Block 1 Wave 4 - GenEpi-BioTrain

Vaccine Preventable Infection (VPI)
A virtual training workshop within GenEpi-BioTrain

Focus on the Agents of Whooping Cough

Whooping Cough Epidemiology and Surveillance

Prof Sylvain Brisse

November 4th 2024

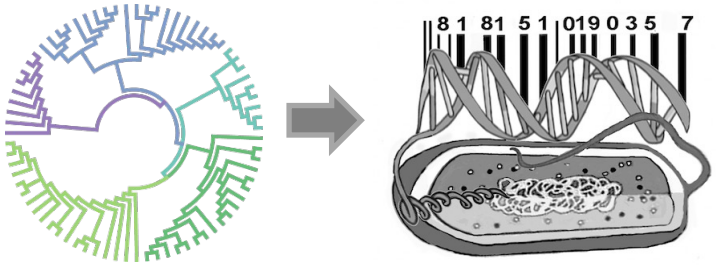
Biodiversity and Epidemiology of Bacterial Pathogens Unit

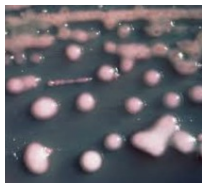
Head: Prof Sylvain BRISSE

Emergence and evolution (of bacterial strains)

- Multidrug resistance
- Vaccine-escape
- Epidemiological surveillance
- One Health
- Links genotype-phenotype

Genomic taxonomies of strains



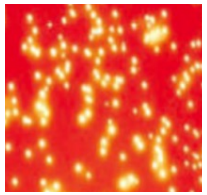


Klebsiella pneumoniae

Multidrug resistance

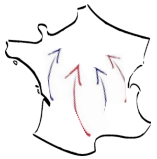
Corynebacterium diphtheriae

Multidrug resistance



Bordetella pertussis

Vaccine-driven evolution



Santé publique France

National Reference Centers for diphtheria and for whooping cough

slido

Please download and install the Slido app on all computers you use

Have you seen an increase in pertussis cases in your countries over the last year?

ⓘ Start presenting to display the poll results on this slide.

Intended Learning Objectives

- Overview of Whooping Cough pathogen & disease
- Surveillance of Whooping Cough through the example of the National Reference Center for Whooping cough at Institut Pasteur Paris (France)
- Epidemiology of Whooping cough across the EU
- Case study : recent 2024 outbreak in France

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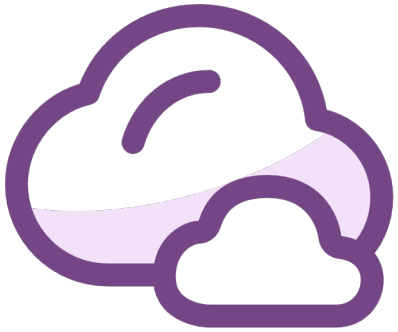

Which country do you work in?

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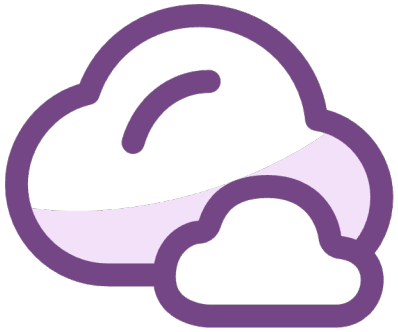

What is your job area?

ⓘ Start presenting to display the poll results on this slide.

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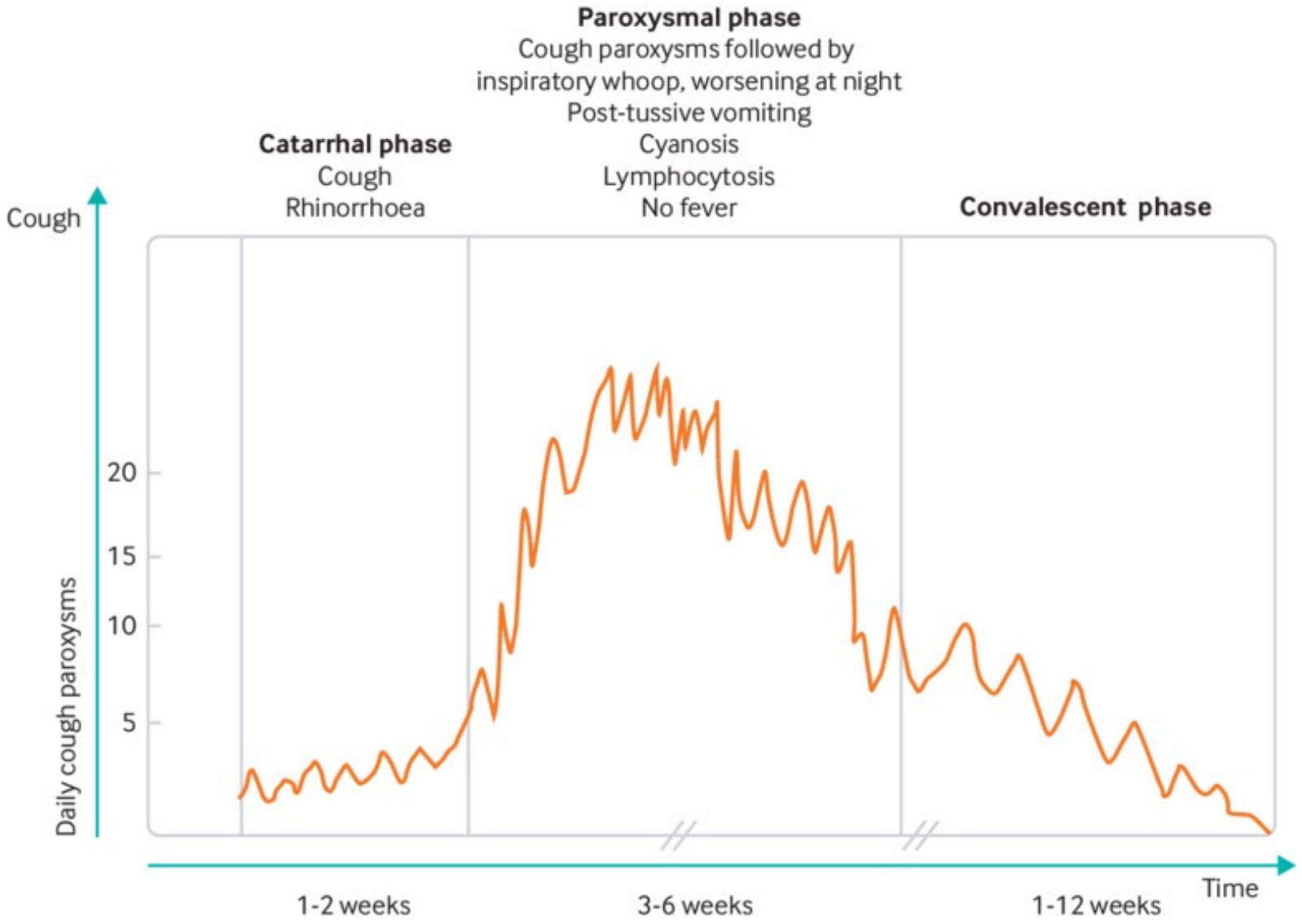
Whooping cough: clinical evolution (Typical course)



Gopal D P, Barber J, Toeg D. Pertussis (whooping cough) *BMJ* 2019; 364 :l401 doi:10.1136/bmj.l401

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What agents are causing pertussis?

ⓘ Start presenting to display the poll results on this slide.

PERTUSSIS : MAIN ASPECTS

24.1 million estimated cases worldwide in 2014

160,700 deaths of children under 5 years of age

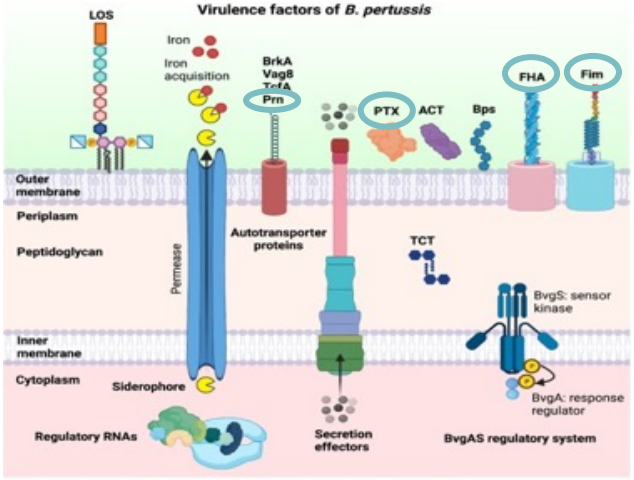
(Yeung, Lancet. Inf. Dis., 2017/WHO)

Bacterial pathogens: ***Bordetella pertussis*** **(and *B. parapertussis*)**

- Gram-negative coccobacillus (strictly aerobic)
- Slow culture on specific media (Bordet-Gengou, Regan-Lowe)

Vaccine-preventable disease - whole-cell vaccine replaced by **acellular vaccine** (aPV)

- Contain **2 to 5 vaccine antigens** (PT, FHA, PRN, FIM2 and 3)
- Amount of antigens varies between primary vaccine and boosters



Mohamed, Yasmine Fathy et al. Trends in Microbiology, Volume 31, Issue 11, 1192 - 1193

Endemic despite vaccination, **cyclical** (every 3 to 5 years), human-to-human transmission

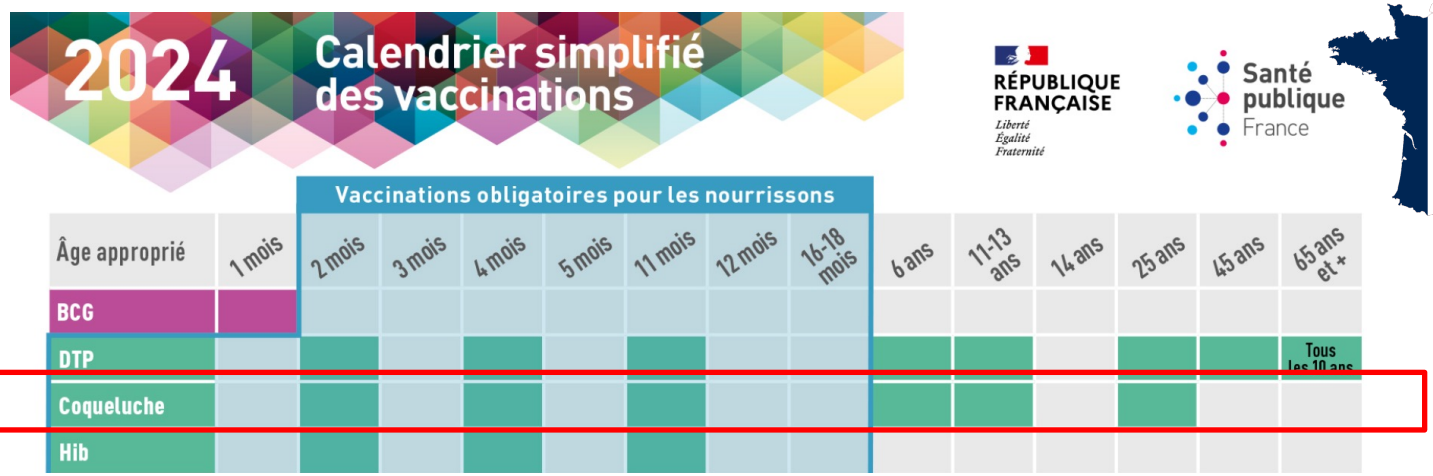
Very severe disease for infants < 6m and other people at risk

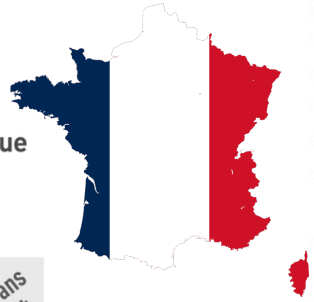
Severe forms ~18% hospitalized in ICU:

apnea/bradycardia, more rarely **fulminant pertussis**

(Tubiana S, Pediatr Infect Dis J 2015)

PERTUSSIS : VACCINATION IN FRANCE





	Prime vaccination	Boosters
aPV-2 components PT+FHA	Hexyon®	Tetratavac®
PT	25 µg	25 µg
FHA	25 µg	25 µg
Marketing Authorisation year	2013	1998
aPV-3 components PT+FHA+PRN	InfanrixHexa® InfarixQuinta	BoostrixTetra
PT	25 µg	8 µg
FHA	25 µg	8 µg
PRN	8 µg	2.5 µg
Marketing Authorisation year	2000	2005
aPV-5 components PT+PRN+FHA+FIM2+FIM3	Vaxelis®	Repevax®
PT	20 µg	2.5 µg
FHA	20 µg	5 µg
PRN	3 µg	3 µg
FIM2-FIM3	5 µg	5 µg
Marketing Authorisation year	2016	2002

Since 2013 : Primary vaccination : **2p + 1**
Boosters : 6yo, 11-13yo, 25yo

Shorter-lived protection induced by the new vaccine schedule → increase of pertussis cases in children aged 2–5 years

(Paireau *et al.* LID2022)

VACCINATION IN PREGNANT WOMEN: officially recommended since **April 2022**

but coverage levels remained **below 20%** between June 2022 and May 2024

RECOMMANDATION VACCINALE

Recommandation vaccinale contre la coqueluche chez la femme enceinte

https://www.has-sante.fr/upload/docs/application/pdf/2024-07/recommandation_strategie_de_vaccination_contre_la_coqueluche_dans_le_contexte_epidemique_de_2024_-_r_2024-07-18_14-11-55_706.pdf

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How can I confirm the diagnosis of pertussis?

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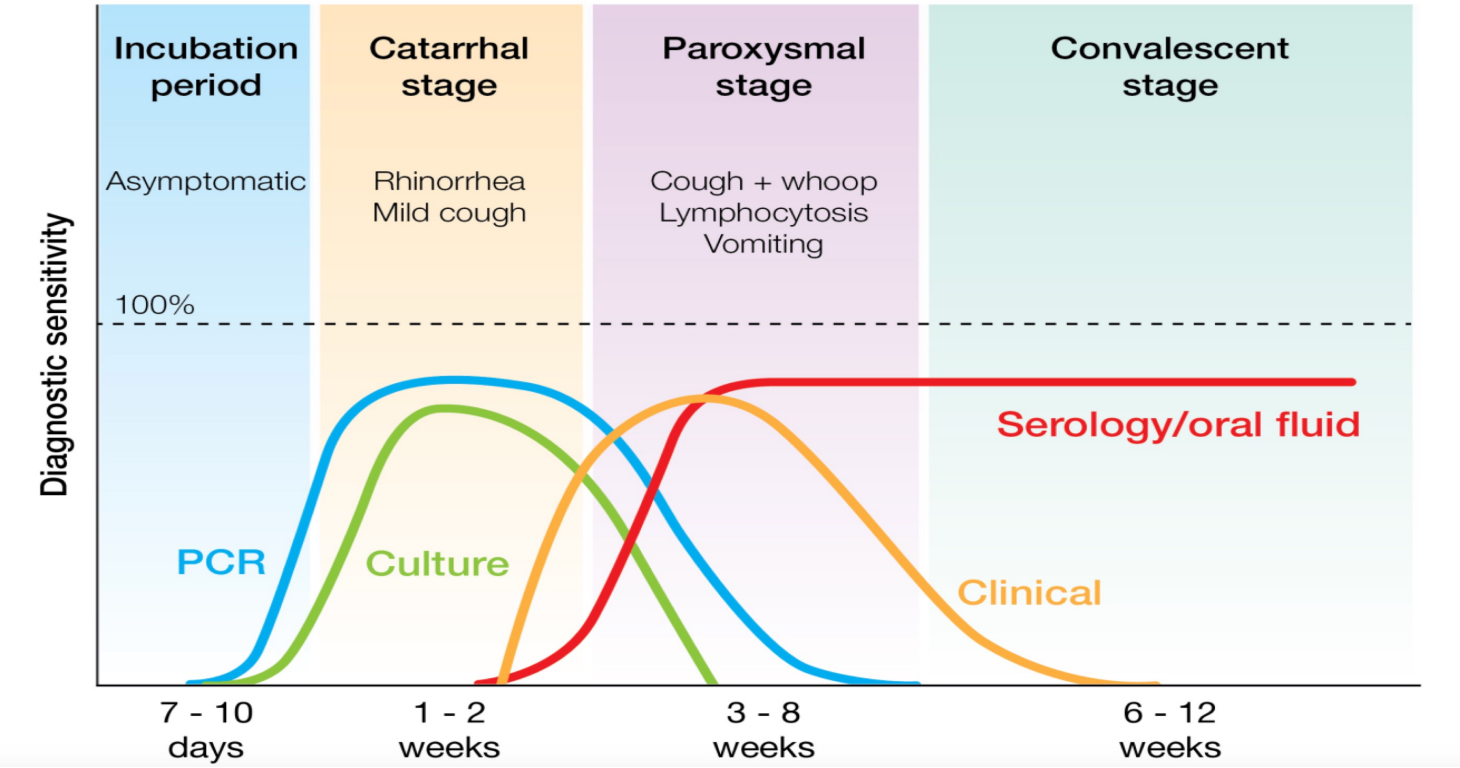
Biological diagnosis : guidelines & timing

Figure 1. Pertussis diagnostic guidelines and timing*



BACTERIA

DNA

ANTIBODIES

(Laboratory diagnosis and molecular surveillance of Bordetella pertussis - Stockholm: ECDC; 2022.)

Fry et al., Bordetella pertussis and whooping cough (pertussis): still a significant cause of infant morbidity and mortality, but vaccine-preventable. J. of Medicine. 2021. Vol 70. Issue 10.

NRC workflow

French hospitals (mainly paediatric) and outpatient laboratories

(1st line diagnostics not carried out at the NRC)

Surveillance/confirmation

Bacterial Strains

- Identification (MALDI-TOF, biochemical tests)
- Antibiogram (disk diffusion, e-test)
- Western-Blot (PT, FHA, PRN)
- Serotyping (FIM2/FIM3)
- WGS (Illumina, Nanopore) and bioinformatic analysis (genotyping - BIGSdb)

Respiratory Samples

DNA

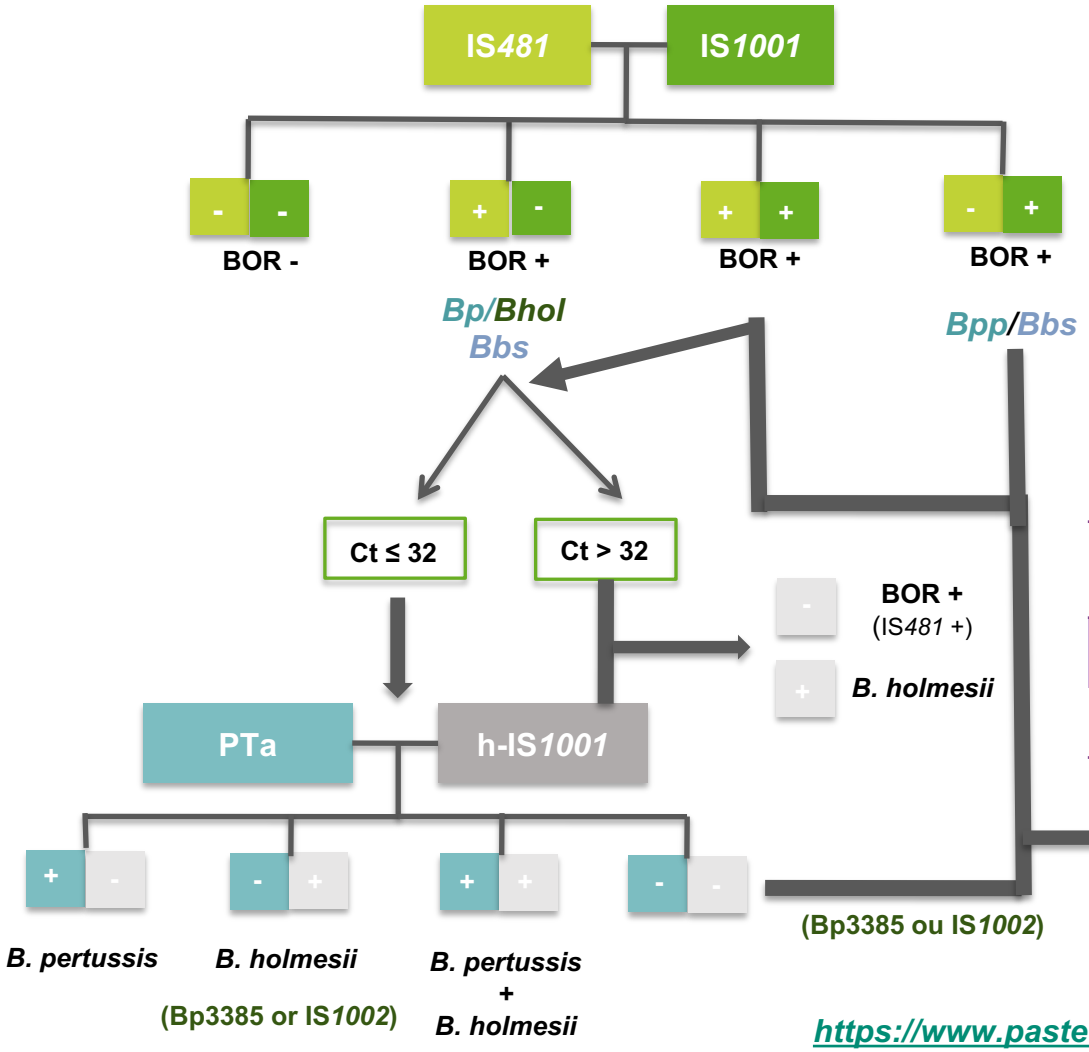
qPCR

(combines multiple PCR targets to gain sensitivity and specificity for species ID - Pta, h-IS*1001*, flagellin and a qPCR for detection of the mutation responsible for macrolide resistance)

CULTURING
(Ct IS*481* < 20)

Biological diagnosis using real time PCR

Example of the PCR flowchart from the French NRC for Whooping cough



Combining highly sensitive and specific qPCR

	FLA BB_BPP	BPP2
B. parapertussis	+	+
B. bronchiseptica	+	-

Target	Present in*	Copy number per genome*
IS481	B. pertussis	50-200
	B. holmesii	8-10
	Some B. bronchiseptica	<5
IS1001	B. parapertussis	~20
	Some B. bronchiseptica	1–7
IS1002	B. pertussis	4–9
	B. parapertussis	9
	B. bronchiseptica	1
h-IS1001	B. holmesii	3–5
ptxP	B. pertussis	1
recA	B. holmesii	1

Van der Zee et al. JSB. 1996[10]; Tatti et al. JCM. 2011[11]; Loeffelholz. JCM. 2012[12]; Tizolova et al. EJCMID. 2013[13].

https://www.pasteur.fr/fr/sante-publique/CNR/les-cnr/coqueluche-et-autres-bordetelloses

BOR : *Bordetella*

Biological diagnosis performed at the French NRC for Whooping cough

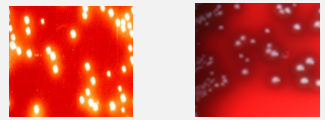
Identification:

Macroscopic and microscopic examinations (Gram)

Biochemical characteristics: hemolysis, oxidase, urease and pigment

MALDI-TOF: ID of the different species

	Bp	*Bpp*
urease	-	+
oxydase	+	-
pigment	-	+ (brown)



Antibiotic susceptibility testing:

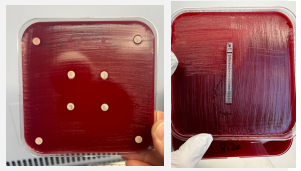
No CA-SFM/EUCAST recommendation

Surveillance of susceptibility to anti-infectives (macrolides)

Antibiograms from isolates grown in MH medium using disk diffusion method, confirmed using Etests

qPCR directly from clinical samples

WGS & BIGSdb macrolide resistance scheme

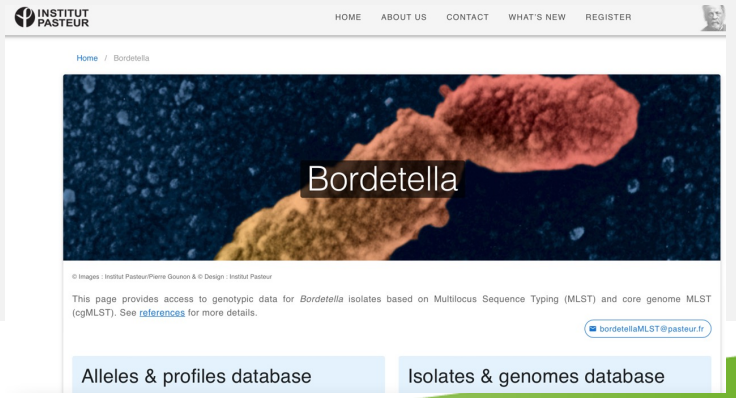


Characterization of bacterial strains:

Genomic Genomic Sequencing of Bacterial Strains (cgMLST)

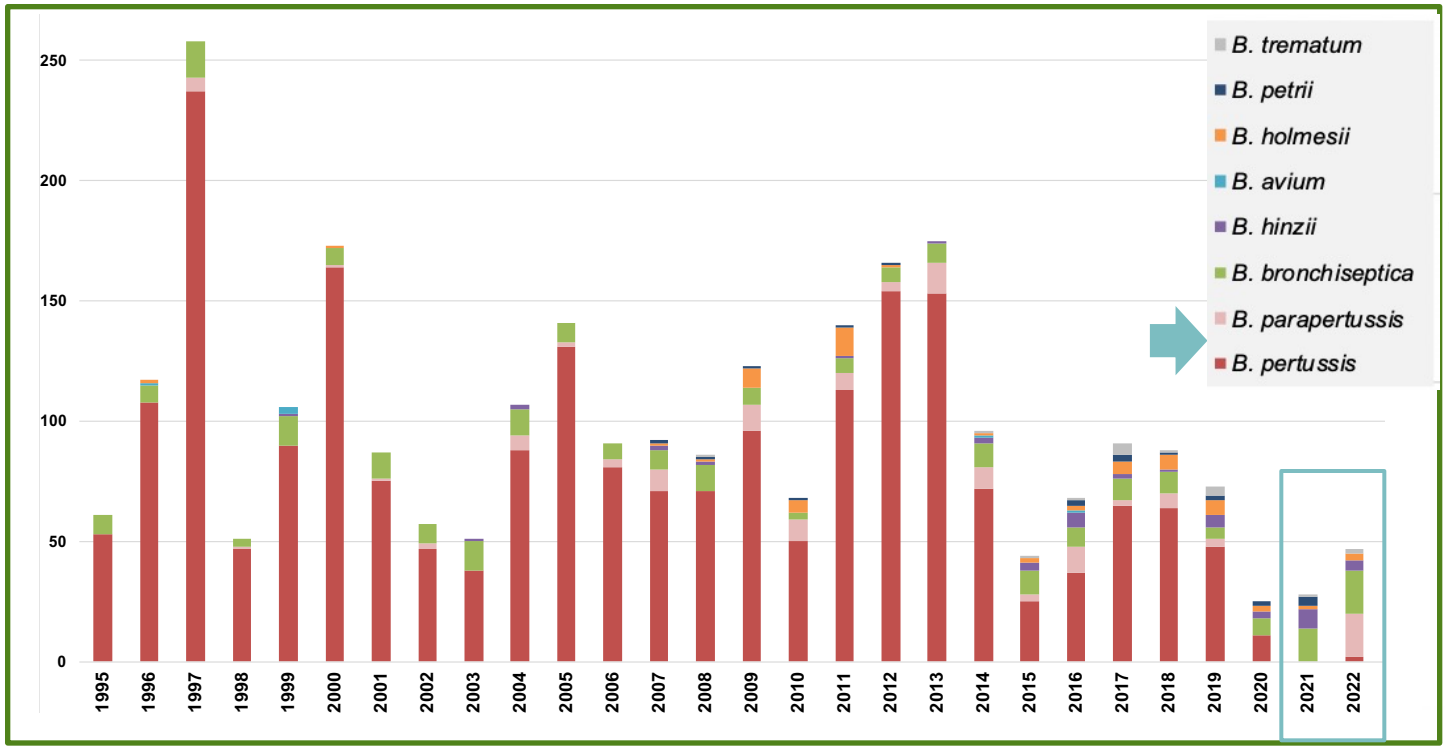
Typing of vaccine antigen genes

Verification of vaccine protein production (virulence determinants)

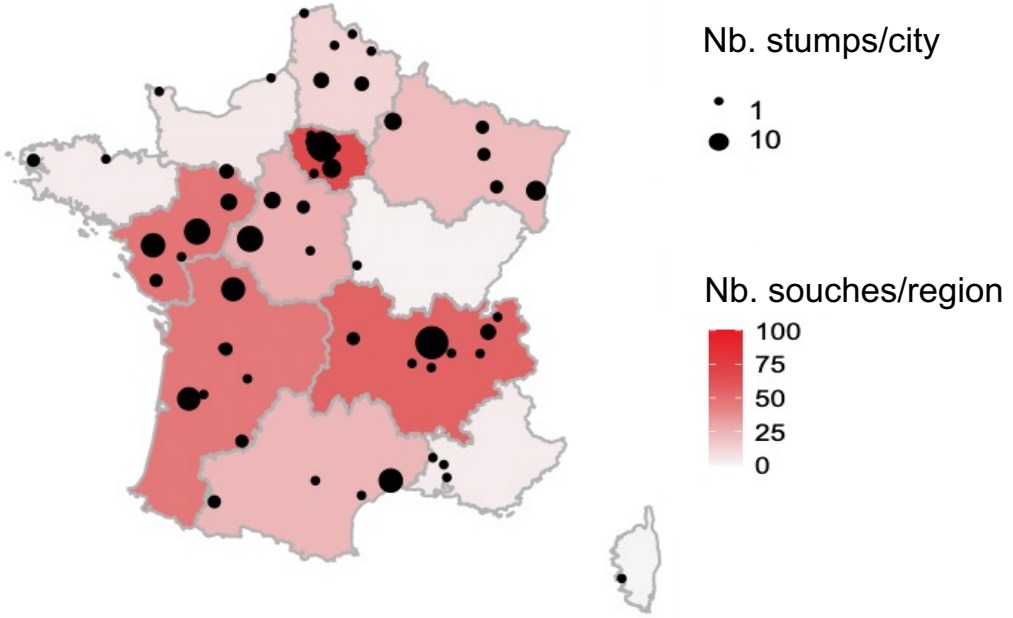


Pertussis surveillance in France and role of the NRC

The NRC characterizes all isolates of the genus *Bordetella* collected using a surveillance system set up since 1996 involving several pediatric hospitals (RENACOQ network) & other laboratories (Cerba and Biomnis) and networks (ACTIV, Sentinelles, REMICOQ)



NRC data (1995-2022)



Geographical origin of Bordetella isolates collected by the NRC of pertussis and other bordetelloses in France (2017-2021)

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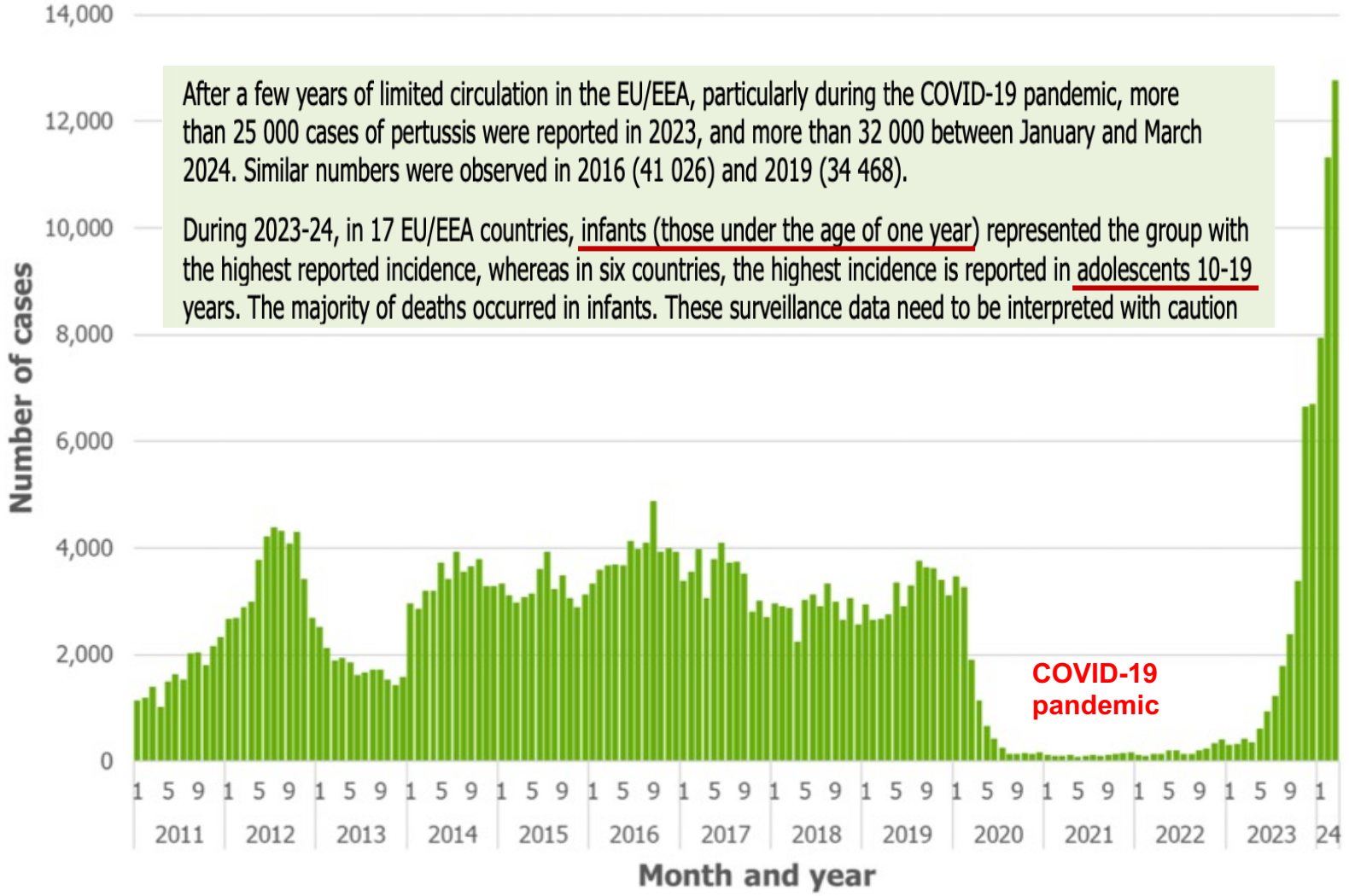
PERTUSSIS IN EUROPE IN 2023-2024

Figure 1. Number of pertussis cases reported to ECDC, by month and year, 1 January 2011 to 31 March 2024[2], EU/EEA[3]



https://www.ecdc.europa.eu/sites/default/files/documents/Increase%20in%20pertussis%20cases%20in%20the%20EU-EEA%20-%20May%202024%20FINAL.pdf

PERTUSSIS IN EUROPE IN 2023-2024

After a few years of limited circulation in the EU/EEA, particularly during the COVID-19 pandemic, more than 25 000 cases of pertussis were reported in 2023, and more than 32 000 between January and March 2024. Similar numbers were observed in 2016 (41 026) and 2019 (34 468).

During 2023-24, in 17 EU/EEA countries, infants (those under the age of one year) represented the group with the highest reported incidence, whereas in six countries, the highest incidence is reported in adolescents 10-19 years. The majority of deaths occurred in infants. These surveillance data need to be interpreted with caution

HIGH risk for infants < 6m (not vaccinated or partially vaccinated)

Risk assessment

The risk from pertussis was assessed for four different population groups as a product of the probability of infection and its impact. The overall risk is assessed as **high** for unimmunised or partially immunised **infants <6 months of age**, as they represent the group with the highest morbidity and mortality from pertussis.

https://www.ecdc.europa.eu/sites/default/files/documents/Increase%20in%20pertussis%20cases%20in%20the%20EU-EEA%20-%20May%202024%20FINAL.pdf

AND WHAT ABOUT FRANCE ??

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RAPID COMMUNICATION

Resurgence of *Bordetella pertussis*, including one macrolide-resistant isolate, France, 2024

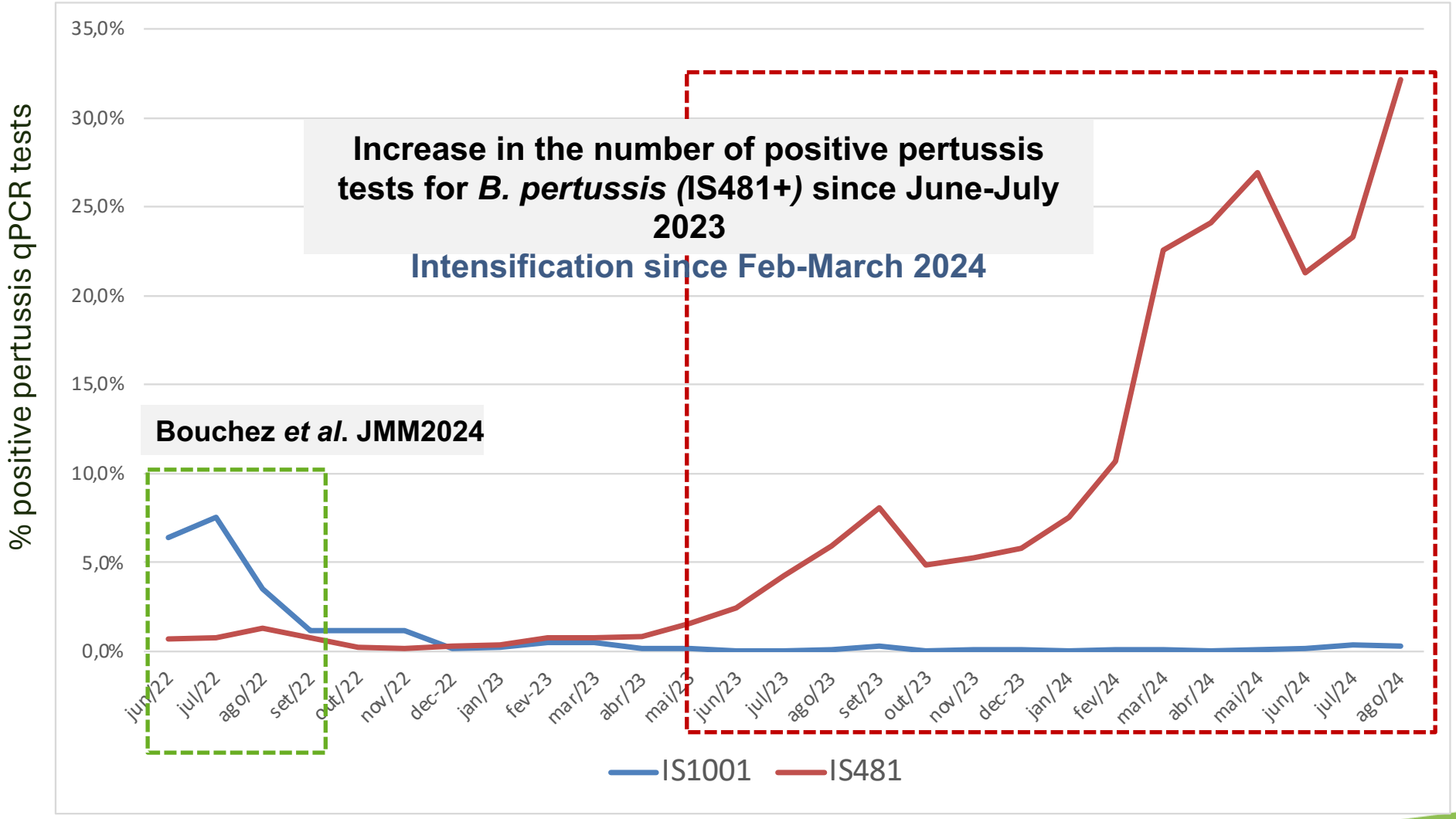
Carla Rodrigues[1,2,*], Valérie Bouchez[1,2,*], Anaïs Soares[3], Sabine Trombert-Paolantoni[4], Fatima Aït El Belghiti[5], Jérémie F Cohen[6,7], Nathalie Armatys[1,2], Annie Landier[1,2], Thomas Blanchot[3], Marie Hervo[3], REMICOQ study group[8], Julie Toubiana[1,2,6,**], Sylvain Brisse[1,2,**]

Analyze the evolution of the number of **outpatient qPCR diagnostics** of pertussis performed since mid-2023 till August 2024 (8-months period).

Conduct **microbiological and genomic analyses** on all isolates collected by the French National Reference Center for Whooping Cough (NRC) during this period.

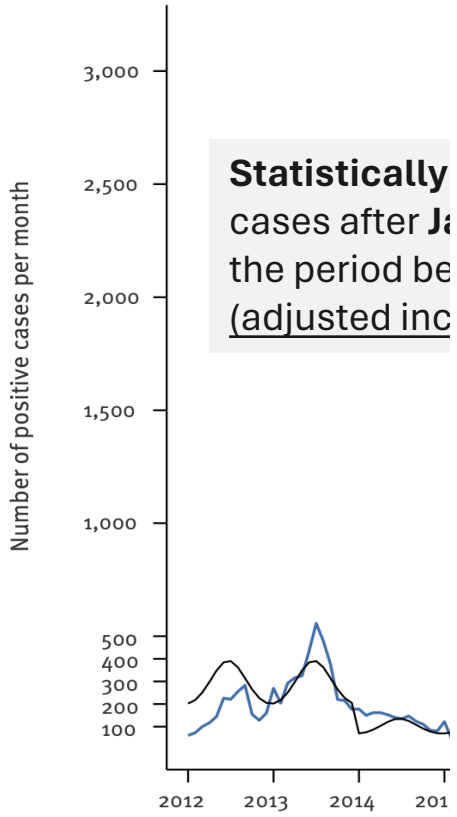
OUTPATIENT LABORATORY SURVEILLANCE BY qPCR

Very important in the context of real-time monitoring

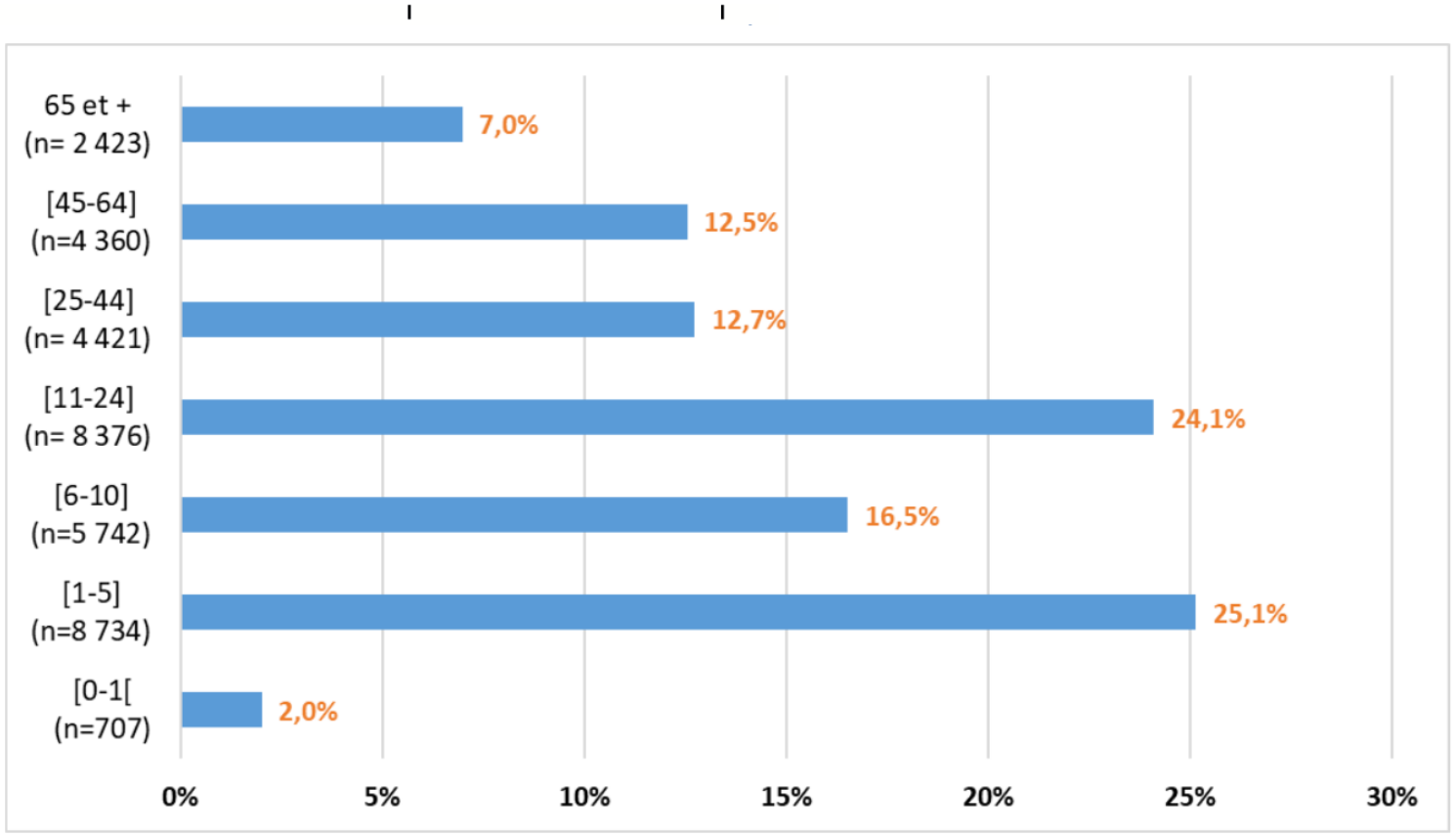


OUTPATIENT LABORATORY SURVEILLANCE BY qPCR

Time series analysis of positive qPCR tests targeting IS*481*, France, 2012–2024



Statistically
cases after **Ja**
the period be
(adjusted inc



es (jan-aug), 27%

ests performed)

o. of nthly	Median age
l 250)	17.7 (IQR): 8.4–42.9)

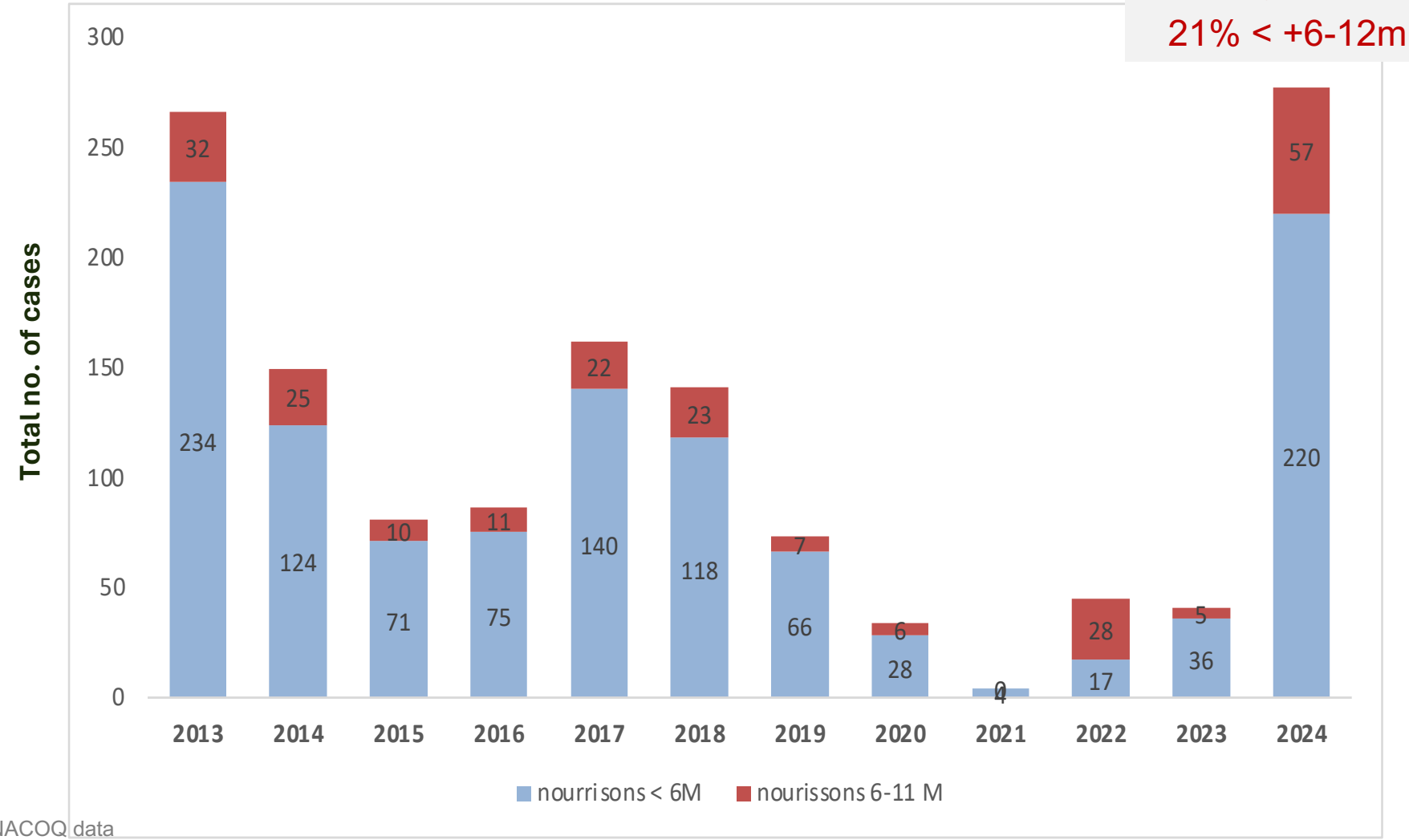
Source : Réseau 3Labos, Santé publique France, données mises à jour au 11 septembre 2024

The black line reflects the values predict
beginning of the year (January). Note t
indicates the beginning of the first COVID-19 lockdown (1 April 2020). The second vertical dashed line corresponds to the start of the current outbreak and subsequent national alert (1 January 2024).

https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-a-prevention-vaccinale/coqueluche/documents/bulletin-national/coqueluche-en-france.-point-au-18-septembre-2024

RENACOQ : hospital pertussis monitoring, infants hosp. < 12m

79% < 6m
21% < +6-12m



Several infants **< 2m admitted to ICU** in several localities in France – some of whom presented **fulminant pertussis forms**

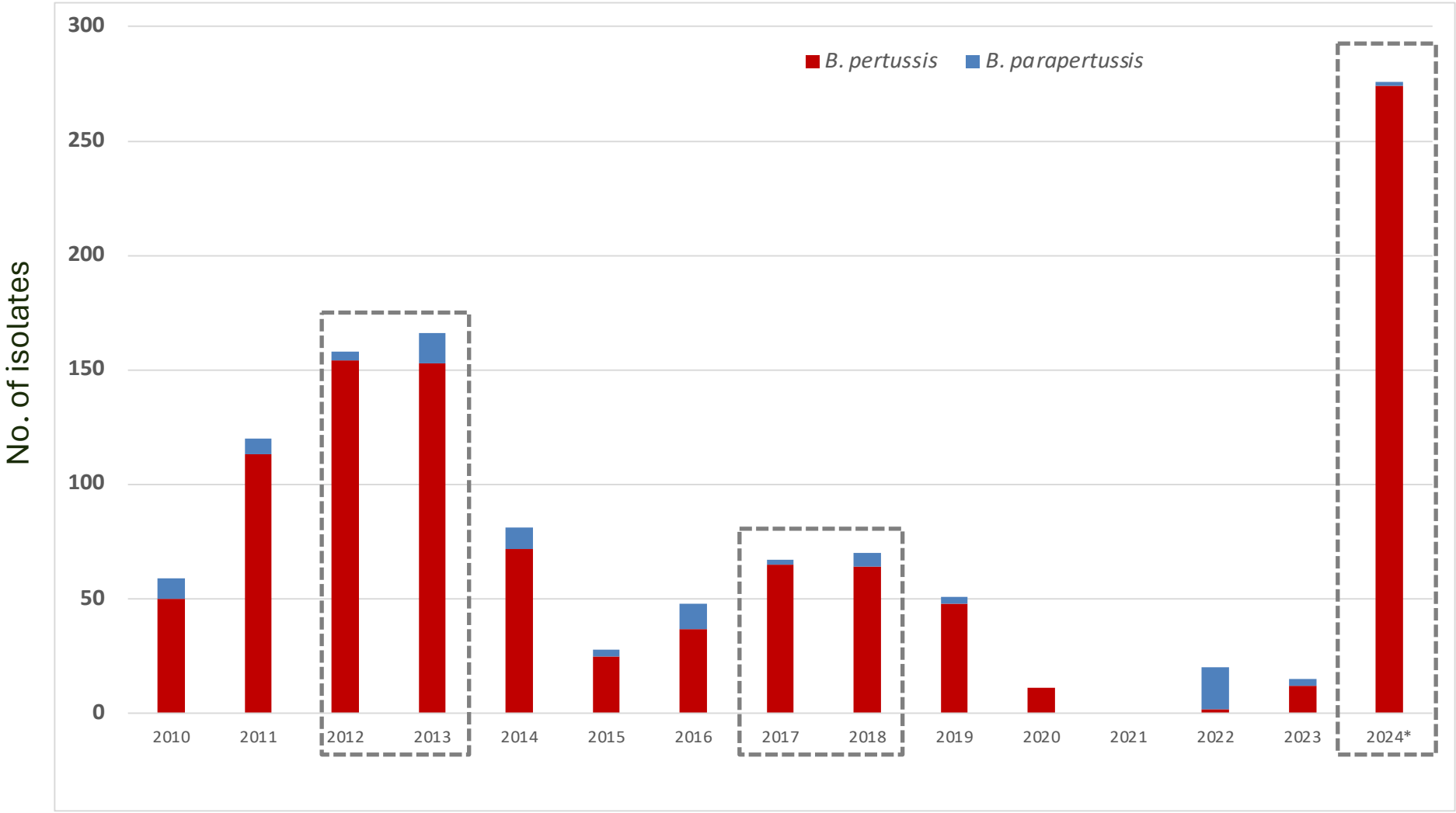
35 DEATHS
(20 were under children < 1 year old)

RENACOQ data
2024 - not consolidated

https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-a-prevention-vaccinale/coqueluche/documents/bulletin-national/coqueluche-en-france.-point-au-18-septembre-2024

ISOLATES RECEIVED OR ISOLATED AT THE NRC (2010 to 2024)

REMICOQ network (coord. by the NRC)



Jan-Aug 2024: 274 Bp

This graph is not an epidemiological curve. It must be interpreted with caution because many laboratories have stopped cultivating *Bordetella* in recent years

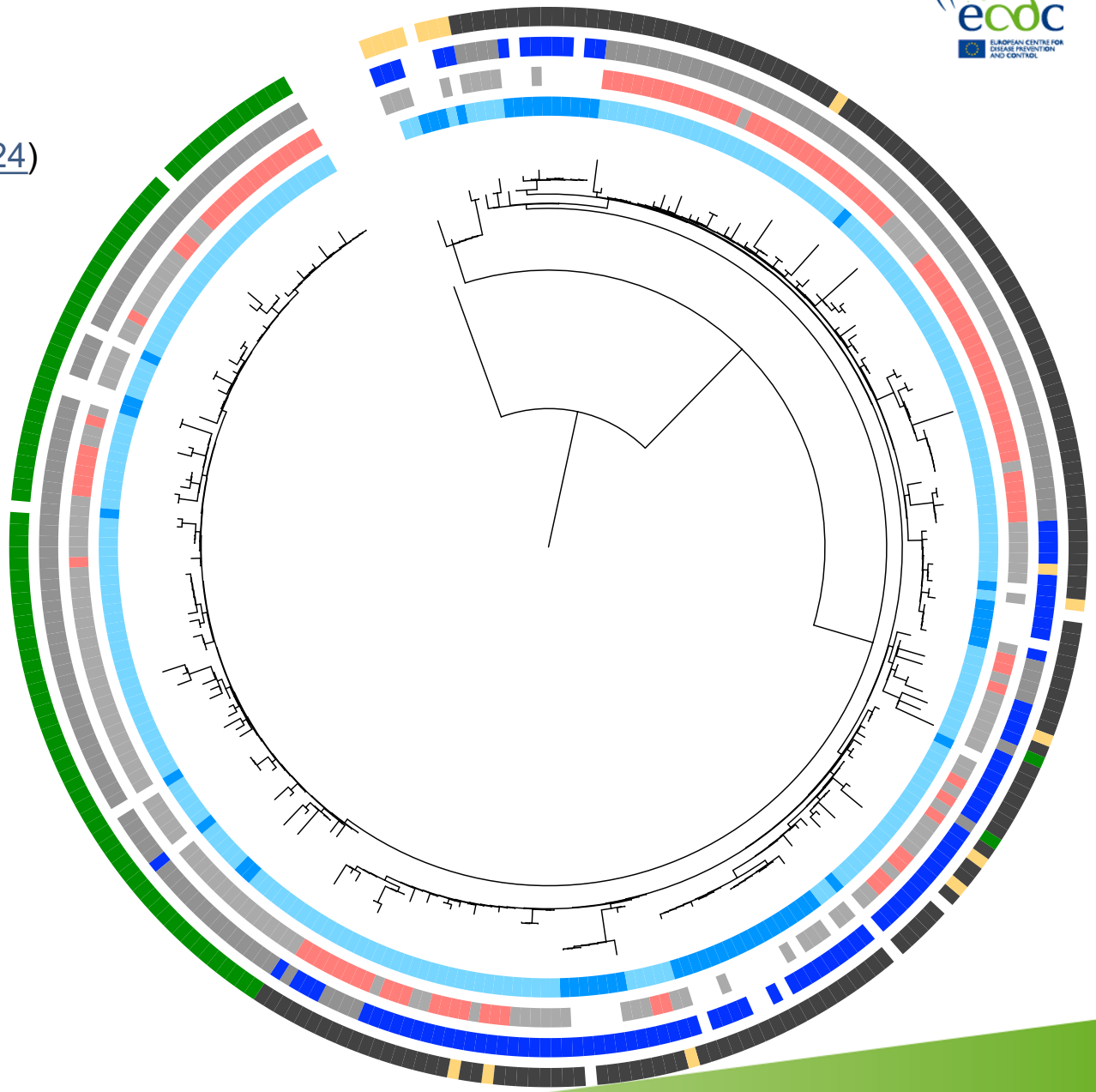
BORDETELLA PERTUSSIS POPULATION, FRANCE, 2016 - 2024

1. **Period**
   - 2016-2020 (n=215)
   - 2021-2024 (n=69, 2 in 2022, 9 in 2023, 58 (Jan-May 2024))

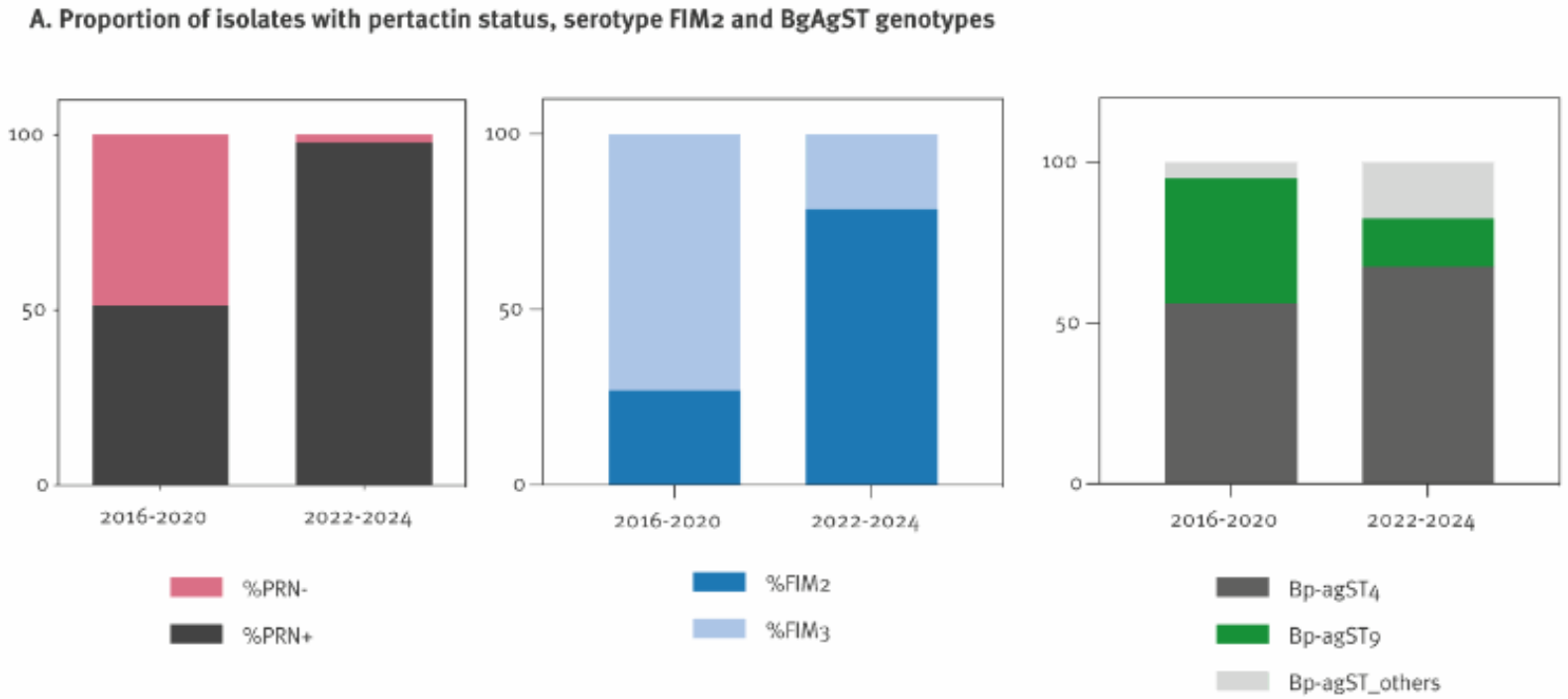
2. **PRN production**
   - PRN+
   - PRN-

3. **Serotype**
   - FIM3
   - FIM2

Bp-agST genotype
- Bp-agST4
- Bp-agST9
- others



BORDETELLA PERTUSSIS POPULATION



- **99%** produce the vaccine antigen **pertactin (PRN+),** in contrast to isolates collected in France just before the COVID-19 period (nearly 50% PRN-negative)

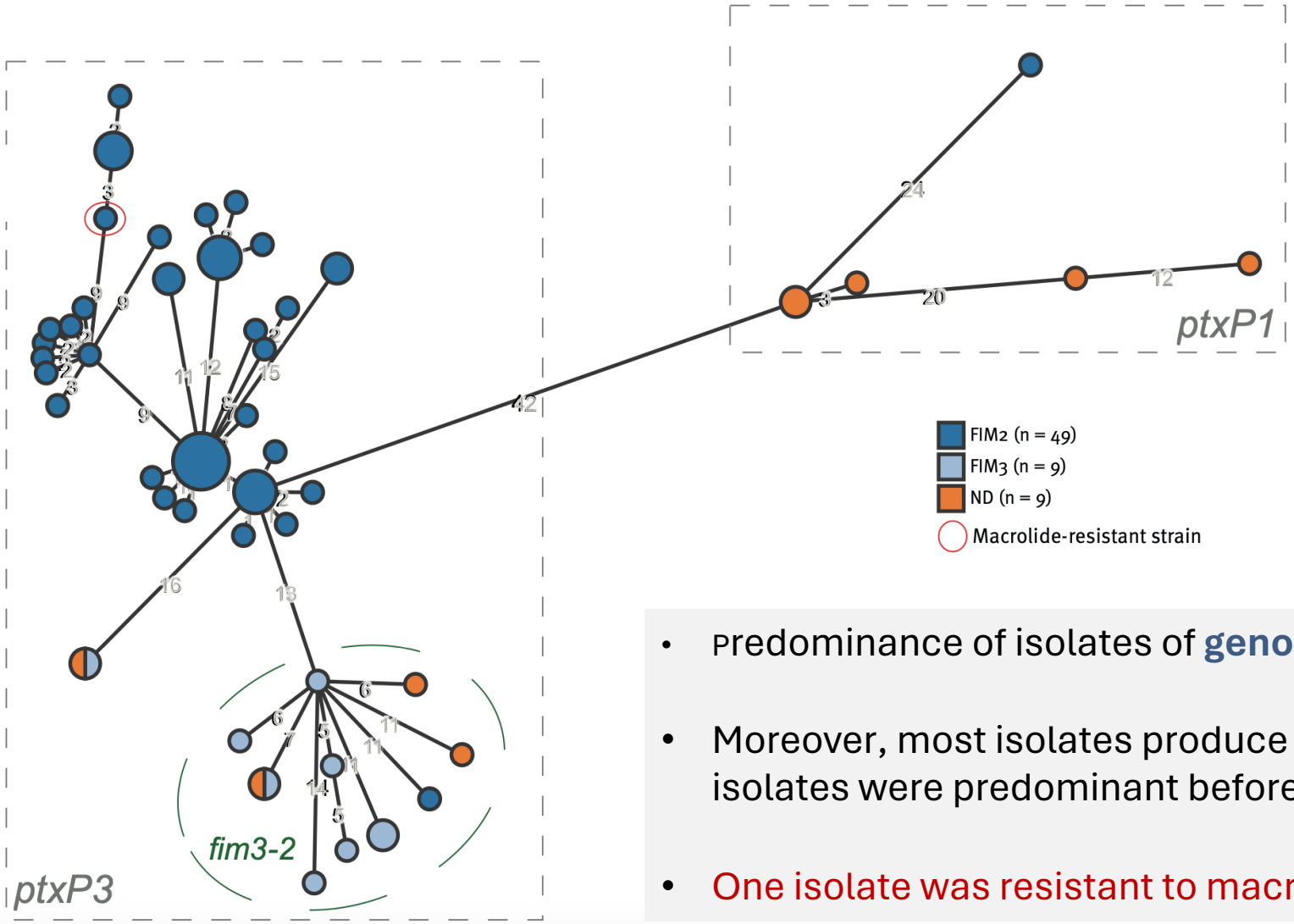
Recent study by the NRC and pediatricians from the Pediatric Infectious Pathology Group / Renacoq network

› Clin Microbiol Infect. 2024 Sep 19:S1198-743X(24)00440-3. doi: 10.1016/j.cmi.2024.09.009.
Online ahead of print.

Association between pertactin-producing Bordetella pertussis and fulminant pertussis in infants: a multicenter study in France, 2008-2019

BORDETELLA PERTUSSIS POPULATION, FRANCE 2023-2024

- Genomic sequencing (Illumina)
- cgMLST (2 038 loci)



- Predominance of isolates of **genotype *ptxP3***
- Moreover, most isolates produce **FIM2**, whereas FIM3-producing isolates were predominant before 2020
- One isolate was resistant to macrolides

67 Bp isolates (June 2023 – May 2024)

In summary

- Whooping Cough is a severe disease for neonates and other at-risk persons
- Heterogeneity of vaccines across time, countries and schedules
- Surveillance of Whooping Cough can use multiple sources of data
- Current resurgence of Whooping cough in multiple countries: natural cycle, atypical magnitude
- Macrolide-resistance

References

- Mohamed, Yasmine Fathy *et al*. Trends in Microbiology, 2023. Volume 31, Issue 11, 1192 – 1193.
- Yeung KHT, *et a*l. An update of the global burden of pertussis in children younger than 5 years: a modelling study. Lancet Infect Dis. 2017 Sep;17(9):974-980.
- Tubiana et al., Pediatr Infect Dis J. 2015;34(8):814-20.
- Gopal D P, Barber J, Toeg D. Pertussis (whooping cough) *BMJ* 2019; 364 :l401 doi:10.1136/bmj.l401
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