CONSULTATIVE SIGNAL ASSESSMENT

PRIMARY RISK ASSESSMENT

INCREASE IN CASES OF PERTUSSIS

Date of the signal	Date of the RA	Signal provider	Experts consultation	Method
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Date of update	**Closing date**			

(final data extraction 19/09/2023, data included up to 31/08/2023)

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SIGNAL	An increase in Belgian cases of whooping cough has been noted since several months, with a particularly high number of cases during summer. The increase is noted in all three regions. Questions are raised particularly about the occurrence of whooping cough in vaccinated children. Additionally, there is a worry that diagnosis would be delayed, as clinicians are wrong-footed by the vaccination history. This signal is mirrored by a signal from Denmark, where case numbers in August were 4-times higher than usual. Incidence in Denmark is highest in children <1y of age, 9-19y of age and adults 40-50y. Also in The Netherlands, the number of monthly whooping cough notifications has been increasing markedly since May, but is still lower than before the covid pandemic

DESCRIPTION

Event

There are several surveillance systems for whooping cough in Belgium, each with its own strengths and limitations:

1. **National reference Centre (NRC) (Sciensano-UZ Brussel**) :
   Start PCR reimbursement 2019 resulted in decreased sample analysis by NRC. In this analysis NRC data for July and August are incomplete (PCR data is missing for August from UZ Brussel and July-August from Sciensano).
2. **Sentinel labs (SL)**:
   Not geographically representative (no comparison between regions), but possible to follow up trends. Unclear effect of recent use of multiplex panels and drop-out of several labs.
3. **Mandatory notifications (MN)**:
   Different criteria between different federated entities (since 2020 only PCR or serological confirmed cases in Brussels and only PCR positive cases <3y in Wallonia).
4. **PediSurv**:
   Voluntary sentinel surveillance by pediatricians and, in Brussels, GPs of certain diseases in children under 15y. Since June 2022, hospitalized cases of pertussis in children <3y of age are asked to be reported. Till now only few registrations.

- Reported cases declined sharply between 2019 and 2021 (likely due to measures taken during the COVID-19 pandemic), also noted in other countries (eg. the Netherlands). In 2022, there was a slow increase, mainly observed in mandatory notifications in Flanders/sentinel labs. This increase continues in 2023 and is now also clearly observed in the NRC data and the mandatory notifications from the other regions, albeit to a lesser extent than in Flanders (Figures 1-3 in Annex).

- Till August 2023 there were already 767 mandatory pertussis notifications reported in Flanders and 418 cases by the NRC, comparable with numbers reported for the whole year of 2013 and 2018. Especially the number of monthly notifications in Flanders since June is and remains very high (June: 92, July: 121, August: 202).
  Cases show a geographic disparity in Flanders, mostly occurring in West-Flanders (where the increase started September 2022, exceeding numbers of pre-covid years 2017-2019). East-Flanders has a sharper increase since summer 2023, but is not yet reaching pre-coved numbers.

- In 2023 the highest incidence is noted in the age groups 5-9y and 10-14y (pertussis cases in NRC, SL, MN Flanders) (Figure 4).

- In all data sources, data on vaccination status cases is missing for the majority of cases. Hence, no conclusive analysis can be performed and caution is needed when interpreting results below. However, there seems to

be an increase in proportion of vaccinated patients (Figure 5 and table 1-3) (see also 'type of risk' below). The ratio of pertussis infections in the vaccinated population in Flanders for 2023 exceeds the expectations (see table below), proportionally the most in children 1-4y old (1-4y: 54%, 5-9y and 10-14y: 42%).

Cases with vaccination appropriate for age (proportion of total) (2018)			
	Y	N	UNK
MN AVIQ &COCOM	48 (13%)	47 (13%)	265 (74%)
MN AZ	147 (15%)	81 (9%)	728 (76%)
NRC	85 (10%)	172 (20%)	595 (70%)

Cases with vaccination appropriate for age (proportion of total) (2019)			
	Y	N	UNK
MN AVIQ & COCOM	19 (5%)	24 (7%)	322 (88%)
MN AZ	168 (14%)	109 (9%)	959 (77%)
NRC	50 (7%)	152 (23%)	483 (70%)

Vaccination appropriate for age (proportion of total) (2023)			
	Y	N	UNK
MN AVIQ & COCOM	11 (15%)	35 (49%)	25 (36%)
MN AZ	**277 (36%)**	76 (10%)	414 (54%)
NRC	85 (20%)	72 (17%)	261 (63%)

- Severe presentations of pertussis primarily affect children <1y of age. Therefore, it is reassuring that the biggest increase of infections is in the age group 1-9y (NRC and MN) (figure 4).
  Data on hospitalisations is limited. Data from mandatory notifications and NRC confirms severity of infections in the age group <1y with a high proportion of hospitalisations, but does not show an absolute increase in the number of infections in this age group (Figure 6-7, table 4).

Type of risk

Unusual but not unexpected

Pertussis outbreaks have a tendency to occur in cycles of 3-5 years. Between 2014-2017, Belgium saw a large outbreak of pertussis. During the pandemic years 2020-2021, pertussis case numbers were particularly low. Hence, an increase in case numbers now is not unexpected. However the number of reported cases in July and August by the mandatory notifications of Flanders (mainly in West- and East-Flanders) exceeds peak years 2017 and the proportion of fully vaccinated cases is higher than usual.

With regards to a possible reduced effectiveness of vaccination:

- Cases in vaccinated individuals are expected.
  With a vaccination coverage of 94% and vaccine effectiveness of 80-85%, we would expect **2.35 times** more cases in vaccinated than in unvaccinated individuals, because of the much larger size of the vaccinated population. Moreover, waning immunity, despite the introduction of several booster doses, is known for the acellular pertussis vaccine used in Belgium (VE 62% at 4-7 years since last vaccination and 41% at 8 years or more since last vaccination).

- There are currently no indications of an increased mismatch between the circulating strain and the vaccine antigens
  Genotyping is performed by the NRC on all strains that are successfully cultured. The focus is on absence of pertactin expression, as strains without pertactin-expression partially escape vaccine-induced immunity. In years pre-Covid-19, more than half the number of strains were negative for pertactin *expression*. So far, no tests for pertactin expression have been performed for the 2023 strains. However, on WGS all strains *contain* the pertactin gene. This

	strongly suggests that the proportion of pertactin-negative strains will not be higher than in recent years.
Severity of the risk	***High in incompletely vaccinated young children*** ***Low for the rest of the population*** Fortunately, deaths due to pertussis are rare and less than 5% of adults with pertussis are hospitalized. However, about 50% of infants younger than 1 year who get pertussis, require hospitalization.
Exposed population	Incidence is particularly high in infants. However, previous studies have shown that household members (primarily parents) are the source of infection for infants in >75% of cases. A Belgian seroprevalence study from 2013 also showed the presence of a pertussis reservoir among the supposedly healthy adult population, where pertussis infection is often paucisymptomatic.
Risk of (inter)national dissemination	***High*** Pertussis is highly contagious and infects 80-90% of susceptible persons. Transmission is from human-to-human through inhalation of infectious respiratory droplets. Also Denmark and the Netherlands have already reported a similar increase in case numbers as Belgium.

PREPAREDNESS & CONTROL MEASURES ALREADY IN PLACE

Preparedness	- ***Prevention by vaccination***
	  ○ The Belgian vaccination schedule consists of 3+1 doses of hexavalent vaccine (IPV-DTPa-Hib-HBV) at 8-12-16 weeks and 15 months. A first booster is given at 6y, repeated at 14y and should be repeated every 10years later on.
	  ○ Despite good efficacy of the acellular pertussis vaccine (vaccine effectiveness: 80-85%), rapidly declining immunity is known (VE 62% at 4-7y, 41% at ≥8y since last vaccination).
	  ○ DTaP4 had a vaccination coverage of 94% in 2019-2020.
	  ○ Maternal vaccination is recommended since 2013 and available free of charge in all regions. Maternal vaccination coverage is 85.5% Flanders, 40% Wallonia, 30% Brussels (survey infants vaccination 2020). A more complex division of competences on vaccination, with sometimes logistic struggles to access vaccine doses and reluctance on the side of gynecologists to recommend the vaccination are mentioned as factors that explain the lower coverage in FWB.
	
	- ***Diagnosis***
	  ○ Since 2019, PCR <16y is reimbursed under strict criteria. This seems to decrease the number of samples sent to the NRC (decreasing the diagnosis confirmation and serotyping with impact on the surveillance)
	  ○ Several labs have implemented a multiplex PCR testing for several respiratory pathogens at once, including pertussis. It is unclear what the impact of this change on case ascertainment is.
	
	- ***Surveillance***
	  ○ Several surveillance systems already exist (cf. supra). Surveillance of severe cases of pertussis (requiring hospitalization) <3years has been added to PediSurv network since 06/2022. However, only very few registrations have been performed until now.

Specific Control Measures	- ***Control***
	  ○ It is mandatory to report pertussis cases in young children to the regional health authorities in all regions in Belgium. Household contacts at risk of severe disease (not/incompletely vaccinated child <1y, pregnant woman incompletely vaccinated, person with comorbidities) will then be offered antibiotic prophylaxis < 3 weeks after start cough of index patient.
	  ○ Of note, Denmark implemented maternal vaccination as a new control measure, but this is already in place in Belgium. Coverage is however suboptimal in Wallonia and Brussels.
	- ***Communication***
	  ○ In September 2022 clinicians in West-Flanders were asked to be vigilant for Pertussis. In October 2022 gynaecologist, paediatricians and infection prevention departments of hospitals in West-Flanders were sensibilized by letter on maternal and cocoon vaccination.
	  ○ The increase of cases has been mentioned in the "Nieuwsbrief Infectieziekten" of September, which also reminded clinicians of the mandatory notification.

RISK ASSESSMENT FOR PUBLIC HEALTH IMPACT IN BELGIUM

(specify expected public health impact as very low, low, medium or high)	**Low**

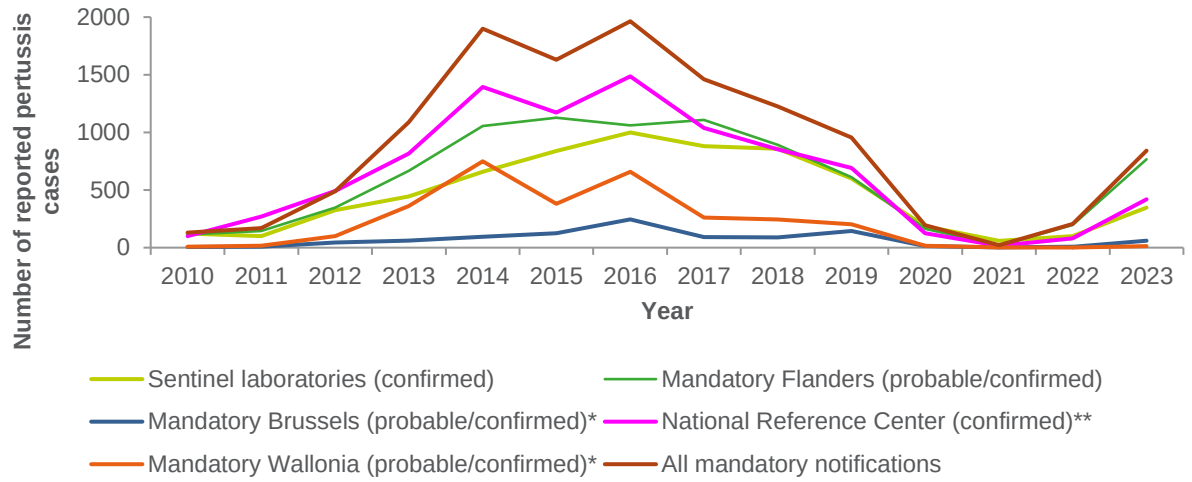
RECOMMENDATIONS

(Surveillance, control, communication)	1. **Communication**:
	- Raise awareness on pertussis in GPs and paediatricians. Elements to include:
	  ○ Currently higher incidence
	  ○ Known waning of vaccine effectiveness and hence need to consider pertussis in differential diagnosis.
	  ○ Confirm diagnosis if possible by PCR (not using UTM swabs), and send positive samples to NRC
	  ○ Mandatory notification to regions important so that antibiotic prophylaxis can be given to vulnerable groups.
	  ○ Maternal vaccination important to protect most vulnerable newborns.
	  ○ Possible to provide more detailed clinical information on severe cases through PediSurv
	
	2. Improve surveillance
	- Increase participation to Epilabo and PediSurv to allow for better surveillance of trends and severity of disease.
	- Improve quality of data collection on hospitalisation and vaccination status through mandatory notifications.
	  ○ Always explicitly request the information for acute cases.
	  ○ Have an intra-operable vaccination registry in all three regions, integrated in the electronical medical files and allow regional health authorities access to these databases.
	- Continue genotypying of circulating pertussis strain by the NRC to follow up on a possible mismatch with the vaccine.
	
	3. Control
	- Increase coverage for maternal vaccination, especially in Wallonia and Brussels.

ACTIONS	
(What, who)	1. **Communication to GPs and paediatricians:** a. **Sciensano** to provide template for harmonized communication b. **Sciensano** to include (again) in monthly newsflash infectious diseases c. **Federated entities** to further spread messaging to physicians, using e.g. professional networks 2. **Improve surveillance** a. **Sciensano** to continue ongoing work on EpiLabo 2.0 for better and more stable participation of sentinel labs. b. **Sciensano** to continue analysis of sentinel lab data to understand potential importance of multiplex testing c. **Sciensano** to include alert on pertussis in PediSurv newsletter and alerts PediSurv participants again on the need to notify pertussis cases d. **AVIQ** to clarify whether mandatory notification of all pertussis cases (regardless of age) should be done, and adapt website/legal basis accordingly e. **AVIQ/COCOM/ONE** to continue and where possible speed up ongoing work on integrated vaccine registries f. **All federated entities** to ensure access/linkage of vaccination data with data from mandatory notifications for health inspectors. g. **All federated entities** to ensure information on hospitalisation status is always record for notifications of pertussis. 3. **AVIQ and COCOM** to reach out to **ONE** about the need to improve maternal vaccination because of the current epidemiological situation. If needed, gynaecologists can be contacted through the HOST networks of AVIQ/COCOM. The German community will reach out to perinatal centres, gynaecologist and centers for healthy development of children/adolescents (Kaleido). Existing information on benefits of maternal vaccination can be re-used and practical information about vaccine procurement should be included. If maternal vaccination is not possible/acceptable, cocoon vaccination should be promoted.

FIGURES & TABLES

Figure 1: Number of reported pertussis cases by year (all surveillance sources)

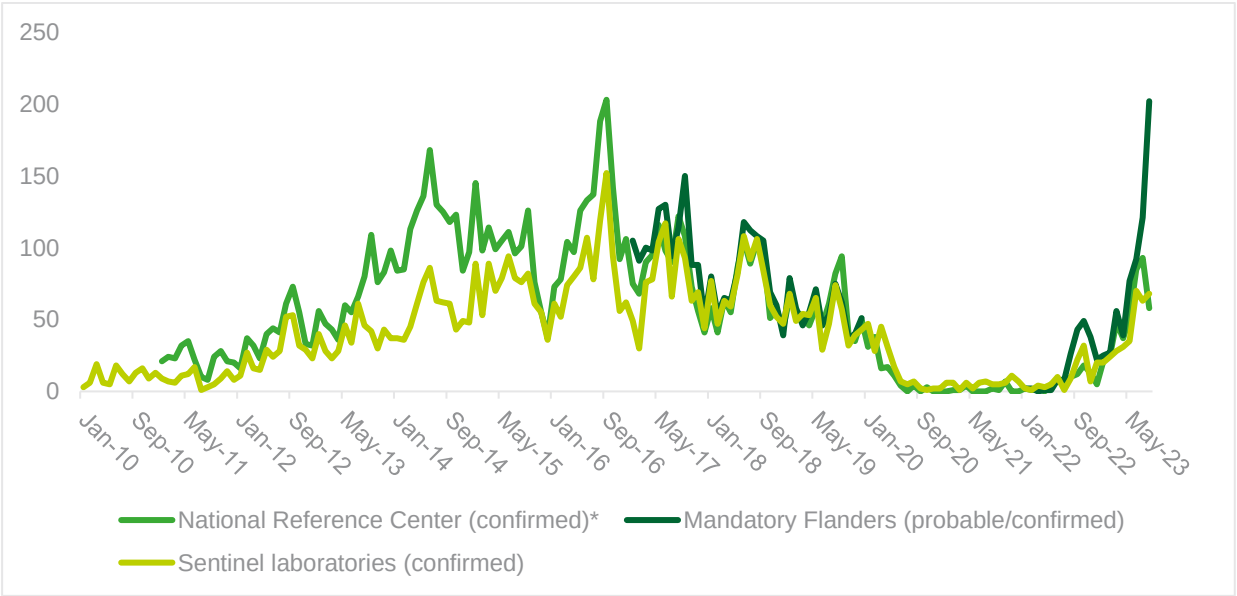


** From 2020, the reported mandatory notifications in Brussels applies only to confirmed cases and in Wallonia only to confirmed cases less than 3 years old, where previously both possible, probable and confirmed cases were reported.*

*** Data for July-August 2023 is incomplete.*

Number of pertussis cases	2017	2018	2019	2022	2023
NRC	1032	852	685	80	418
MN Wallonia	261	245	203	1	13
MN Brussels	88	143	15	7	60
MN Flanders	1108	892	610	198	767

Figure 2: Number of reported pertussis cases by month and year (NRC, sentinel labs)



** Data for July-August 2023 is incomplete.*

Figure 3: Mandatory notifications (<3years, confirmed)

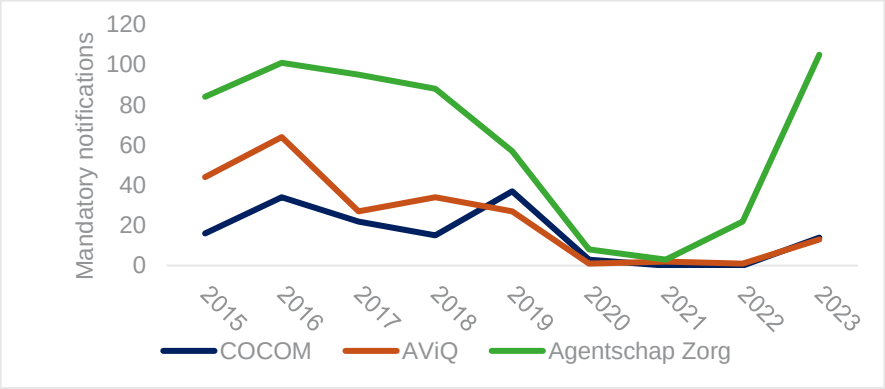
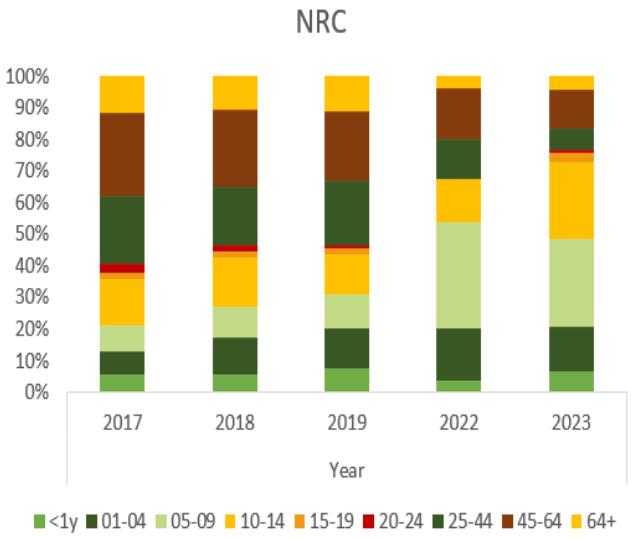
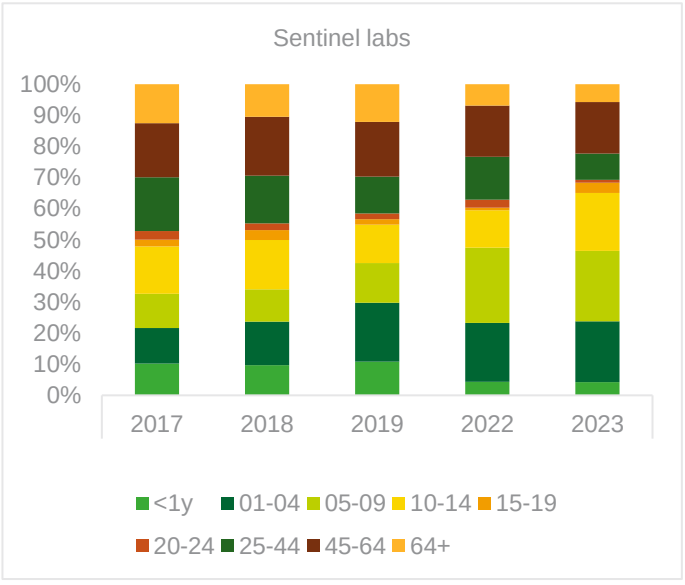
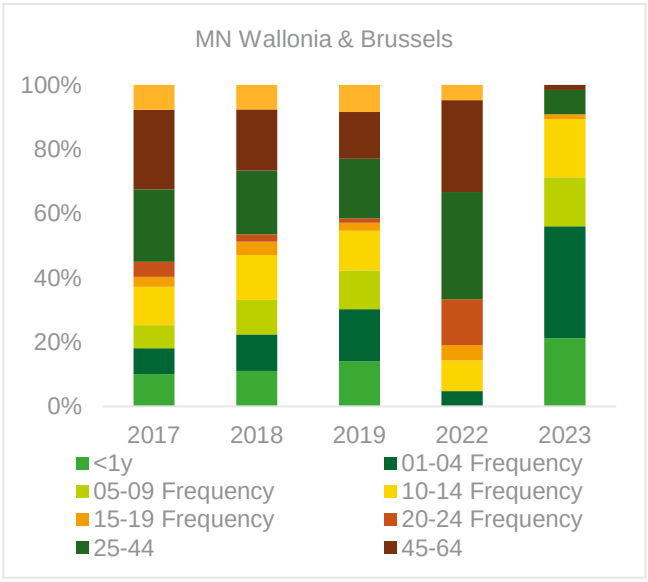


Figure 4: Proportion of reported pertussis cases by age group and year







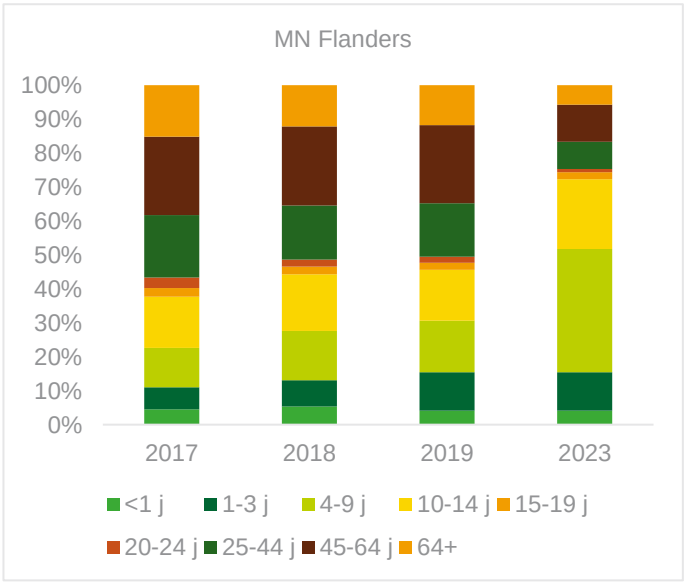
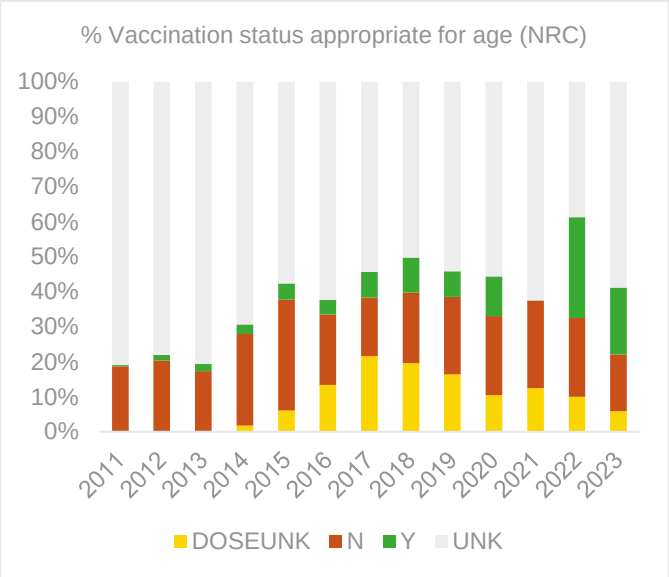


Figure 5: Vaccination status appropriate for age (% and absolute numbers) in pertussis cases (NRC)



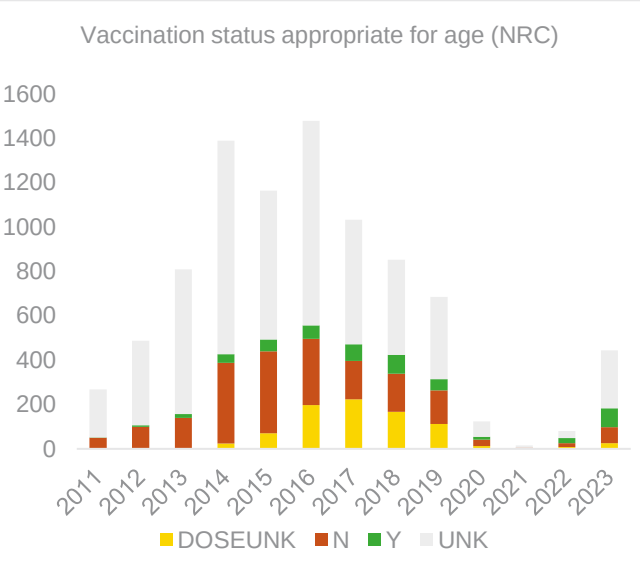


Table 1: Vaccination status by age group for 2023 (NRC)

NRC age	age in month	1 dose	2 dose	3 dose	4 dose	5 dose	6 dose	NOTVACC	UNK	DOSEUNK	Total
0	0-1	0	0					2	5		7
	2	1						1	4		6
	3-4		1						3		4
	5-11							3	7	1	11
1	12-14			1					6		7
	15-16										0
	17-21								7	1	8
2-04				1	17			2	17	7	44
5					20				21	1	42
06-09		0	0	3	22	8		2	28	10	73
10-14		0	0	0	10	26	2	1	50	12	101
15-19		0	0	0	0	1	0	0	8	5	14
≥20		0	0	1	0	1	6	9	60	24	95

Table 2: Vaccination status by age group for 2023 (COCOM, AVIQ)

Aviq & Cocom age	age in month	1 dose	2 dose	3 dose	4 dose	4+	NOTVACC	UNK	Total
0	0-1						8	2	10
	2						2	2	4
	3			1			1	1	3
	5-11				1			5	6
1	10-14							3	3
	15-16					1	1	1	3
	17-21						1		1
2-4			1			3	1	11	4	20
5								1		1
6-9						1	4	2	1	8
10-14								3	3	6
15-19									1	1
≥20						1		2	2	5

Table 3: Vaccination status by age group for 2023 (Departement Zorg)

Agentschap Zorg age	Age in month	UNK	niet gevaccineerd	onvolledig	volledig maar afwijkend schema	volledig volgens schema	Total
0	0-1	**4**	**3**	**1**			8
	2	**2**	**2**				4
	3			**1**			1
	4	**1**	**2**		**3**		**6**
	5-11	**10**	**5**	**2**		**7**	**24**
1	12-14	**7**	**1**	**1**		**8**	**17**
	15-16	**3**				**3**	**6**
	17-23	**6**	**5**	**2**		**11**	**24**
2-4		47	3	1	0	66	117
5		38	7			21	66
6-9		75	1	12	0	74	162
10-14		65	2	7	5	50	129
15-19		11	0	0	1	4	16
≥20		145	6	12	3	21	187

Table 4: Hospitalisations for pertussis (Minimal clinical hospital data (primary diagnosis), NRC)

Year	Min. Hospital data		NRC	
		<1y only		<1y only
2016	108	60 (56%)	17	1 (6%)
2017	76	34 (45%)	42	18 (43%)
2018	64	30 (47%)	40	17 (43%)
2019	61	26 (43%)	31	16 (52%)
2020	21	13 (62%)	10	4 (40%)
2021	<5	<5	0	0
2022	*NA**	NA*	3	1 (33%)
2023	*NA**	NA*	18	12 (67%)

* *minimal hospital data is available only after a delay of 2 years*

Figure 6: Evolution of proportion of hospitalizations among all cases (data NRC)

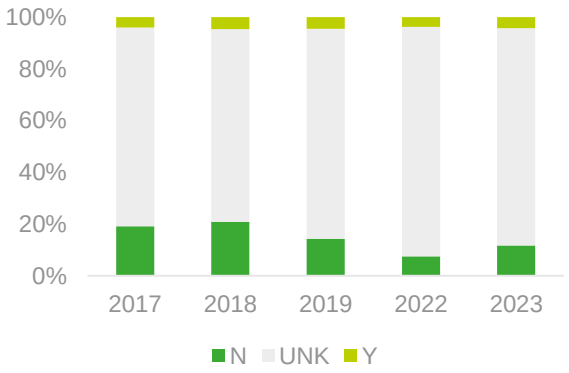
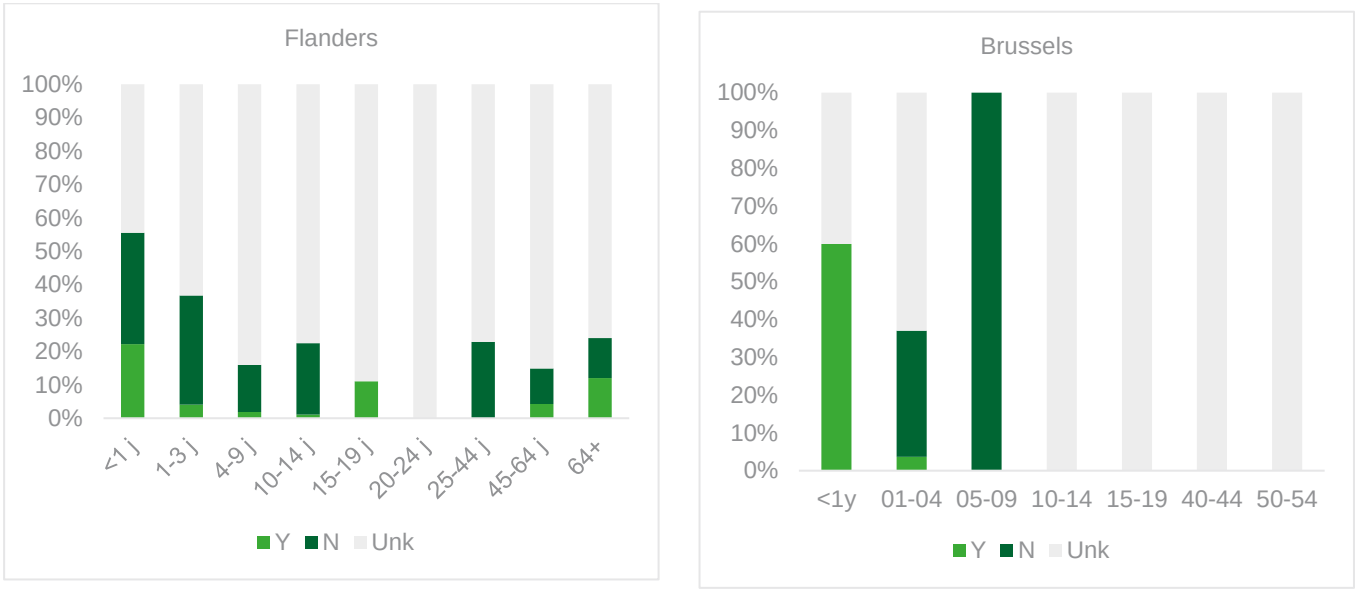


Figure 7: Hospitalization by age group for 2023 (mandatory notifications)



From the 13 pertussis notifications from Wallonia <3y, 6 were hospitalized.

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