- Incidence of pertussis is highest in infants (< 1 year), predominantly in those younger than 4 months. The previous peak in infants in 2007 consisted of 125 cases, in 2014 132 cases were reported through SNL. The proportion of 40-60 year olds among pertussis cases is increasing (Figure 3 & 4).
- Up to 2012, no increase in hospitalization or mortality due to *Bordetella pertussis* could be detected (Table 2 and 3).

Cases reported per surveillance system

The number of pertussis cases increased since 2012 in all different surveillance networks.

In 2014, the *network of sentinel laboratories* registered 658 cases of pertussis. This is more than in 2011 (N=103), 2012 (N=324) and 2013 (N=447).

In 2014, 1048 cases of pertussis were notified through the system of *mandatory notification* in Flanders, compared to 666 cases in 2013. In the Walloon region and in Brussels the number of notified cases in 2013 versus 2014 was 429 vs 828 and 82 vs 117 respectively.

In 2014, the *NRC* reported 1501 cases of pertussis, compared to 848 in 2013.

The preliminary results for the first semester of 2015 are less conclusive. Some systems report a further increase (SNL and mandatory notification in Flanders and Brussels), whereas the trend is decreasing in others (NRC and mandatory notification in Wallonia). (Figure 1)

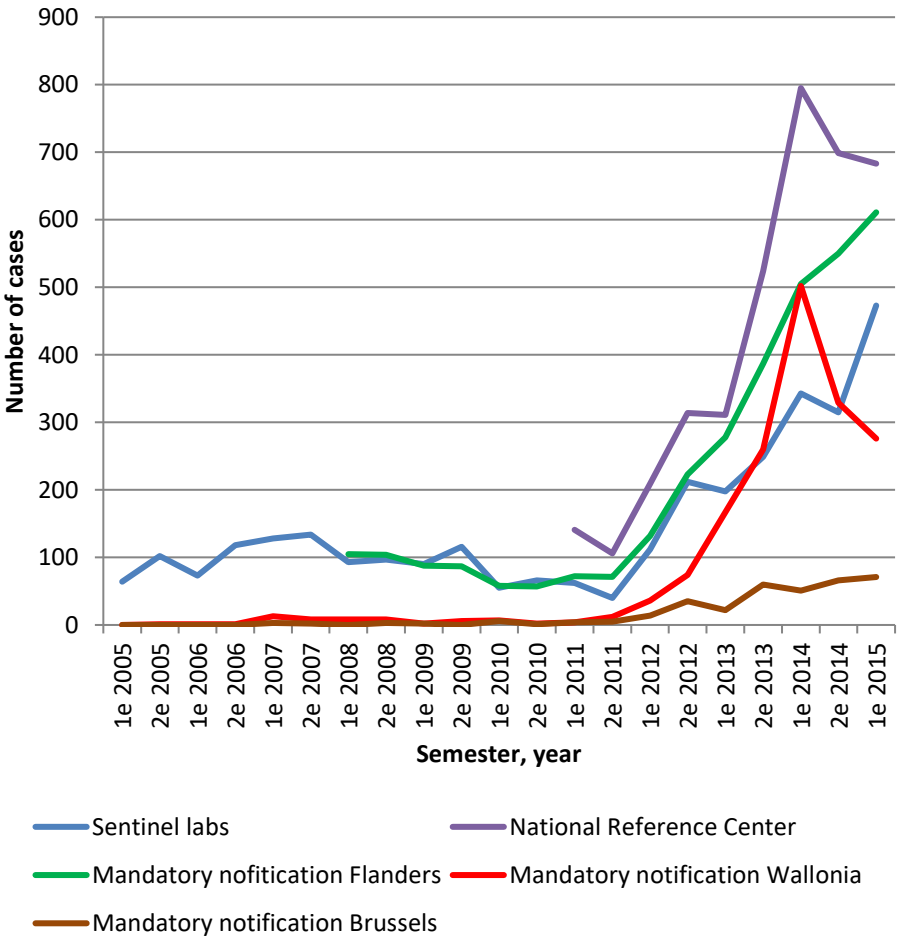

Figure 1: Total number of reported pertussis cases by semester and by surveillance system, 2005-2015 (first semester), Belgium.

Cases reported per region

The number of pertussis cases has increased in all the regions. According to the reports of the network of sentinel laboratories, the largest increase (123%) from 2013 to 2014 was observed in the Walloon region. In Flanders, the increase was 33% and in Brussels 22%. This results in a total increase of 48% for Belgium from 2013 to 2014 (Figure 2). The number of reported cases in the first semester of 2015 as compared to the first semester of 2014 is declining in Wallonia (31%) and increasing in Flanders (78%) and Brussels (85%).

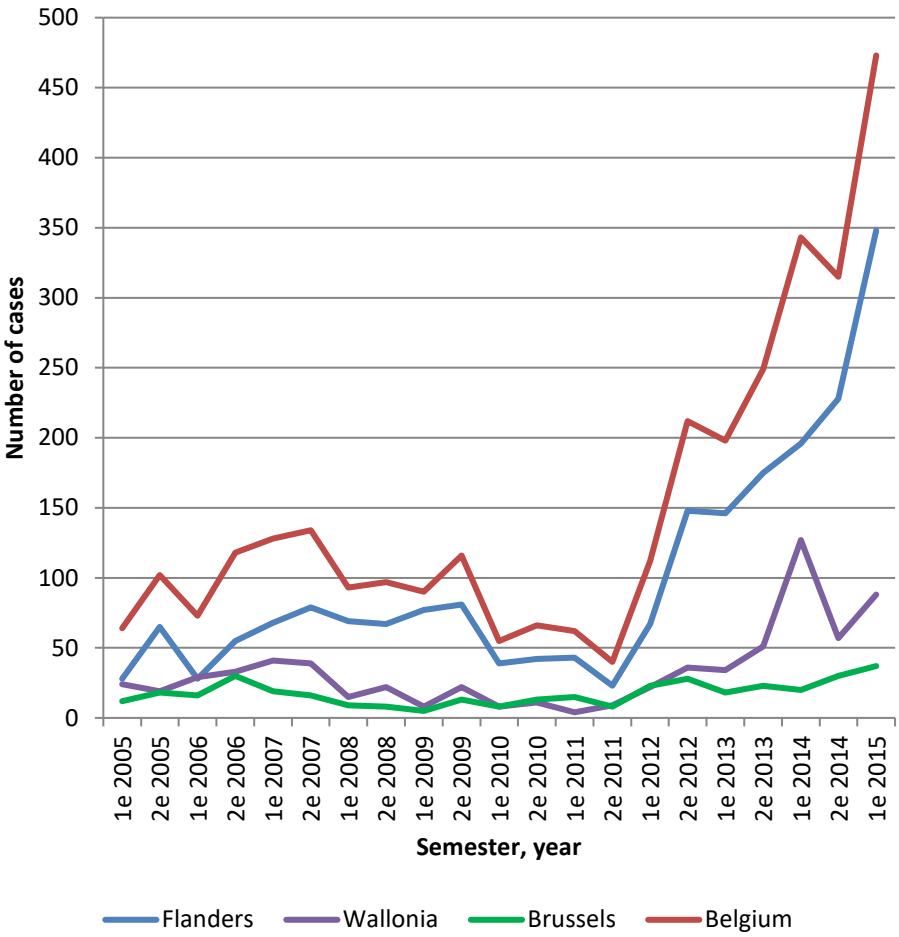

Figure 2: Number of reported pertussis cases by region as reported by the sentinel laboratory network by semester, 2005-2015 (first semester), Belgium.

Increase by age group

Although incidence is highest in infants (<1 year), the proportion of cases in this age group decreased in 2013-2015 compared to the previous years (2005-2012), with an increase in the proportion of adults (especially 40-60 years old) among the pertussis cases (Figure 3). Among the infants, most cases are reported in those <4 months of age (Figure 4).

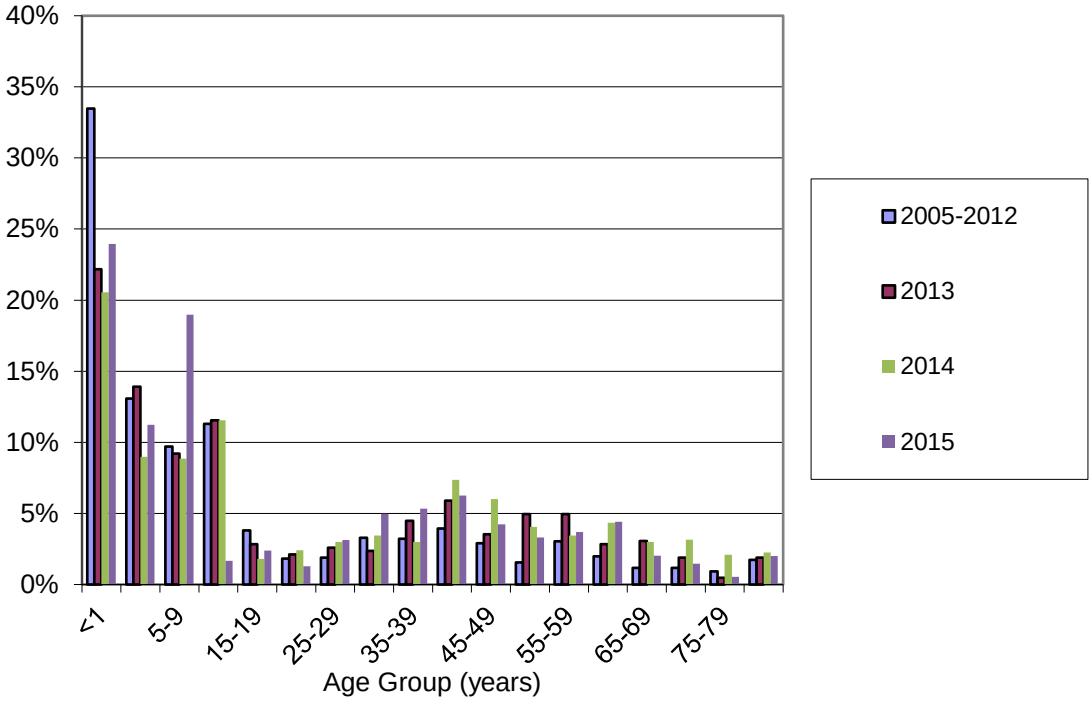

Figure 3: Age distribution of pertussis cases as reported by the sentinel laboratory network, 2005-2015 (first semester), Belgium.

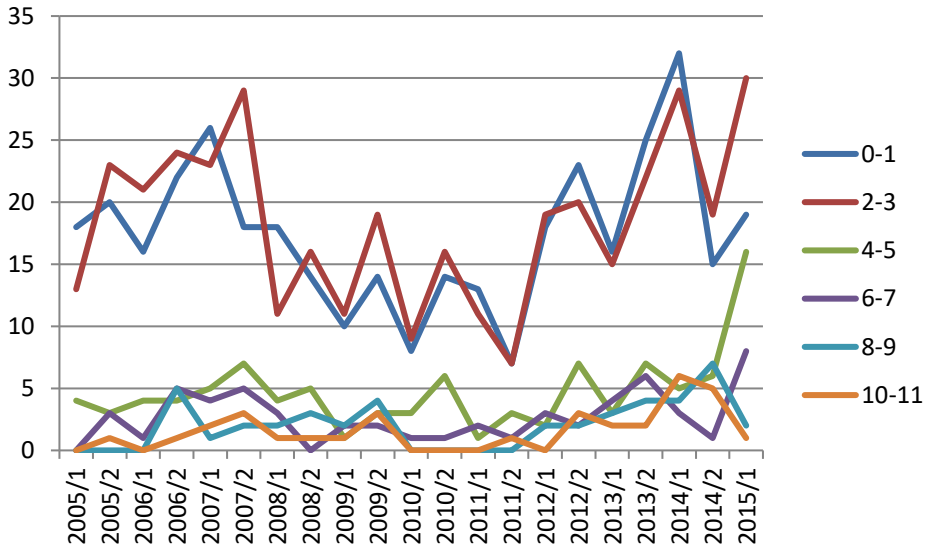

Figure 4: Number of pertussis cases in infants (0-11 months) by semester, as reported by the sentinel laboratory network, 2005-2015 (first semester), Belgium.

For additional epidemiological data on Belgium, see page 15.

Reliability of the signal

Possible biases related to the surveillance are the following:

Notification bias

Although a notification bias, because of increased awareness for example, cannot be ruled out, we consider it highly unlikely that the observed increase is solely attributed to a notification bias. A six-fold rise in cases over 4 years observed in the 3 different surveillance systems indicates the likeliness of a true increase.

Bias by augmented laboratory capacities

Since the early 2000's, molecular techniques to diagnose pertussis have been in use. Although this coincides with an initial moderate increase in reported pertussis cases, it can however not explain the six-fold increase in cases since 2010.

Since 2012, laboratories of the WIV-ISP (serology) and UZBrussel (molecular diagnosis) have joined forces as the NRC for pertussis. Previously it was the UZBrussel alone that functioned as a reference laboratory. This increase in diagnostic capacity in the NRC (mainly for the diagnosis in adults through serology) may have contributed to the increase in the number of cases reported through the NRC. However, the increase is also noted in the sentinel laboratory network, of which the WIV-ISP lab is not part.

BACKGROUND INFORMATION

Description of the context

Pertussis is an acute vaccine-preventable bacterial infection of the respiratory tract, caused by the bacterium *Bordetella pertussis*. After inhalation of the bacteria, they first colonize the respiratory tract. In a second phase the bacteria start spreading toxins, which are responsible for the long term coughing that is typical for a pertussis infection (see paragraph Clinical presentation and incubation period).

The disease is known to primarily affect infants (<6 months) and mortality and morbidity are highest in this age group. Belgium, as well as several other European countries, has observed a bimodal curve in recent years, with a peak in children and a second peak in the age group of 40-60 year olds (see Figure 3).

Belgian pre-vaccination incidence is not well described. Vaccination started at the end of the fifties, beginning of the sixties. Originally a whole cell vaccine (containing entire inactivated bacteria) was used. From 1999 onwards, it was gradually replaced by an acellular vaccine (containing certain components of the bacteria) because of concerns about side effects. The vaccination schedule was frequently adjusted and booster doses were added because of concerns of increasing incidence possibly due to waning immunity (see paragraph Prevention: Vaccination).

Pertussis outbreaks have the tendency to occur in cycles of 3-5 years. The peak that is currently observed is however more than twice as high as the previous peak in cases, registered in 2007.

Transmission, infectious dose and period of communicability

Pertussis is a highly contagious disease that infects 80-90% of susceptible persons. The herd immunity threshold is estimated to be 92-94%.

It is transmitted from human-to-human through inhalation of infectious respiratory droplets. The infectious dose is not known. People are infectious from the start of the symptoms until about 3 weeks after the onset of the paroxysmsal of coughing.

Adolescents and adults are significant sources of transmission of *B. pertussis* to unvaccinated young infants. A 2003 Belgian study by De Schutter *et al.* already suggested that identical strains can cause full pertussis disease in children and asymptomatic infection in adults and adolescents. A study conducted in Canada, France, Germany and the United States showed that when pertussis occurred in infants, household members – primarily parents – were the source of *B. pertussis* in 76–83% of cases. Similar findings have been reported from Brazil and Australia.

A 2013 Belgian seroprevalence study by Huygen *et al*. on leftover samples showed that 4% of adults between 20-39 years had an antibody titer suggestive of a pertussis infection in the last 2 years and 4% had an antibody titer suggestive of an acute infection. This indicates the presence of a reservoir of pertussis among a supposedly healthy population, that is likely contributing to the transmission of pertussis to infants.

Clinical presentation and incubation period

The incubation period of pertussis is commonly 7-10 days (range 4-21).

In infants younger than 6 months, the clinical presentation is often atypical, with minimal cough and without whooping. The primary symptom can be gasping and apnoea, with a risk for exhaustion.

In young children, pertussis is a disease that has 3 distinct stages:

1. Catarrhal phase (1-2 weeks):
The initial (catarrhal) phase shows the symptoms of a common upper respiratory tract infection, with nasal congestion, tearing, conjunctival suffusion, rhinorrhoea and sneezing. Low fever may be present.

2. Paroxysmal phase (1-6 weeks)
In this phase, patients have paroxysms of intense coughing, sometimes followed by a loud whoop. Post-tussive vomiting is common in affected children.

3. Convalescent phase (2-3 weeks, sometimes longer)
The stage is characterized by gradual recovery. The cough becomes less paroxysmal. However, paroxysms may recur with subsequent respiratory infections for many months.

Older children, adolescents, and adults may not exhibit distinct stages. Symptoms in these patients include uninterrupted coughing, feelings of suffocation or strangulation and headaches. Vaccinated adults usually develop only prolonged bronchitis without a whoop, whereas unvaccinated adults are more likely to have whooping and post-tussive emesis.

Immunity after infection is not permanent and is estimated to last between 7-20 years.

Complications

International literature
About 50% of infants younger than 1 year who get pertussis, are hospitalized. The younger the infant is, the more likely he will be hospitalized. Of the infants who are hospitalized:

- apnoea occurs in 67%
- pneumonia occurs in 23%
- convulsions occur in 1.6%
- encephalopathy occurs in 0.4%.

About 1.6% of hospitalized infants die.

Less than 5% of teens and adults with pertussis are hospitalized. Among those hospitalised:

- loss of bladder control occurs in 28%
- loss of consciousness occurs in 6%
- severe coughing with rib fractures occurs in 4%
- pneumonia occurs in 2%.

For Belgian data on hospitalisation, see p18.

Diagnosis

Real-time PCR
Real-time PCR is the diagnosis of choice. For this test, a nasopharyngeal swab less than 3 weeks after the start of the infection, is required.

This technique is recommended in:

- patients younger than 1 year who present with cough, dyspnoea, sudden unexplained death, regardless of the duration of the symptoms
- asymptomatic contacts of less than 6 months
- patients older than 1 year that have symptoms for less than 3 to 4 weeks.

The usefulness of this technique is limited:

- in patients under antibiotic treatment
- to distinguish between a low concentration of the bacteria and contamination or cross reaction with other *Bordetella species.*

In the Belgian National Reference Center a combination of 4 primer pairs is used in order to be able to distinguish *Bordetella pertussis*, *Bordetella parapertussis*, *Bordetella holmesii* and *Bordetella bronchiseptica.*

Serology
In serological testing, anti-pertussis toxin IgG antibodies are determined. These antibodies stay present in the patient after the bacteria has disappeared. Therefore, this technique is recommended when the suspicion of pertussis was not immediate and the specimen collection is not done within 3 weeks after the start of infection. This is more frequent among adults, who generally have less specific symptoms.
The technique is more sensitive than PCR in patients under antibiotic treatment.

This technique is recommended in:

Non-vaccinated patients:

- presenting with symptoms for more than 3 weeks
- presenting with symptoms for less than 3 weeks who are PCR negative (2 samples are needed to evaluate the rise in IgG titre, one sample <3 weeks after onset of symptoms and the second one 2-4 weeks later).

Patients vaccinated in the previous year (2 samples are needed to evaluate the rise in IgG titre, one sample <3 weeks after onset of symptoms and the second one 2-4 weeks later).

Culture
Culture of the bacteria has a high specificity of about 100% but a low sensitivity of about 50%. Therefore culture is not useful for diagnosis of the infection. The culture becomes negative after one month, but can remain positive for a longer period in children younger than 1 year. Antibiotic sensitivity testing and molecular typing tests are performed on positive culture isolates for research and surveillance.

Reimbursement of diagnosis
Neither the serology, nor the real-time PCR are included in the nomenclature of RIZIV-INAMI. The project of the National Reference Centers covers the expenses of tests performed at the NRC. Because of the increase in number of tests, the NRC requested and was accorded an emerging disease budget for 2014.
The specific missions of the NRC pertussis are:

1) To perform or confirm the diagnosis.
2) To contribute to the quality assurance.
3) To characterize the isolated strains by genotyping, determination of antibiotic susceptibility …
4) To participate in national surveillance and in the assessment of the vaccination impact.
5) To actively collaborate to national and international networks.
6) To transfer microbiological data (through e-health reporting) and scientifically report the analysed data for public health concerns.

Tests performed in other laboratories are paid by the patient (around 10€ for serology, 20€ for PCR).

Treatment

The evolution of the disease is influenced only little by the administration of antibiotics, unless they are given in the catarrhal phase. However, antibiotic treatment is useful in prevention of transmission of the disease. Treatment should therefore be considered in patients with onset of symptoms less than 3-4 weeks. After a treatment of 5 days, the bacteria are eliminated from the respiratory tract of the patient.

Azithromycin, clarithromycin (children and adults) and roxithromycin (adults) are the first-line antibiotics of choice.

Prevention by vaccination

Types of vaccination
Two types of *Bordetella pertussis* vaccines exist, namely the whole-cell vaccine (wP), and the acellular vaccine (aP).

- Whole-cell pertussis vaccines are developed and used since the 1950's. They consist of a suspension of the entire inactivated bacteria. Immunization with wP vaccines is effective and the vaccine is relatively inexpensive, but local adverse reactions such as redness and swelling at the site of injection, have been frequently reported. More severe systemic events (convulsions and hypotonic hyporesponsive episodes) occur less frequently (one case to 1,750 doses administered). wP-containing vaccines are usually not recommended for use in children aged ≥7years, adolescents and adults.
- Acellular pertussis vaccines were developed because of concerns about adverse reactions upon wP vaccine administration. From 1980 to around 2005, wP vaccines were gradually replaced by aP vaccines in most developed countries. The aP vaccines contain components of the bacteria, such as inactivated pertussis toxin either alone or in combination with other *B. pertussis* components such as filamentous haemagglutinin, fimbrial antigens and pertactin.

Belgian vaccination schedule
In Belgium, pertussis vaccination started around the end of the fifties, the beginning of the sixties. Since the nineties, routine vaccination consisted of 4 doses, administered to all children. Due to an observed increase of pertussis cases, under this vaccination scheme, more doses were added in subsequent years.

Basic pertussis vaccination in infants:
- The first 4 doses are given at 8, 12 and 16 weeks and 15 months.
- In 1999, the fourth dose was replaced by an acellulair vaccine in Flanders. Since 2001, whole cell vaccine have been replaced by acellulair vaccines (aP) for all 4 doses.
- Currently, a hexavalent vaccine is used that also includes poliomyelitis, tetanus, diphtheria, *Haemophilus influenzae* type b and hepatitis B.

Booster doses in children:
- A first booster dose at 5-7 years, using a tetravalent vaccine that also includes poliomyelitis, tetanus and diphtheria, was added in 2001 in Wallonia and in 2004 in Flanders.
- In 2009 a second booster was recommended and implemented in the vaccination programmes at the age of 14-15 years with a trivalent vaccine that also includes tetanus and diphtheria. This vaccine contains lower doses of diphtheria, tetanus and pertussis antigens as compared to the children's vaccine (Tdap).

Adult vaccination:
- In 2009 a booster was recommended for adults in close contact with infants under the age of 12 months (household, caregivers, healthcare personnel). This is known as cocoon vaccination. It is part of the vaccination programme in Flanders since July 2014.
- Since 2013, the Superior Health Council recommends to vaccinate all adults with one dose of Tdap, regardless of pertussis vaccination history (especially those adults who come in contact with newborns). Wallonia follows this recommendation. In Flanders it is recommended to use a Tdap booster for all adults at the moment of the booster dose for tetanus en diphtheria (last dose more than 10 years ago). In the vaccination programme Tdap replaces the formerly used Td since July 2014.
- In 2013, a booster was recommended for pregnant women in the 24th to 32nd week of the pregnancy. Since July 2014 the recommended vaccination is part of the vaccination programme in Flanders and the vaccine can be ordered and obtained free of charge. In Wallonia it is included in the vaccination programme free of charge since September 2015.

The currently (2015) used vaccines in Belgium are:

- Hexyon® (Flanders and Wallonia) - polio, diphtheria, tetanus, pertussis, *H. influenzae type b*, hepatitis B (basic vaccination schedule 8, 12, 16 weeks, 15 months)
- Tetravac® - polio, diphtheria, pertussis, tetanus (booster 5-7 years) – for reasons of international shortage of acellular pertussis vaccines temporarily replaced by Repevax® (Tdap-IPV)
- Boostrix® - diphtheria, pertussis, tetanus (booster 14-15 years) - recommended for vaccination of adults, cocoon vaccination (including health care providers), pregnant women (24th to 32nd week).

Belgian vaccination coverage

Coverage estimates of pertussis vaccination among infants

The oldest available and most recent data on vaccination coverage for pertussis come from studies conducted in 1999 (2000 for Brussels) and 2012 respectively. At both moments, infant vaccination against pertussis consisted in a 4 dose-schedule with a multivalent vaccine (at least containing diphtheria, tetanus and pertussis, DTP). Table 1 shows the vaccination coverage for the 3rd and the 4th dose of the vaccine in infants aged 18-24 months.

	Brussels		**Flanders**		**Wallonia**	
	2000	**2012**	**1999**	**2012**	**1999**	**2012**
Vaccination coverage DTaP-3 (in %)	92.1	98.7	94.5	98.7	96.6	99.8
Vaccination coverage DTaP-4 (in %)	81.1	91.1	89.2	93.0	84.4	90.4

Table 1: Belgian diphtheria, tetanus and pertussis vaccination coverage for 3rd and 4th dose in infants 18-24 months per region, 1999 (2000 for the Brussels region) and 2012.

In 2012, the coverage of the booster dose at 5-7 years in Flanders was 90.8% and 78.7% in Wallonia.
In Wallonia, among adolescents in the 4th grade of secondary school, vaccination coverage was estimated to be 53.4% in 2013-2014.

In Flanders in 2012, twenty percent of mothers of young children (18-24 months) and 27% of fathers recalled being vaccinated with Tdap, 43% of mothers and 33% of fathers recalled not being vaccinated, the rest did not recall this information.
Seventeen percent of mothers of adolescents born in 1998 and 25% of fathers recalled being vaccinated with Tdap, 45% of mothers and 37% of fathers recalled not being vaccinated, the rest did not recall this information.

Coverage estimates of pertussis vaccination among pertussis cases

Limited information is available on the vaccination status of cases. The information below is obtained from the system of mandatory notification.

In Flanders in 2014, the self-reported vaccination status among 534 pertussis cases with a known vaccination status was:

- 24.5% unvaccinated
- 4.5% incompletely vaccinated
- 71% completely vaccinated.

In Wallonia in 2013, the self-reported vaccination status among 287 pertussis cases was:

- 33% unvaccinated

- 49% vaccinated with an unknown number of doses
- 18% unknown vaccination history.

Note: In the age group from 2 months up to five years, 45% is unvaccinated.

The figure below (taken from Lopez *et al.,* 2014) shows the vaccination status of reported pertussis cases in Wallonia in 2014 for those cases for whom the vaccination status was known.

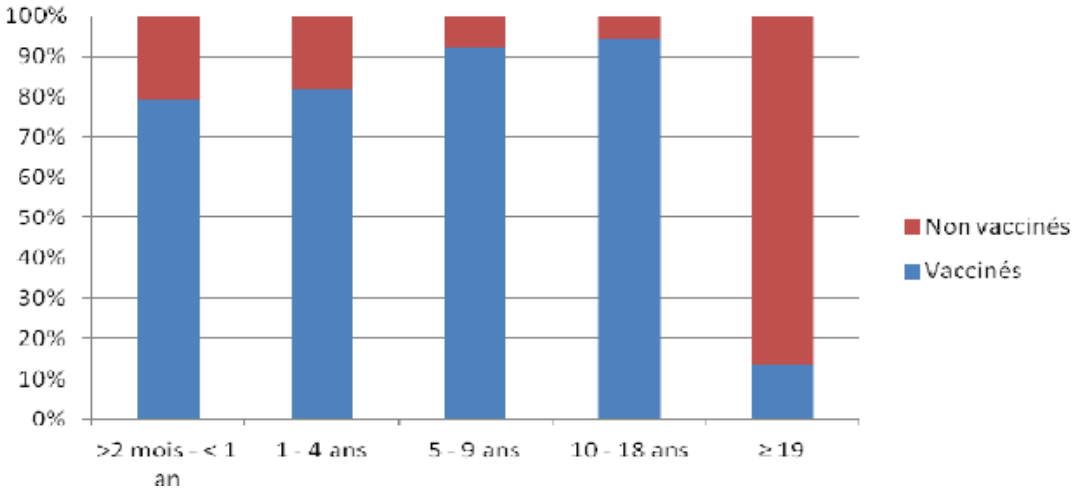

Figure 5: Proportion of vaccinated and non-vaccinated cases among reported pertussis cases for whom vaccination status is known per age group in Wallonia, 2014.
Original figure by Lopez *et al.*, 2014.

Coverage estimates of pertussis vaccination among pregnant women

A Belgian study in 2013-2014 of 250 pregnant women attending the University Hospital UZ Leuven showed a documented vaccination coverage of 39.2% for pertussis. Self-reported vaccination coverage for pertussis was 46%. Women from non-European origin were less likely to be vaccinated than women from Belgian or European origin.

A recent study by Maertens *et al.* conducted in 2015 in 823 women short after delivery showed a vaccination coverage against pertussis, given during the pregnancy, of 64% (personal communication).

In Wallonia in 2014, 25% of mothers of pertussis cases of less than 1 year old were vaccinated during pregnancy, 5% were vaccinated in the previous 10 years but not during pregnancy and 70% were not vaccinated in the previous 10 years.

A recent Belgian study by Maertens *et al.* (2015) showed that pertussis vaccination during the third trimester of pregnancy resulted in significantly increased antibody response to all five vaccine components in the mother, comparable to the increase observed in non-pregnant control women. However, antibodies (particularly against pertussis toxin) decreased again after one year. This supports the recommendation for repeated vaccination in repeated (or following) pregnancies.

No increased risk of acute adverse events or adverse birth outcomes has been found for those who had been previously vaccinated less than 2 years before or 2 to 5 years before compared with those who had been vaccinated more than 5 years before. These findings suggest that relatively recent receipt of a prior tetanus-containing vaccination does not increase risk after Tdap vaccination in pregnancy (Sukumaran *et al.*, 2015).

However, continued monitoring remains essential as antenatal pertussis immunization does result in high infant pre-immunization antibody concentrations, but can also blunt subsequent responses to pertussis vaccine (Ladhani *et al.*, 2015 and Hoang *et al.*, 2015).

Vaccine effectiveness and waning immunity

One of the major difficulties in assessing the protection against pertussis is the fact that it is impossible to correlate protection with a quantifiable immune response against one single antigen. This is due to several factors:

- pertussis produces a range of toxins (e.g. pertussis toxin, endotoxin, adenylate cyclase toxin and tracheal cytotoxin), that play a role in pathogenesis and immune evasion;
- pertussis has numerous virulence factors (filamentous hemagglutinin, pertactin and fimbriae) that aid bacterial persistence in the respiratory tract;
- cell mediated immunity plays an important role in protection.

A 2005 review on immunity data estimated that protection by vaccination (both whole cell and acellular) wanes after 4–12 years, compared to 7-20 years after natural infection. More recent studies have provided more information on waning immunity after aP vaccination and the difference in waning immunity between aP and wP vaccines.

- Several studies indicate that immunity from aP wanes over the years.
    - A 2012 US study by Klein *et al.* have shown effectiveness of DTaP is >85% following the first three vaccinations and >98% following the first booster dose (administered at 4-6 years). However, immunity wanes after that dose, so that after 5 years, DTaP-vaccinated children are 4-fold to 15-fold more likely to acquire pertussis relative to the initial protection.
    - A 2013 US study by Tartof *et al.* showed a steady increase in risk of pertussis in the years after completion of the 5-dose DTaP series, likely attributable in part to waning immunity from DTaP vaccines.
    - A 2015 meta-analysis by McGirr *et al.* concluded that 80% of DTaP-vaccinated children are no longer protected against pertussis by the time they receive the second booster at 11-12 years.

- Several studies indicate waning immunity is a bigger problem with the aP than the wP vaccine.
    - A 2013 US study by Klein *et al.* showed that teenagers who received four wP doses were nearly six times less likely to be diagnosed with pertussis than those who received 4 aP vaccines, and nearly four times less likely than those who received a mix of vaccines.
    - A 2013 US study by Witt *et al.* showed that the risk of pertussis was increased in schoolchildren and adolescents who were vaccinated exclusively with aP vaccines compared with subjects who received ≥ 1 wP dose.
    - A 2012 US study by Misegades *et al.* showed that children with pertussis, compared with controls, had lower odds of having received the 5-dose DTaP series; as time since last DTaP dose increased, the odds increased, which is consistent with a progressive decrease in estimated vaccine effectiveness each year after the final dose of pertussis vaccine.
    - A 2012 Australian study by Sheridan *et al.* showed that children who received a 3-dose DTaP primary course had higher rates of pertussis than those who received a 3-dose DTwP primary course in pre-epidemic and outbreak periods. Among those who received mixed courses, rates were highest for children receiving DTaP as their first dose.

A 2015 WHO position paper summarized that:

- although the reasons for the resurgence of pertussis are complex and vary by country, the shorter duration of protection and probable lower impact of aP vaccine on infection and transmission are likely to play critical roles;

- available evidence indicates that licensed aP and wP vaccines have equivalent initial effectiveness in preventing disease in the first year of life, but that there is more rapid waning of immunity, and possibly a reduced impact on transmission, with aP relative to wP vaccines;
- surveillance and modelling data suggest that the use of aP vaccines may result in a resurgence of pertussis after a number of years and such resurgence may also lead to an increased risk of death in those too young to be vaccinated;
- a switch from wP to aP vaccines for primary infant immunization should only be considered if the inclusion in the national immunization schedules of additional periodic booster or maternal immunization can be assured and sustained. However the provision of additional doses may not be sufficient to prevent resurgence of pertussis;
- national programmes currently using aP vaccine may continue using this vaccine but should consider the need for additional booster doses and strategies to prevent early childhood mortality such as maternal immunization in case of resurgence of pertussis.

Vaccine effectiveness of vaccination during pregnancy
Amirthalingam *et al.* estimated vaccine effectiveness of vaccination during pregnancy on hospitalisation rate of infants for pertussis, to be 91% when taking into account infants <3 months and administration of the vaccine at least 1 week before at term delivery; and 90% when taking into account infants <2 months. Dabrera *et al.* found a similar effectiveness of 93% on diagnosis of pertussis in infants <2 months, in family practice settings.

Vaccine escape
Several studies suggest that circulating *B. pertussis* strains are evolving to evade vaccine-driven immunity.

- In some countries strains have emerged that do not express one or more components of pertussis vaccines, in particular pertactin.
  - A 2015 US study by Martin *et al.* showed that individuals up to date on pertussis vaccinations were 3.7-fold more likely to be infected with a PRN-deficient strain compared to a strain expressing pertactin, suggesting a selective advantage for loss of PRN expression in *B. pertussis*.
  - A 2014 Australian study by Lam *et al.* showed that in a large outbreak in Australia in 2008-2012, 30% of isolates did not express pertactin.
  - A 2014 global study by Bart *et al.* on comparative genomics on a worldwide collection of 343 *B. pertussis* strains showed that the worldwide population of *B. pertussis* is evolving in response to vaccine introduction, potentially enabling vaccine escape.

- Worldwide strains that produce higher levels of pertussis toxin have emerged (Mooi *et al*. 2009, Hallander *et al.* 2007).
  - Pertussis toxin plays a role in suppression of the innate and the acquired immune system.
  - Increased pertussis toxin requires higher levels of antibody to neutralize the toxin.

Risk factors

Risk groups for developing illness are:

- infants <1 year and particularly those <4 months
- persons with incomplete vaccination status.

Risk groups for developing severe illness:

- non or partially vaccinated individuals:
  - infants younger than 16 months who have not received 3 doses of the vaccine

  - infants older than 15 months who have not received 4 doses of the vaccine
- individuals with chronic cardiac or respiratory illness
- immunocompromised individuals.

Possible outcome

In most cases, the expected outcome for pertussis cases is very good. Chronic cough can last up to 3 months and some patients experience a relapse of symptoms for 6 months to a year or even longer.

Infants under 1 year of age are at increased risk for serious complications and often are hospitalized for treatment (see complications).

Case definition (ECDC)

The case definition and classification are those stipulated by EU Commission Decision of 8 August 2012.

Clinical criteria
Any person with a cough lasting at least two weeks and at least one of the following three:

- paroxysms of coughing
- inspiratory "whooping"
- post-tussive vomiting

OR
Any person diagnosed with pertussis by a physician
OR
Apnoeic episodes in infants

Laboratory criteria
At least one of the following three:

- isolation of *Bordetella pertussis* from a clinical specimen
- detection of *Bordetella pertussis* nucleic acid in a clinical specimen
- *Bordetella pertussis* specific antibody response

Note: Serology results need to be interpreted according to the vaccination status

Epidemiological criteria
An epidemiological link by human-to-human transmission

Case classification

A. Possible case
Any person meeting the clinical criteria

B. Probable case
Any person meeting the clinical criteria and with an epidemiological link

C. Confirmed case
Any person meeting the clinical and the laboratory criteria

Because existing clinical case definitions of pertussis are largely based on clinical presentation in infants and children and an increasing burden is borne by adolescents and adults who may manifest distinct signs/symptoms, the Global Pertussis Initiative (GPI) developed an algorithm that delineates the signs/symptoms of pertussis most common to 3 age groups: younger than 4 months, 4 months to 9 years, and ≥10 years. These case definitions are based on clinical presentation alone, but do include recommendations on laboratory diagnostics. These definitions however need to be evaluated (Cherry *et al.*, 2011).

Seasonality

In 2014, cases were diagnosed throughout the year, but the number of reported cases was lower in winter months. The same trend cannot be seen in data from other years (Figure 6).

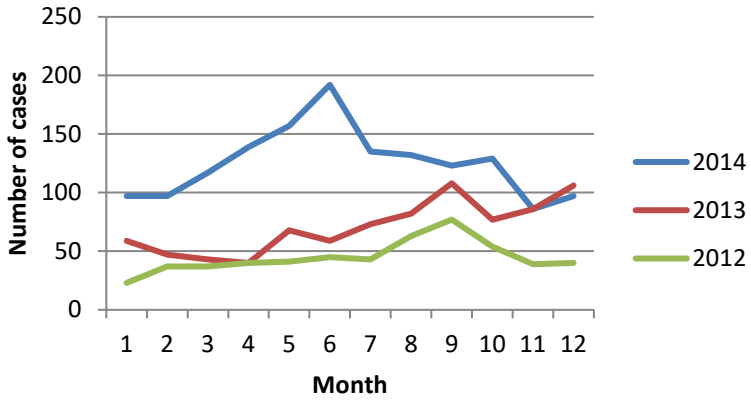

Figure 6: Number of reported cases by month of diagnosis by the NRC, 2012-2014, Belgium.

Cases reported per age group

All surveillance networks show the same age distribution of pertussis cases in all regions, with a higher number of cases reported in children less than 15 years old and in people aged 40-60 years old (except in Brussels) (Figure 7).

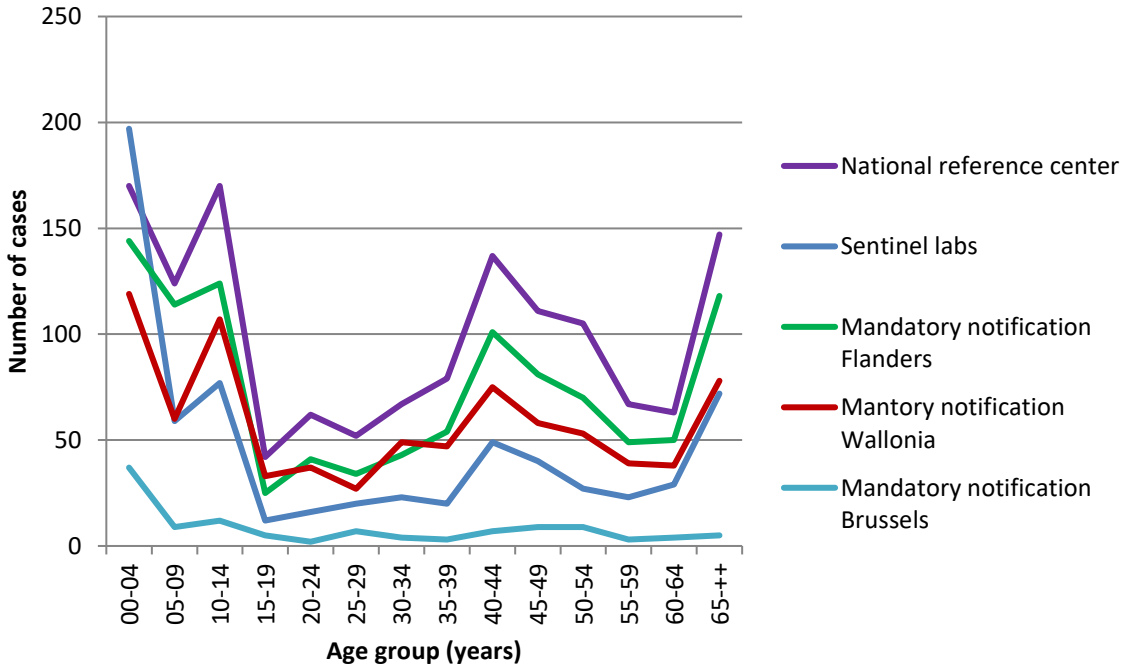

Figure 7: Number of reported pertussis cases by age group by surveillance system, 2014, Belgium.

Incidence is especially high in infants (<1 year) and 11-12 year olds (Figure 7).

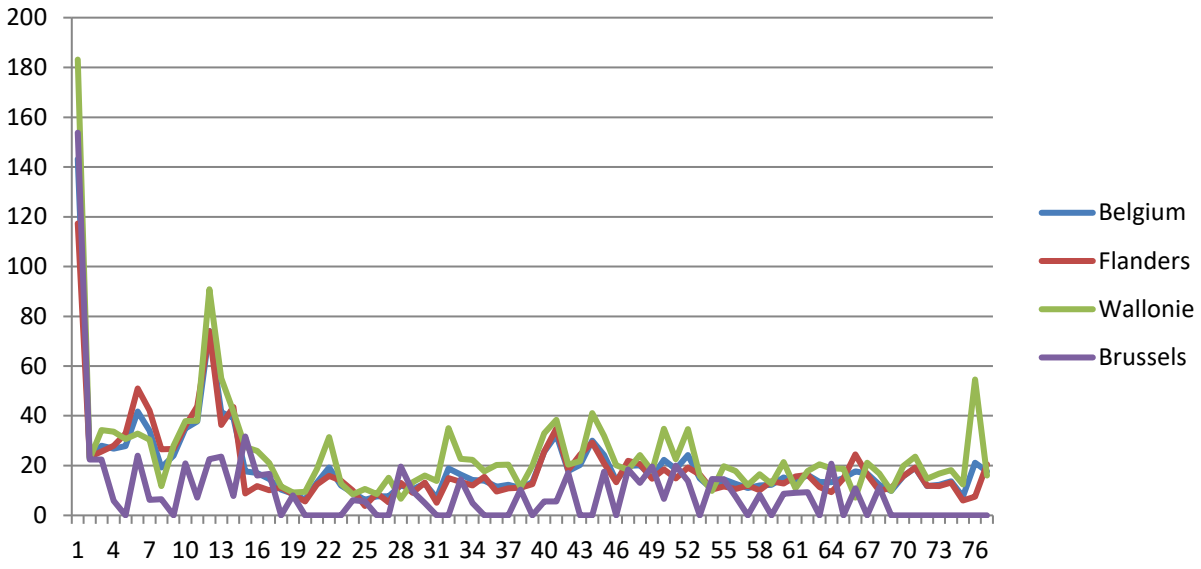

Figure 8: The incidence of the reported pertussis cases by the NRC per region per 100,000, 2014, Belgium (based on 2014 Belgian population data).

Geographical distribution

In 2014, cases were detected all over Belgium. Incidence of reported cases through one of the surveillance networks was highest in the cities of Antwerp and Gent and in the province Waals-Brabant (Figure 9).

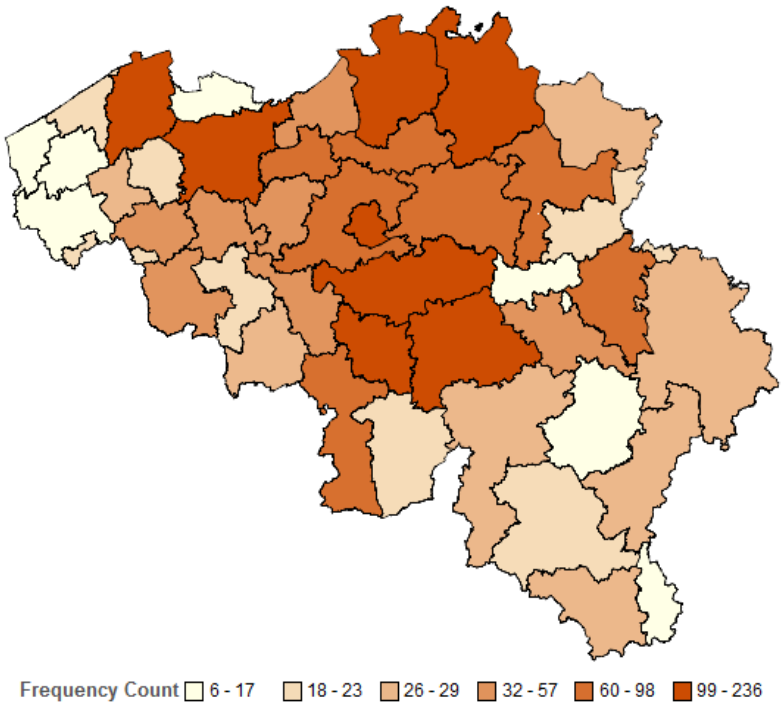

Figure 9: Geographical distribution of reported pertussis cases by borough, 2014, Belgium (NRC, the sentinel laboratory network and the mandatory notification).

Cases reported per gender

The gender distribution in pertussis cases reported by the sentinel laboratory network in 2014 was comparable to previous years, with 56% women (N=362) and 44% men (N=282).

Hospitalisation

Table 2 shows the yearly Belgian hospital admissions available from the Minimal Clinical Dataset (hospitalisation records –using ICD9 codes) for pertussis per age group for the period 2000-2012 (most recent available year). When the yearly number per age group is between 1 and 4, no exact number can be obtained and the number is marked as <5.

These data show the highest admission rate in infants <1 year. There appears to be no increasing trend in the number of hospitalisations in any age group. However, data for the years 2013-2015 are not yet available.

	Age group (in years)											
Year	**<1**	**1**	**2**	**3**	**4**	**5-14**	**15-19**	**20-44**	**45-64**	**65-74**	**75-84**	**>85**
2000	78	16	5	0	0	9	0	0	0	<5	0	0
2001	55	13	<5	<5	0	<5	<5	<5	<5	<5	0	0
2002	49	16	0	<5	0	<5	<5	<5	<5	0	0	0
2003	41	11	<5	<5	<5	<5	0	0	0	<5	0	<5
2004	81	11	0	0	0	<5	<5	<5	<5	0	<5	0
2005	100	21	0	<5	0	<5	0	0	<5	<5	<5	<5
2006	84	30	<5	<5	0	6	<5	<5	<5	<5	<5	0
2007	102	46	0	0	0	13	<5	<5	7	<5	<5	0
2008	70	32	<5	0	0	7	7	<5	<5	<5	<5	0
2009	81	15	0	<5	0	5	5	<5	<5	<5	<5	<5
2010	80	19	<5	<5	0	<5	<5	<5	<5	<5	<5	<5
2011	54	20	0	0	<5	0	<5	<5	<5	0	0	0
2012	105	20	<5	<5	<5	7	0	5	11	<5	<5	0

Table 2: Hospital admissions for pertussis per age group, 2000-2012, Belgium.

In 2013, in Wallonia, a hospital admission was reported for 35 pertussis cases of the 258 in the mandatory notification for which this information was available, this is 13.6%. For the infants younger than 1 year, 81% were admitted into hospital, compared to only 5% of children 1-5 years old.

In 2014, 81.3% of cases younger than 6 months in Wallonia was hospitalized and 42.1% of infants between 6 months and a year. The hospitalisation rate among cases between 1-4 years was 19.4% and among cases aged 5-65 years less than 5%. Eleven percent of patients older than 65 years old were hospitalised. In 2013, in Flanders, a study showed that 42% of pertussis cases between 0-4 years old were admitted into hospital.

Case fatality/mortality

In Belgium reported mortality due to *Bordetella pertussis* is rare, but data are scarce. Although the system of mandatory notification collects data on the outcome of the disease, follow-up data are often missing, so an accurate case fatality ratio cannot be calculated.

Table 3 shows the yearly mortality due to:

- all *Bordetella* infections from 2000 to 2012 according to the mortality data available through the Directorate-general statistics and economic information.

- *Bordetella pertussis* infections from 2000 to 2012 according to the deaths recorded in the Minimal Clinical Dataset (hospitalisation records). When the yearly number per age group is between 1 and 4, no exact number can be obtained and the number is marked as <5.

	Mortality data (all *Bordetella* infections)		**Minimal Clinical Dataset** (*Bordetella pertussis* infections)	
	Number of recorded deaths	**Age group (in years)**	**Number of recorded deaths**	**Age group (in years)**
2000	1	<1	<5	65-74
2001	0	/	0	/
2002	0	/	0	/
2003	0	/	0	/
2004	1	<1	<5	<1
2005	1	<1	<5	45-64
2006	1	<1	0	/
2007	0	/	0	/
2008	0	/	<5	15-19
2009	1	<1	<5	<1
2010	1	<1	<5	<1
2011	2	<1	<5	<1
2012	1	<1	<5	<1

Table 3: Deaths due to *Bordetella (pertussis)* per age group, 2000-2012, Belgium.

The discrepancy in these figures could have several explanations, such as reporting errors and deaths due to *Bordetella* infections occurring outside of a hospital setting. With the available data, it is however not possible to pinpoint the exact reason for the discrepancy.

Since 2000, no increase in mortality due to *Bordetella (pertussis)* is observed.

EPIDEMIOLOGICAL SITUATION IN EUROPE AND THE WORLD

ECDC data (most recent data from 2012)

In Europe, a similar trend of increasing pertussis cases was noticed. In 2012, the notification rate was more than twice as high as in previous years. Increases were mainly observed in the Netherlands, the United Kingdom, Denmark, Latvia, Czech Republic, Austria, Lithuania, Ireland, Poland and Portugal.

The most affected age group in the EU/EFTA countries were the 5–14 year-olds, which is mainly due to this group having been the most affected age group in countries reporting the highest overall notification rate (Norway and the Netherlands). For most of the other countries, the most affected group were young children under five years old.

Specific outbreaks of pertussis were recognised during 2012 in England and in the Netherlands.
The EU/EFTA data show that pertussis is no longer solely a paediatric infection. Incidence is increasing in adolescents and adults.

More recent data for some neighbouring countries

In the Netherlands, a peak in the number of pertussis cases was reached in 2012, which was the highest observed peak since the number of cases has been increasing since the 1990's. The peak was followed by a sharp decrease in 2013, but a rise was observed again in 2014. In 2012, highest incidence was observed among 5-9 year olds, followed by infants of less than 1 year old. In 2014, highest incidence was observed among infants of less than 1 year old. The vaccination schedule is similar to that in Belgium, but without the booster at 14-15 years, without cocoon strategy and without the vaccination of pregnant women.

In the UK, a peak in the number of cases was also reached in 2012 and 2014. Incidence was highest in those 10-14 years old, followed by those of less than 3 months old. The vaccination schedule is similar to that in Belgium, but without the 4th dose at 15 months, without the booster at 14-15 years and without cocoon strategy.

WHO data

A 2014 WHO working group reported on an analysis of pertussis data of 19 countries (Australia, Brazil, Canada, Chile, Cuba, Denmark, Finland, France, Germany, Israel, Japan, Mexico, Norway, Portugal, Singapore, Sweden, Thailand, UK, and USA) in various world regions which have wP- or aP-based programmes, achieve high vaccine coverage rates, have effective disease control, and have the ability to provide high quality data. The main outcome of the report is that pertussis vaccination is highly effective in reducing disease caused by *Bordetella pertussis*, with a large decline in overall global incidence and mortality compared with the pre-vaccination era in both wP- and aP-using countries. No evidence was found of a widespread global resurgence of pertussis (defined as a larger burden of disease than expected when compared to previous cycles in the same setting). There is however evidence that resurgence has occurred in 5 of the 19 countries reviewed, 4 of which were exclusively using aP vaccines.

Possible explanations of increase:

Apart from improved surveillance, increased awareness/notification bias/increased diagnostic possibilities, the following factors may contribute to the observed increase:

1. Vaccination (see background)

1.1 Vaccine effectiveness (baseline effectiveness before possible waning)

The cost-benefit ratios of aP and wP are difficult to compare since wP is currently only used in a number of countries and there is only little available historical data. Observational studies have consistently shown around 50% protection against severe pertussis in infancy following a single dose of either wP or aP pertussis vaccine. Two doses offer at least 80% protection. However, as the evidence is consistent with incremental protection after each additional dose, it is essential to complete a full primary serie to obtain the full protective effects conferred by pertussis vaccine (WHO, 2015).

Effectiveness of vaccine induced immunity might be different for clinical disease as compared to disease transmission. Primate models have shown aP vaccines to protect against disease but to fail to protect against transmission (Warfel *et al.*, 2014). Mathematical modelling of incidence trends has come to similar conclusions on US and UK data (Althouse *et al.*, 2015). In conclusion; though effectiveness on clinical disease directly after vaccination seems good, the effect on transmission is under debate. In order to obtain a good effectiveness, the vaccination schedule (repeated vaccinations) needs to be completed.

1.2 Waning (declining of effectiveness from the baseline over time)

The most debated issue with respect to the increase in pertussis cases is the loss of vaccine-induced immunity over time. A faster loss of aP vaccine induced immunity is established in many articles (as compared to wP and natural infection). Subsequently many countries have incorporated boosters into their vaccine schedule, but it remains unclear how vaccine schedules can best compensate for waning (e.g. waning remains an issue even under booster vaccination) (Riolo *et al.*, 2015). In this context approaches such as 10-year boostering have been suggested.

Some data suggest the duration of protection after booster vaccination might be shorter in persons who never received whole cell pertussis vaccination. This might explain partly why the current epidemics occur several years after replacing all whole cell by acellular pertussis vaccines.

1.3 Vaccination legacy (history of coverage) & coverage

Herd immunity or limiting pertussis transmission by high vaccination coverage is important since the most vulnerable population is too young to be vaccinated (<8 weeks). It is unclear whether herd immunity can be obtained with the current vaccine and vaccine schedule. This depends on estimates for VE and waning (most relevant in the context of herd immunity is the effect of waning on transmission). So it is unclear what the coverage needed is (99%, 90%) and it is hard to compare the coverage between countries (Zepp *et al,.* 2011). Since it seems unlikely that protection can be acquired on a population level, persons in close contact with the most vulnerable group have been advised to get vaccinated (cocoon-vaccination). In this context the vaccination of pregnant women has also been developed.

2 Disease Dynamics

2.1 Changes in genotypes

Apart from problems inherent to the vaccine, changes in the pathogen have also been suggested as reasons for the current increase. It is however unclear whether vaccine escape (antigenic escape, see background) is facilitated under the current vaccine schedule and vaccine composition.

Vaccine with multiple components (>3) have been suggested, are in use and under further development to cover the pathogen more broadly, but it is unclear if these are durable options (e.g. 5-componet vaccines) or if they will induce more genetic drift (Hallander *et al.*, 2011)?

The pathogen is evolving and differences in genotype might also lead to different clinical manifestations (or different manifestations of repeated infections) (e.g. pertussis toxin-deficient, pertactine-deficient, …) (Lam *et al.*, 2014).

2.2 Decline in natural boosting, repeated infections

A certain vaccine schedule in combination with high vaccine coverage might influence the natural occurrence of the 3-5 years epidemic cycle that is associated with pertussis (Riolo *et al*., 2015). This might lead to an absence of probability of natural boosting over a period of time, resulting in a larger increases in the next cycle. So for periods of time vaccination might limit natural boosting, and therefore allow for accumulation of susceptible individuals.

3 Population and social Dynamics

The pool of susceptible individuals is not only influenced by waning of immunity or vaccine escape, but also by demographics.

3.1 Birth rate

3.2 Age demographics and contact patterns

The vaccine schedule in combination with waning immunity might influence the incidence of pertussis in certain age groups, who by having different contact patterns, might increase transmission to other age groups. Age specific contact patterns can explain shifts in prevalence and age stratified incidence (Pesco *et al*. 2014).

SUMMARY OF THE RISK ASSESSMENT

1 - Unusual or unexpected ?	Not unexpected but unusual	We do not consider this outbreak unexpected when taking into account the scientific knowledge about waning immunity and vaccine escape and the increases observed in neighbouring countries with similar vaccination schedules and earlier introduction of aP vaccines. We consider it unusual because vaccination coverage is high, the peak in cases currently observed is a lot higher than previous observed peaks and circulation in adults is not expected, since they were vaccinated with wP but probably with a suboptimal vaccination coverage at that time.
2 - Public health impact?	High in < 1 Low in adults	Morbidity is high among young children, with the majority of pertussis cases in infants younger than 1 year being admitted into hospital. Morbidity in adults can lead to increased cost for the society due to absenteeism and costs for testing. It has to be stated however that because of vaccination, mortality and morbidity have decreased tremendously compared to the pre-vaccination era.
3 - Risk for dissemination?	High	Pertussis is a highly contagious disease. Individuals at highest risk are unvaccinated and incompletely vaccinated individuals and individuals in which immunity against pertussis has waned.
4 - Limitation of international movement of persons/goods?		Not relevant.

RECOMMENDATIONS FROM THE RAG

ACTIONS ALREADY TAKEN

Modification of vaccination strategy

In 2009 a second booster dose was recommended at 14-15 years with a trivalent vaccine that also includes tetanus and diphtheria, because of known waning of antibodies while using aP vaccines among young children. This was implemented in the vaccination programmes of the communities in Belgium. The vaccinations of the basic vaccination schedule for children and adolescents can be given with vaccines free of charge in the vaccination programmes of the communities.

The same year, a booster dose was recommended for adults in close contact with infants under the age of 12 months (household, caregivers, healthcare personnel). This is known as cocoon vaccination. However, this strategy has not been very successful, because of the difficult implementation (need of a prescription of the vaccine and purchase at the pharmacy, with reimbursement procedure).

In 2013, the Superior Health Council recommended to vaccinate all adults with one dose of Tdap vaccine, regardless of their vaccination status. At the same time it was recommended to vaccinate pregnant women in the 24th to 32nd week of pregnancy. Since July 2014 the recommended vaccination (basic vaccination schedule, boosters, vaccination during pregnancy) is free of charge for all adults in Flanders. In Wallonia the recommended vaccination is free of charge (since September 2015) for pregnant women. It is partially reimbursed by the INAMI/RIZIV for other adults.

Extra support for NRC pertussis

In 2014, the increase number of tests performed in the NRC pertussis led to 77.595 EURO extra costs. To (partially) cover for these increased expenses, an "emerging disease budget" of 65.000 EURO was granted to the NRC that year.

RECOMMENDATIONS FOR SURVEILLANCE AND COMMUNICATION

Communication and awareness

Recommendations	Actions by
Increase the awareness of pregnant woman concerning the importance of pertussis vaccination.	Federated entities
Increase the awareness of gynaecologists and midwives concerning pertussis vaccination during pregnancy. In Wallonia, an official recommendation from the society of gynaecologist could improve awareness. Materials (leaflets and posters) of the Flemish campaign could be adapted.	Federated entities
Increase awareness among GPs and peripheral labs to improve correct sampling and diagnosis.	NRC
Increase awareness among GPs and paediatricians on early treatment and identification of (atypical) cases, to prevent further transmission and complications.	Federated entities
Propose a governmental-funded vaccination program for staff of child day-care centres and kindergartens.	Federated entities
Ensure vaccination of staff of maternity and paediatric wards.	Federated entities

Increase awareness among parents and school doctors on the importance of the booster dose at 14-15 years.	Federated entities

Surveillance

Recommendations	Actions by
Allocate an emerging disease budget to the NRC for 2015 and until the end of the peak.	MTAO
Increase awareness among GPs and peripheral labs on the importance of clinical data in order to perform correct analyses and interpretation (serology vs PCR).	NRC
Evaluate the impact of the newly recommended vaccination strategies on the epidemiology of pertussis (possibly through serological studies in mothers at delivery and in adolescents) especially close follow-up of pertussis data in infants.	Federated entities
Perform a vaccine effectiveness study (of maternal vaccination) in infants.	Federated entities
Perform a vaccination coverage study in pregnant women (Wallonia and Flanders).	Federated entities
Perform a study to understand what the true diagnosis is in the cases for which the pertussis test comes back negative (should be done during a whole year to include the seasonal variations).	NRC and federated entities.
Perform a study to assess the impact of aP vaccination on infection, disease and circulation of pertussis.	NRC and federated entities.
Develop a plan to follow-up the impact of vaccination on the long term.	RMG
Determine the burden of disease of pertussis in children and adults (mortality, morbidity, costs of treatment, costs of diagnosis, etc…).	WIV-ISP

RECOMMENDATIONS ABOUT CONTROL MEASURES

Recommendations	Actions by
Better implement the current recommendations for pertussis vaccination, keeping in mind that the primary focus concerns the protection of infants. Therefore high vaccination coverage in pregnant women is of upmost importance.	Federated entities
Ask RIZIV/INAMI to facilitate the procedure for reimbursing Boostrix vaccination for adults (cocoon vaccination).	RMG
Closely monitor problems of vaccine shortages. Priority should be giving to preserving the infant primary immunisation schedule.	RMG and FAGG
Include pertussis diagnosis (serology and PCR) in the RIZIV/INAMI nomenclature.	RMG and RIZIV/INAMI

The most recent data on vaccination, infection, disease and circulation of pertussis (more specifically, data on the reduced impact of the aP vaccine on the infection with and transmission of pertussis) should be further evaluated by an expert committee in order to adapt current case and outbreak management guidelines.	HCH for advice RMG for case and outbreak management guidelines

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