

Exploring Pertussis Vaccination Through Systems Vaccinology

Barry Grant
UC San Diego

<http://thegrantlab.org>

Pertussis is a leading causes of vaccine-preventable deaths

Pertussis, or **whooping cough**, is a highly contagious lung infection caused by the bacteria *Bordetella pertussis*.

- Estimated 16 million cases and 200,000 associated infant deaths annually*.
- Can infect people of all ages but is most severe and life threatening for **infants under a year old**.
- Transmission occurs primarily through bacteria laden **respiratory droplets** produced when an infected individual coughs and sneezes.

* (Black et al. 2010)

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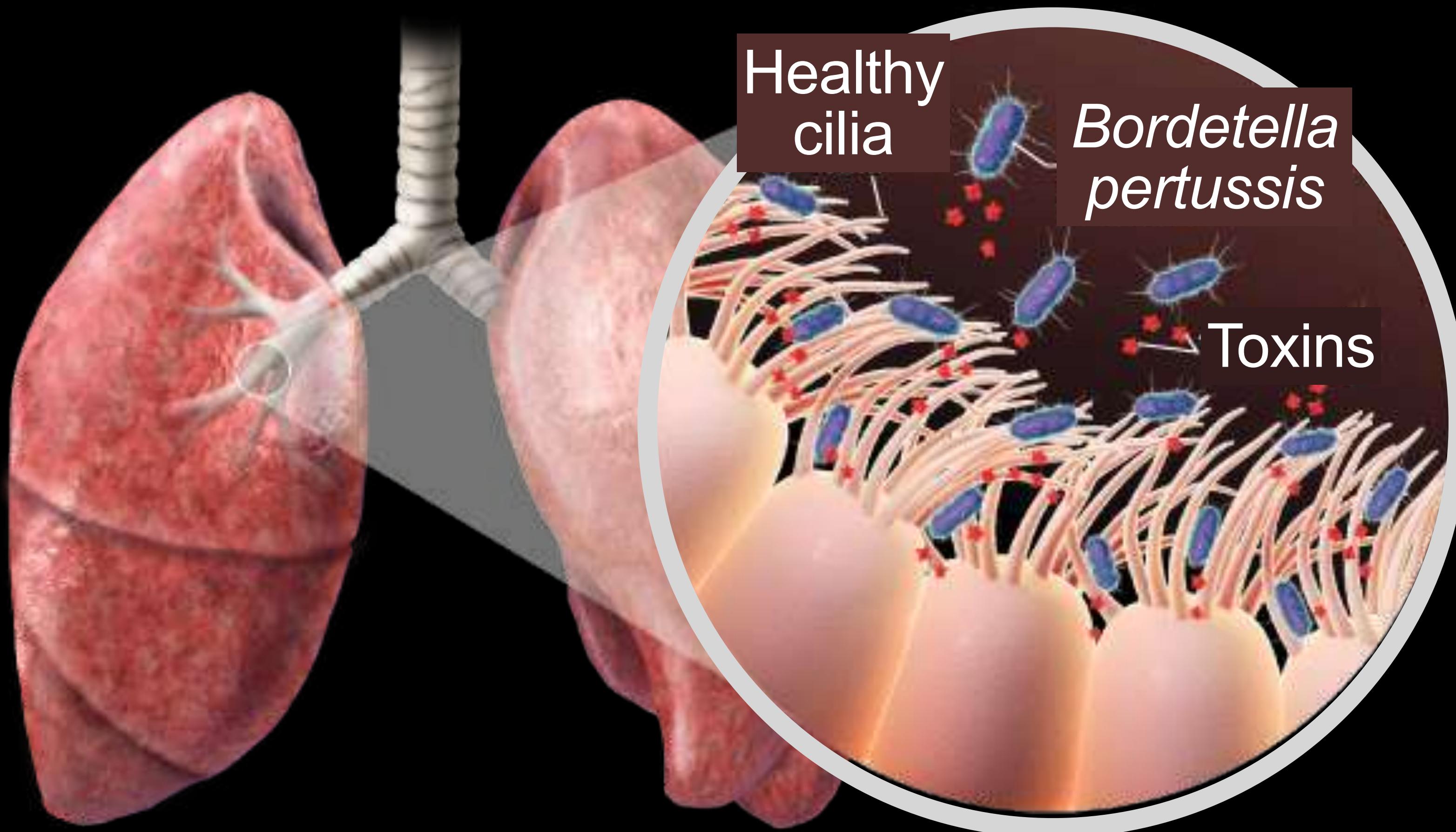
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Bordetella pertussis attacks cells lining the airways

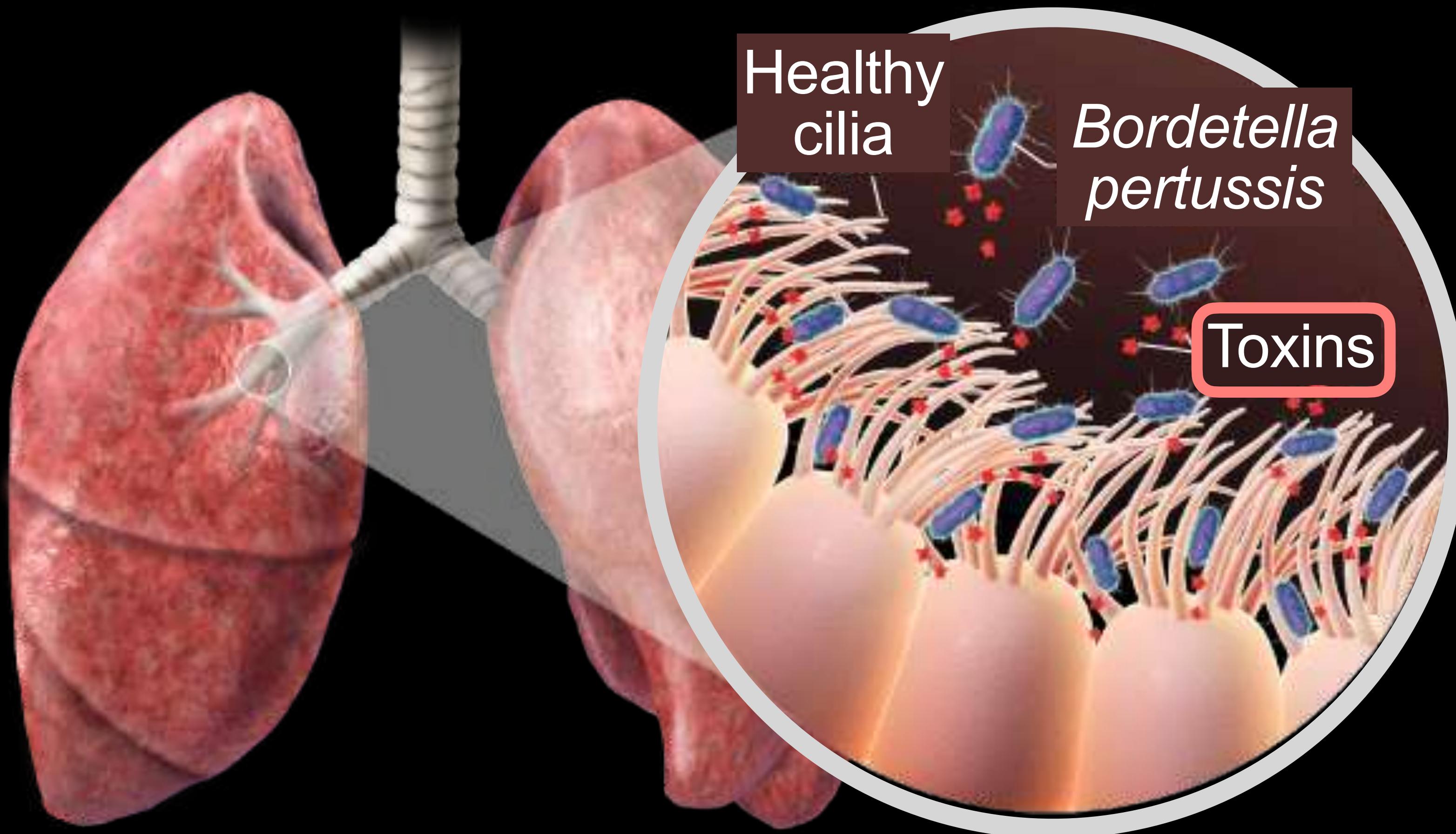
The bacteria use adhesive proteins to stick to **ciliated cells** whilst releasing **toxins**



[More details >](#)

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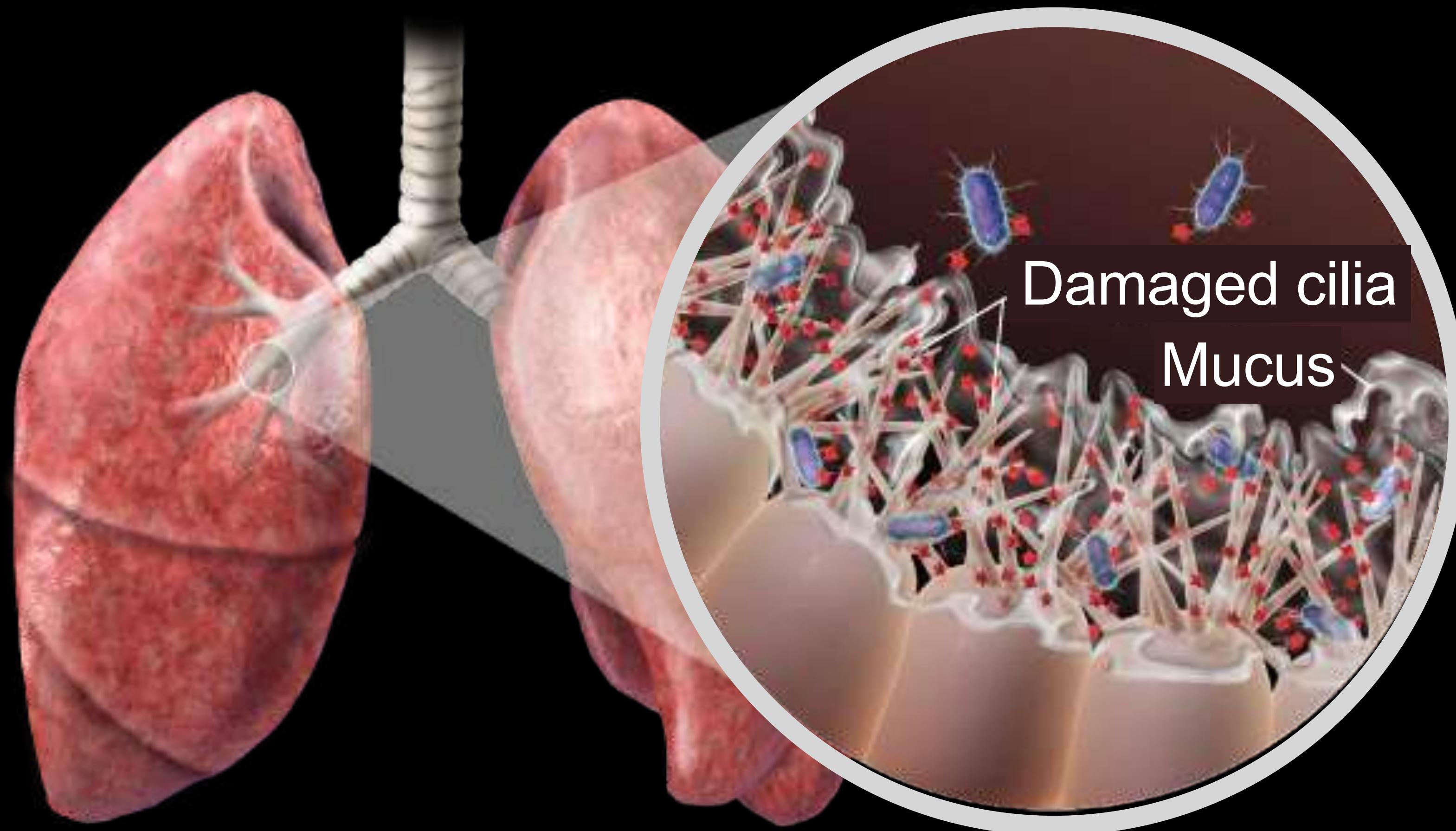
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[More details >](#)

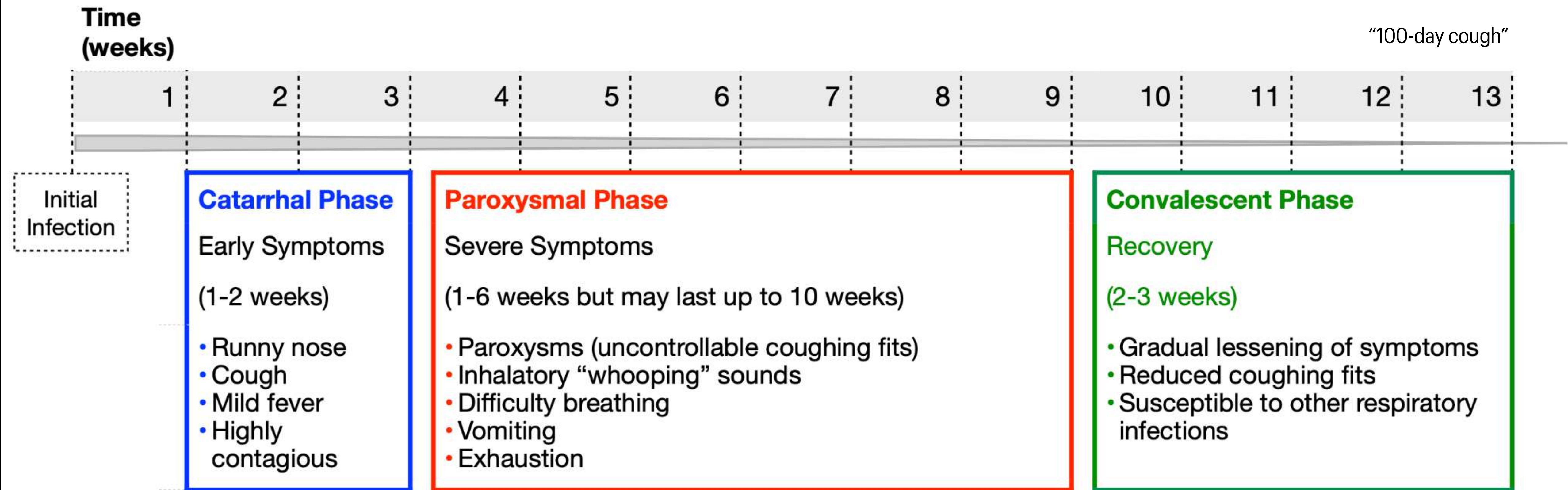
Pertussis is primarily a toxin-mediated disease

These toxins damage cilia, suppress the immune response and disrupt signaling leading to **inflammation**, **mucus buildup** and **impaired function**



[More details >](#)

Pertussis develops in three main phases



[More details >](#)

Fascinating history

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www.cmi-pb.org

1578



First Epidemic Reported

The oldest known pertussis epidemic is thought to be the Paris outbreak of 1578. This was documented in detail by the French physician Guillaume de Baillou who described the classic symptoms of the disease.

[Read more](#)

1679



The Name "Pertussis" First Appears

The name pertussis (from Latin for "intensive cough") was first introduced by the English physician Thomas Sydenham in 1670. This name took over by the end of the decade. Earlier names included hooping cough, tuis perennis, tussis epidemica infantum, and tuis quinta.

[Read more](#)

1900



[Timeline >](#)



1942

First DPT Vaccine

Pearl Kendrick at the Michigan Department of Health combined a refined whole-cell pertussis vaccine with Diphtheria and Tetanus toxoids to create the first combination DPT vaccine.



First Whole-cell Pertussis Vaccine Tested on a Wide Scale

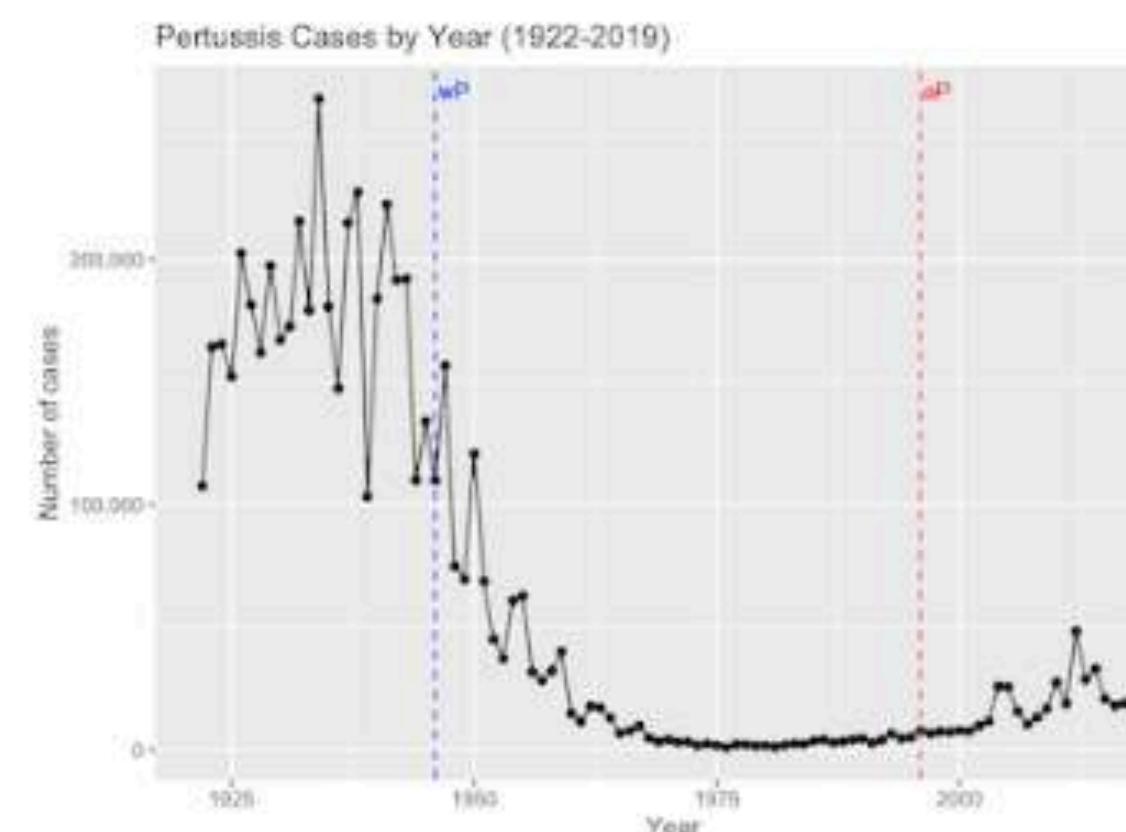
Danish physician Thorvald Madsen tested a whole-cell pertussis vaccine on a wide scale for the first time reporting promising results.



1947

Routine Vaccination

In 1944, the Committee on Infectious Diseases of the American Academy of Pediatrics suggests routine use of pertussis vaccine and, in 1947, recommends its use in the form of the DPT combination. Routine childhood vaccination begins and is made compulsory in some states by the end of the decade.



1970

Decline of Whooping Cough

There was a massive decline of pertussis cases in the U.S. and other

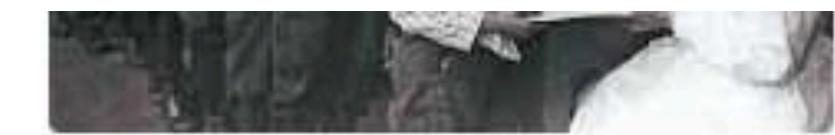
[Timeline >](#)



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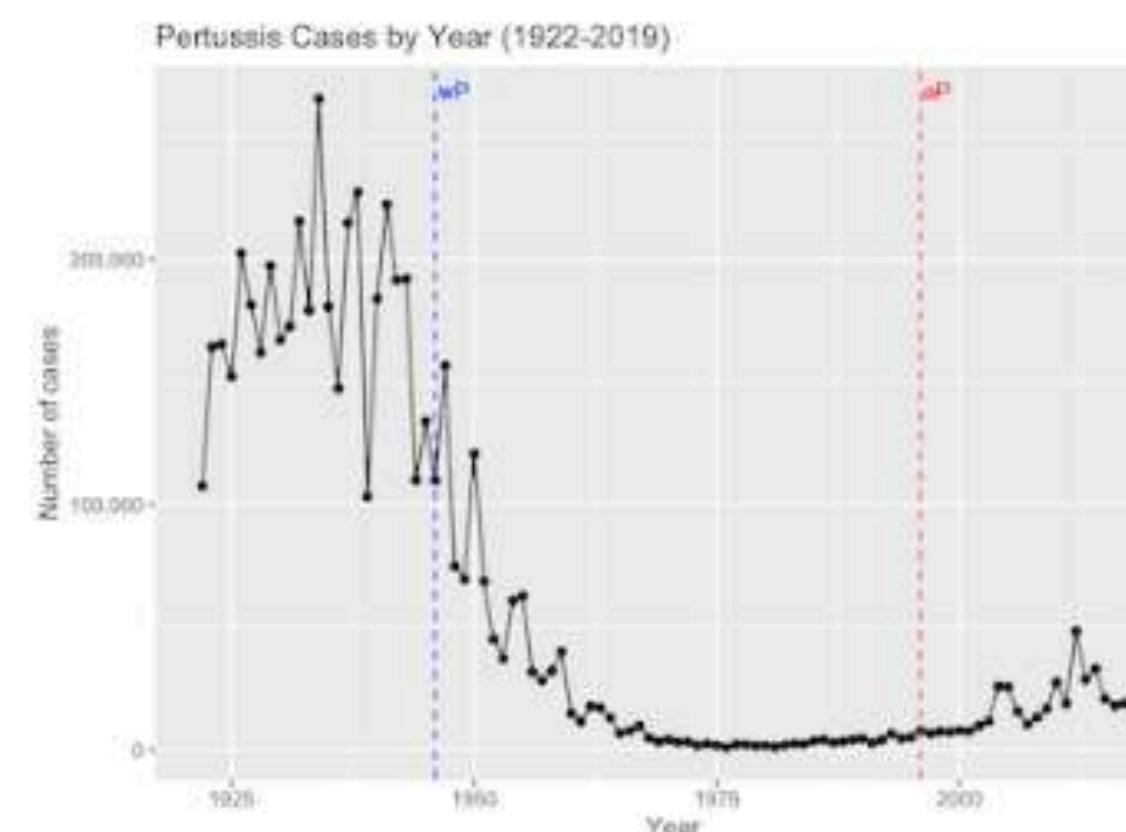


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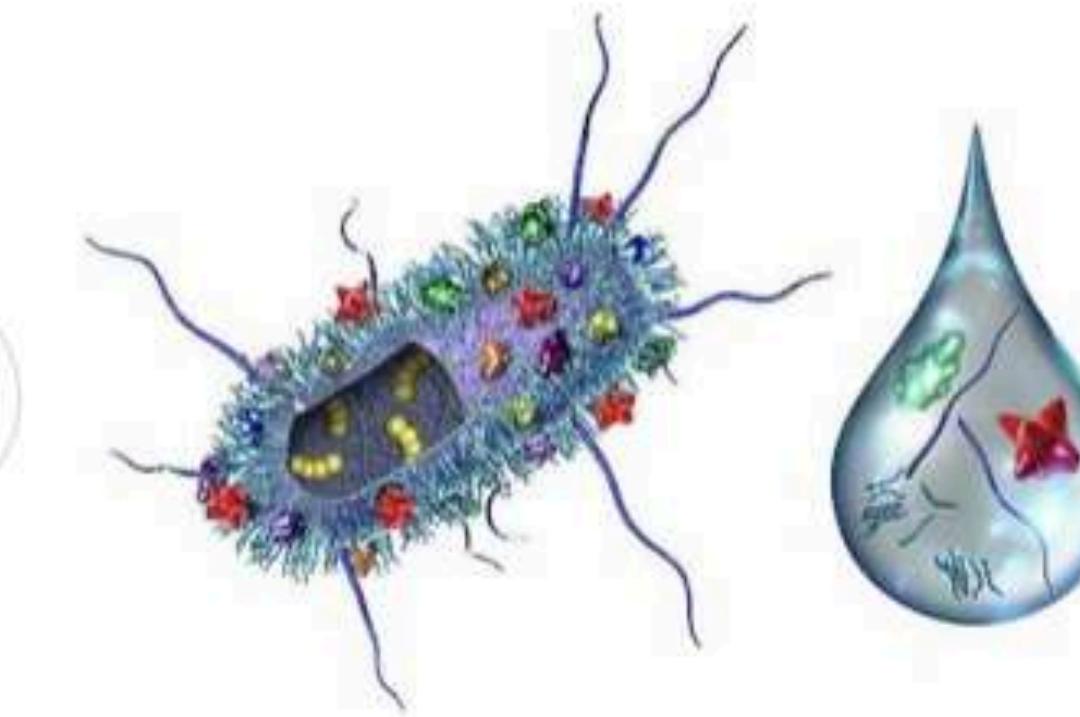
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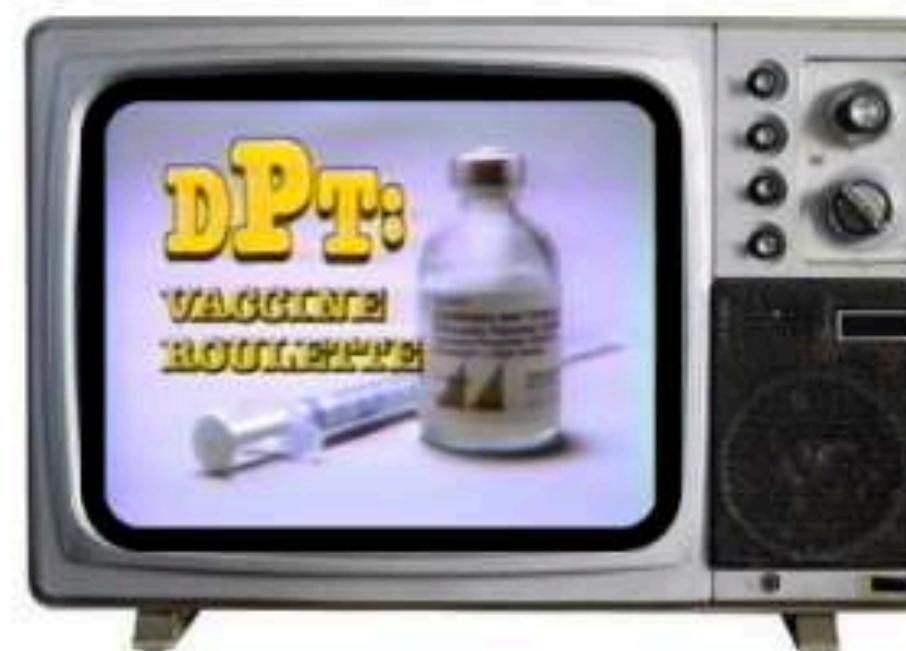
[Timeline >](#)



1981

Creation of DTaP Vaccine

Japanese scientist Yugi Sato created an acellular pertussis vaccine that contained purified haemagglutinins from *B. Pertussis*. This **aP vaccine** was first used in Japan soon after and was demonstrated to have fewer side effects than the whole-cell (**wP**) vaccine. It was later used in other countries (with additional components of *B. Pertussis*) as the combined DTaP vaccine.

[Read more](#)

1982

"DPT: Vaccine Roulette"

In 1982 negative publicity was encouraged from a documentary called "DPT: Vaccine Roulette", which led to a massive amount of lawsuits against the vaccine manufacturers. This documentary depicted the lives of children whose severe disabilities were **incorrectly blamed** on the DPT vaccine.

[Read more](#)

1984



Liability

By 1984 DPT vaccine manufacturers had a hard time obtaining liability insurance. By the end of the year, only one DPT manufacturer remained. Scientists respond by ramping up development and testing of safer new acellular pertussis vaccines. These would replace the older whole cell vaccine in many countries with a decade.

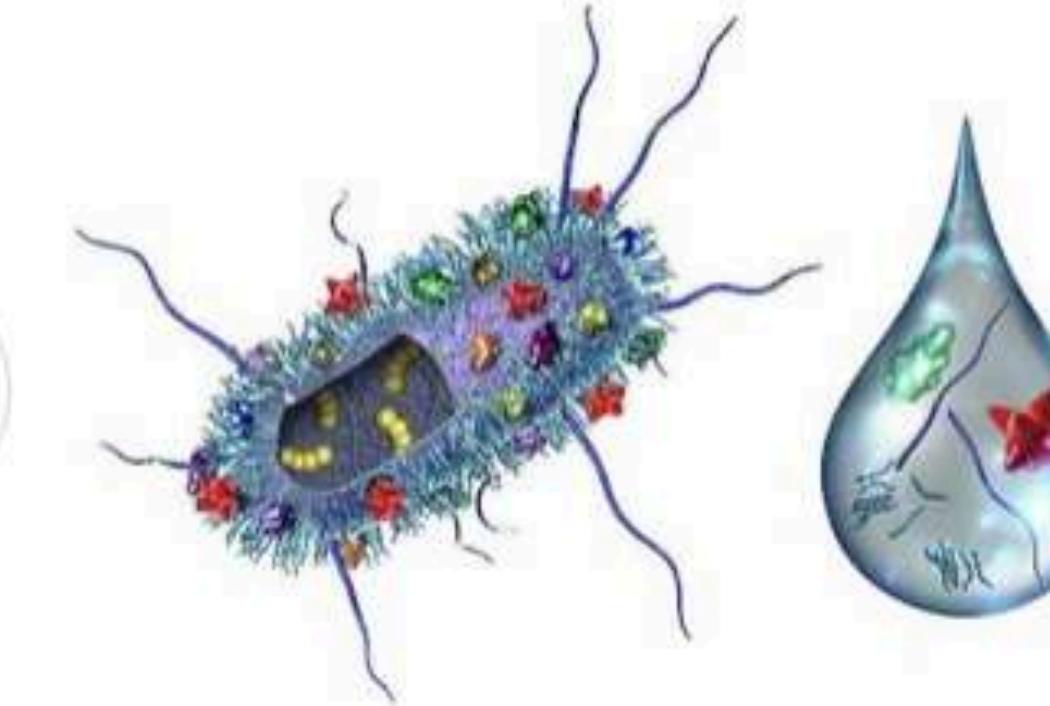


1985

[Timeline >](#)



1981



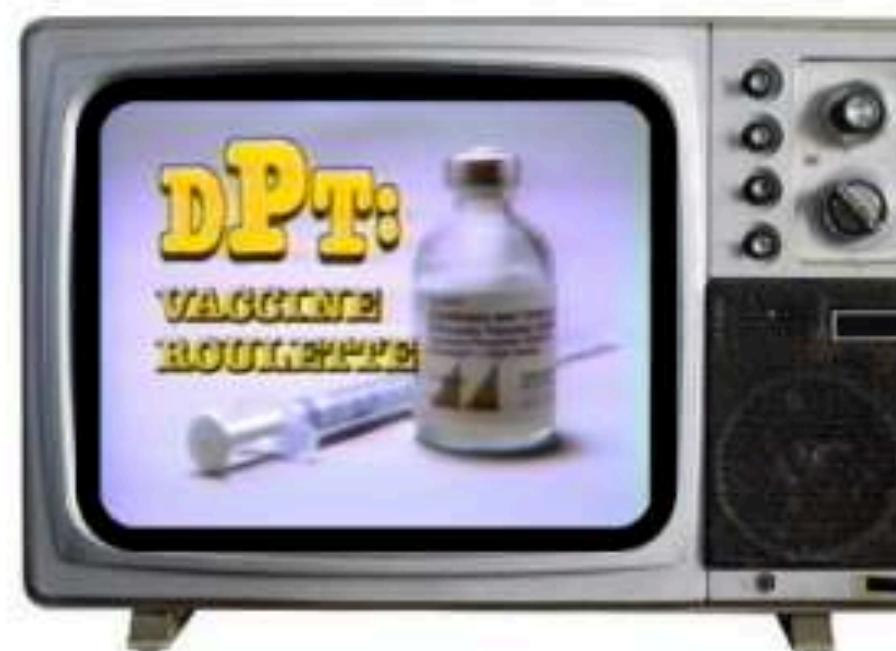
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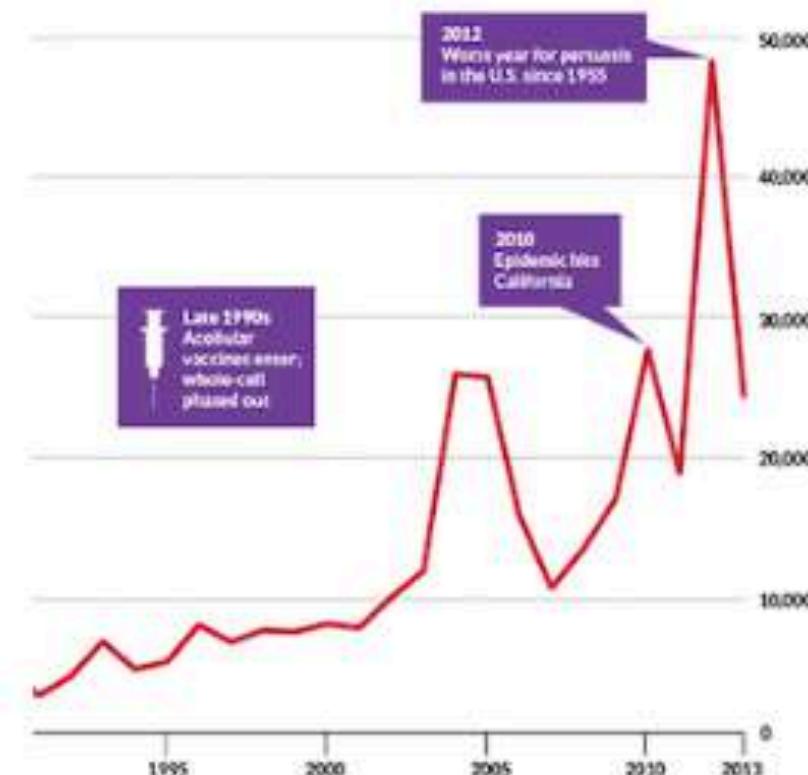
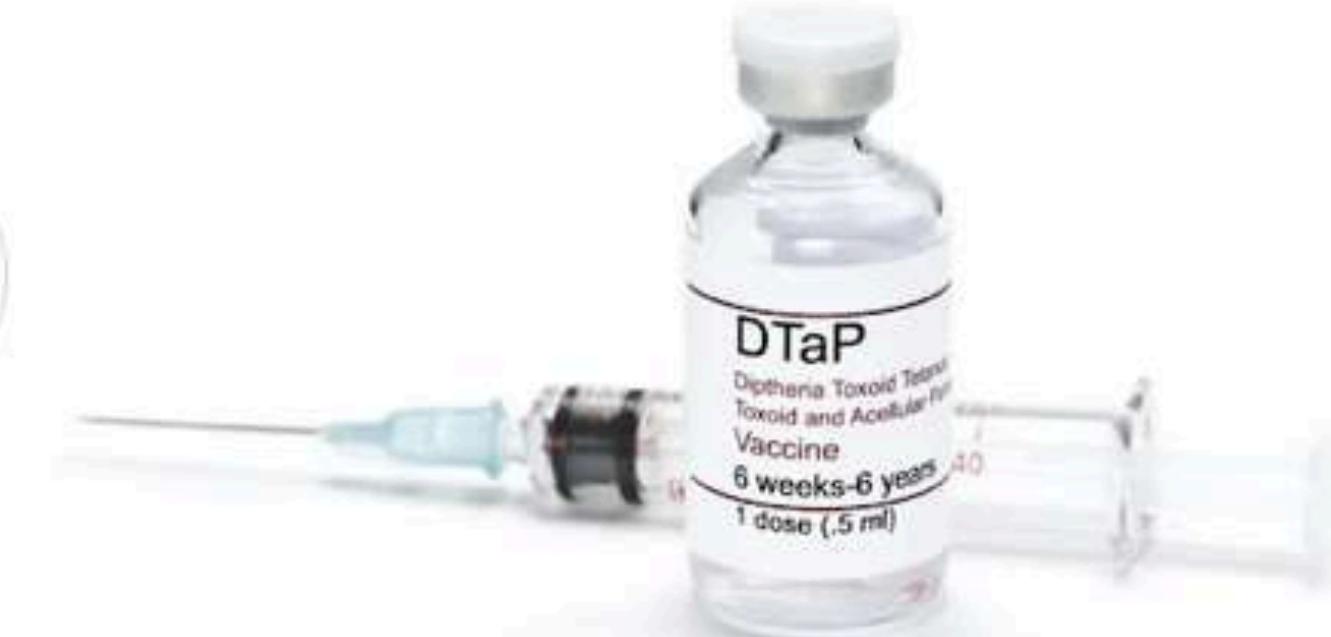


1985

[Timeline >](#)

Later studies showed that there was no connection between the DPT vaccine and the permanent brain damage. It was in fact called a "Myth" and "Nonsense" by the Journal of American Medical Association in 1990.

1992



Pertussis Outbreaks

Major pertussis epidemics and outbreaks are once again a major public health concern. With epidemics typically occurring every 3 to 5 years in the U.S. as was evident in the pre-vaccine years. TO FINISH mention CA outbreak.

2010

aP Vaccine Approved in the U.S.

The acellular pertussis (aP) vaccine was approved in the U.S. in 1992, the older wP formulation was phased out and completely replaced with the DTaP vaccine combination in 1996.



CMI-PB Project

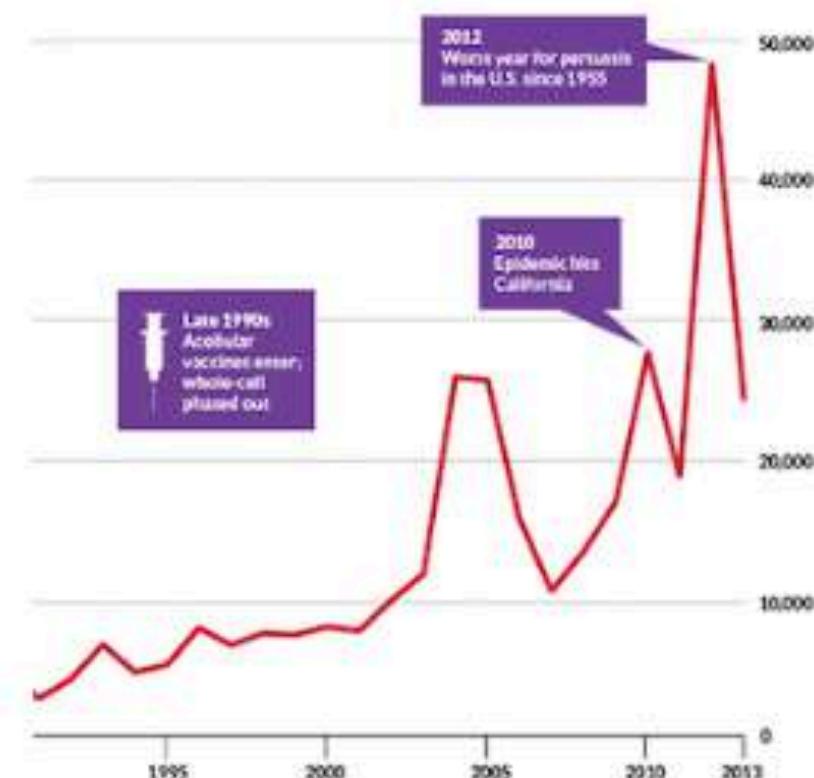
A new [systems vaccinology project](#) is launched that combines systems biology and genomics to provide a more holistic picture of protective pertussis-specific immune mechanisms. The project provides the scientific community with comprehensive, high-quality, and freely accessible resources related to Pertussis booster vaccination.

These resources, and associated [prediction challenges](#), are geared towards engaging both experts and enthusiasts in developing and improving **computational models** of the immune response to vaccination and in turn informing new intervention strategies to curb the increasing frequency of *B. pertussis* infection.

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2020



CMI-PB
COMPUTATIONAL MODELS OF IMMUNITY
PERTUSSIS BOOST

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[Timeline >](#)

Hands-On Lab

The screenshot shows a web browser window with a dark theme. The address bar displays the URL: bioboot.github.io/cmi-pb_teaching/introduction/intro_to_cmi-pb.html. The page content is titled "1. Investigating pertussis cases by year". It contains text about CDC data and a bullet point for a question. A "Hint" button is present. To the right, there's a sidebar with sections like "Background", "Sections", and "Edit this page".

1. Investigating pertussis cases by year

The United States *Centers for Disease Control and Prevention* (CDC) has been compiling reported pertussis case numbers since 1922 in their *National Notifiable Diseases Surveillance System* (NNDSS). We can view this data on the CDC website here: <https://www.cdc.gov/pertussis/surv-reporting/cases-by-year.html>

- Q1. With the help of the R “addin” package [datapasta](#) assign the CDC pertussis case number data to a data frame called `cdc` and use [ggplot](#) to make a plot of cases numbers over time.

Hint

Key point: Pertussis vaccination is, in general, highly effective at preventing the disease. In the pre-vaccine era (before 1946) pertussis was a much more common disease and a major cause of infant mortality [2](#). As we see clearly from analysis of the CDC tracking data above, introduction of the first pertussis vaccination in the United States in 1946 resulted in a dramatic reduction in the number of yearly cases from > 200,000 in the 1940s to < 2,000 in the 1970s.

2. A tale of two vaccines (wP & aP)

Two types of pertussis vaccines have been developed: **whole-cell pertussis (wP)** and **acellular pertussis (aP)**. The

[Link >](#)

A screenshot of a web browser window showing the CDC Pertussis Surveillance: Cases by Year page. The browser has a tab bar with various icons and links at the top. The main content area features the CDC logo and navigation links for Pertussis, Vaccination, Pregnancy & Whooping Cough, Outbreaks, Clinicians, and Public Health Professionals. A sidebar on the left lists these categories with a green vertical bar next to 'Surveillance & Reporting'. The main title is 'Pertussis Cases by Year (1922-2019)'. Below it is a 'Print' link. A text block explains the table shows reported pertussis cases in the United States since 1922, with related trend charts available on the 'Surveillance and Reporting' page. A table lists the number of reported cases for each year from 1922 to 1926.

[cdc.gov](#)

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CDC Pertussis Surveillance: Cases by Year | CDC

Español | Other Languages

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Pertussis (Whooping Cough)

CDC > Pertussis Home > Surveillance & Reporting

[Pertussis Home](#)

About Pertussis

Vaccination

Pregnancy & Whooping Cough

Outbreaks

Clinicians

Public Health Professionals

Surveillance & Reporting

Pertussis Cases by Year (1922-2019)

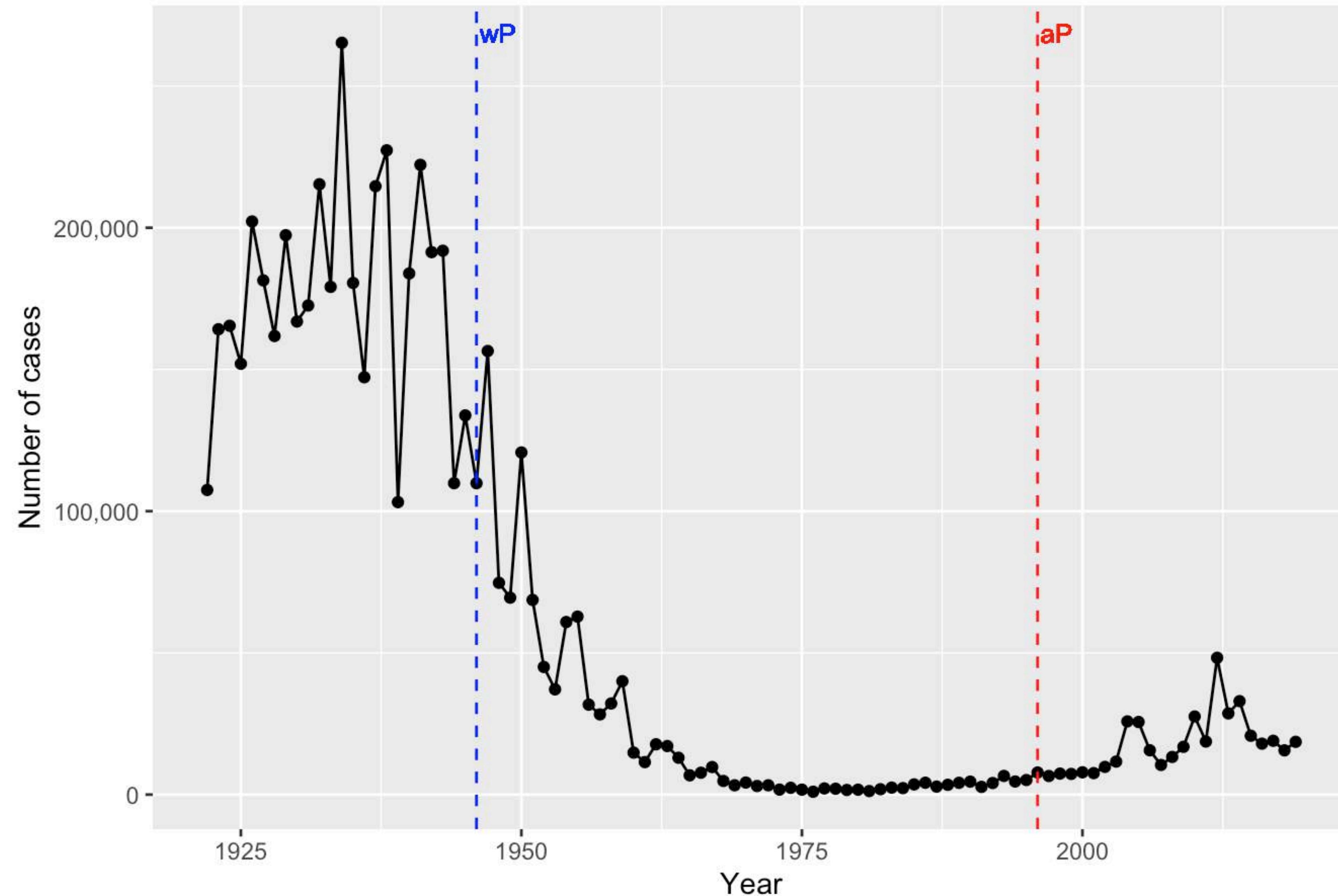
[Print](#)

This table shows reported pertussis cases in the United States since 1922. The related trend charts can be found on the [Surveillance and Reporting](#) page.

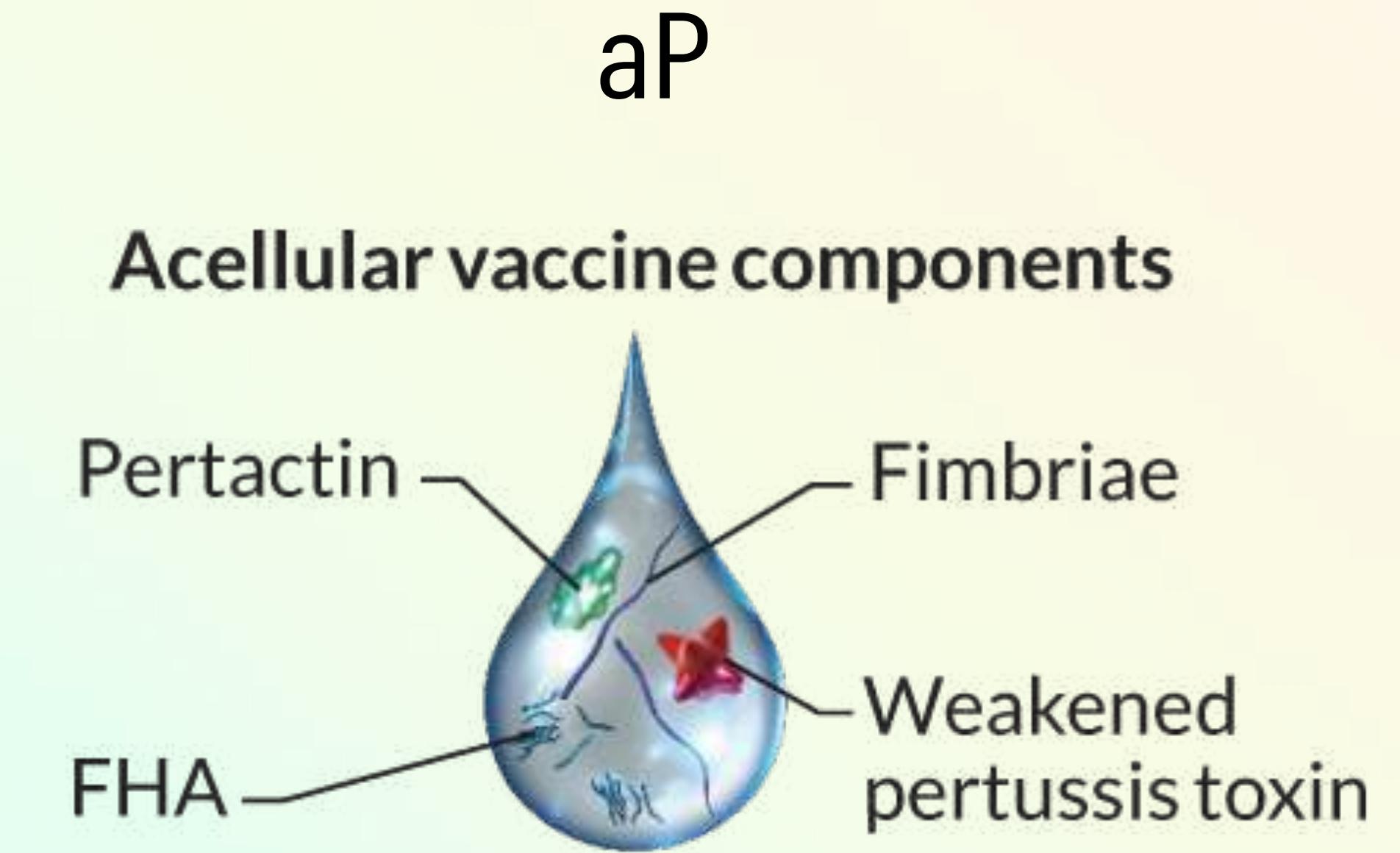
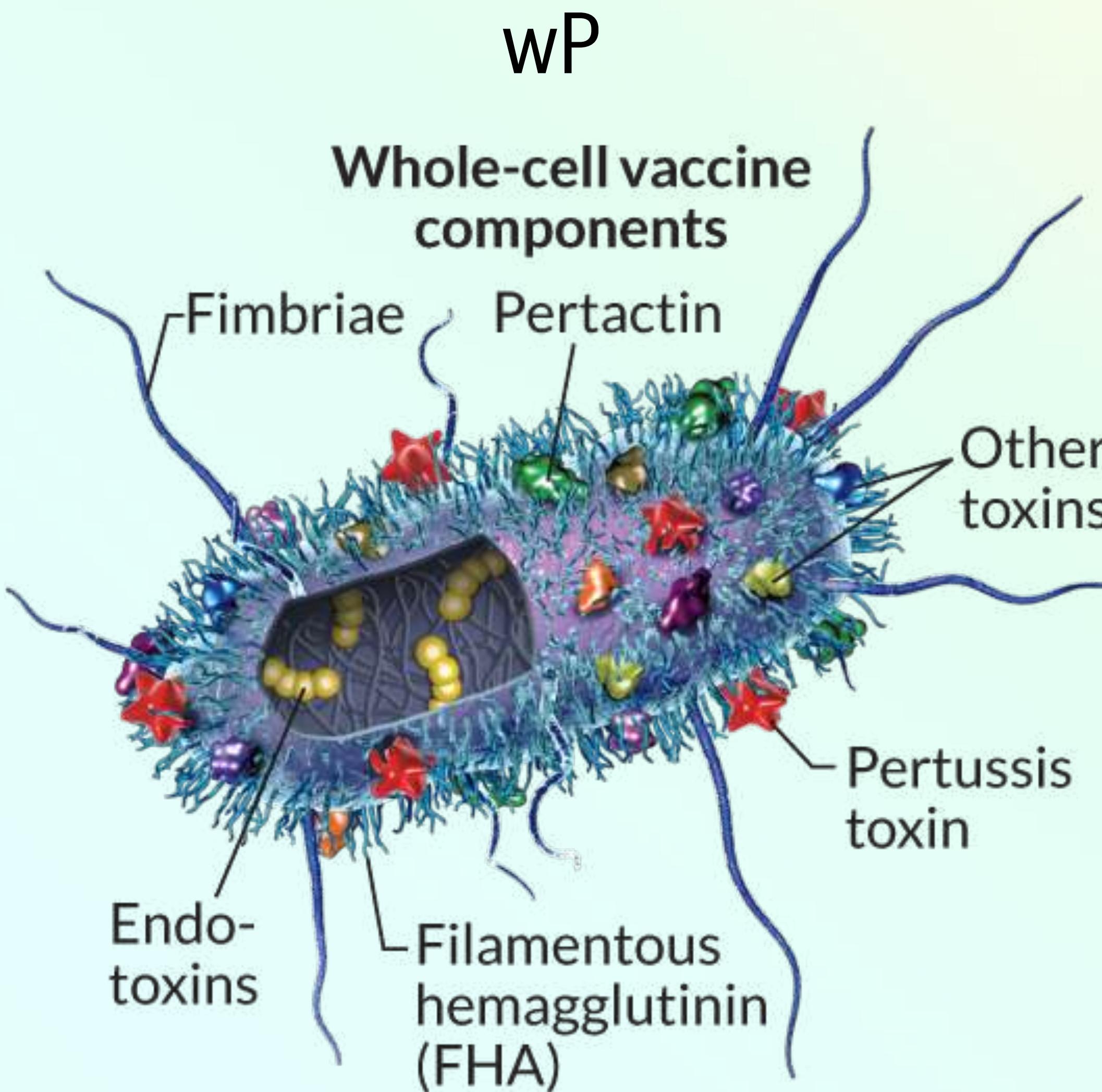
Year	No. Reported Pertussis Cases
1922	107,473
1923	164,191
1924	165,418
1925	152,003
1926	202,210

Link >

Pertussis Cases by Year (1922-2019)



A tail of two vaccines



[More details >](#)

Major aP vaccines (US)

Vaccine	Trade Name	Manufacturers	Components (Concentrations)
DTaP	Daptacel, Infanrix	Sanofi Pasteur, GlaxoSmithKline	Inactivated PT: 10-20 µg, FHA: 5-20 µg, PRN: 3-5 µg, FIM 2+3: 5-10 µg
Tdap	Adacel, Boostrix	Sanofi Pasteur, GlaxoSmithKline	Inactivated PT: 2.5-8 µg, FHA: 5-8 µg, PRN: 3-5 µg, FIM 2+3: 5-8 µg

[More details >](#)

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The two aP vaccine formulations (DTaP and Tdap) differ in their concentrations of Pertussis derived antigens.

Higher concentrations are thought to be necessary for the initial building of immunity in young children

[More details >](#)

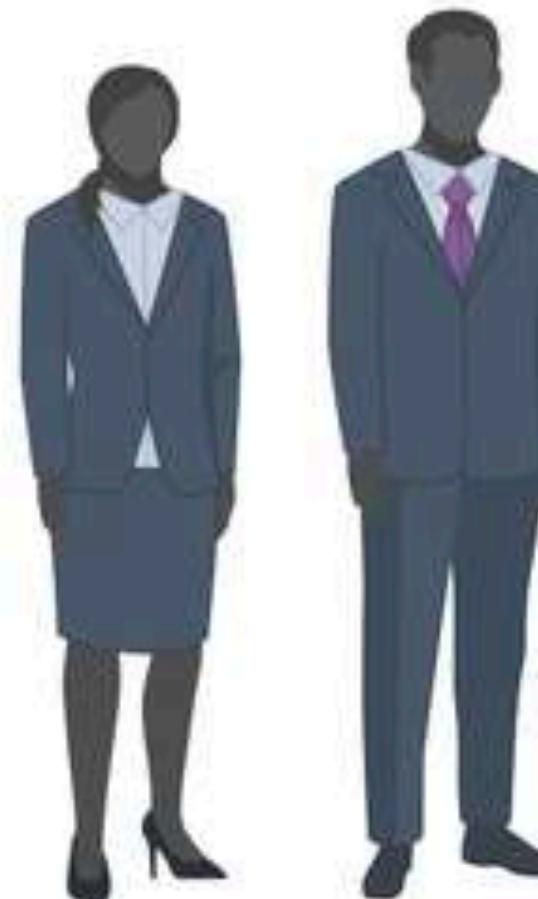
Major aP vaccines (US)



DTaP
for young
children



Tdap
for preteens



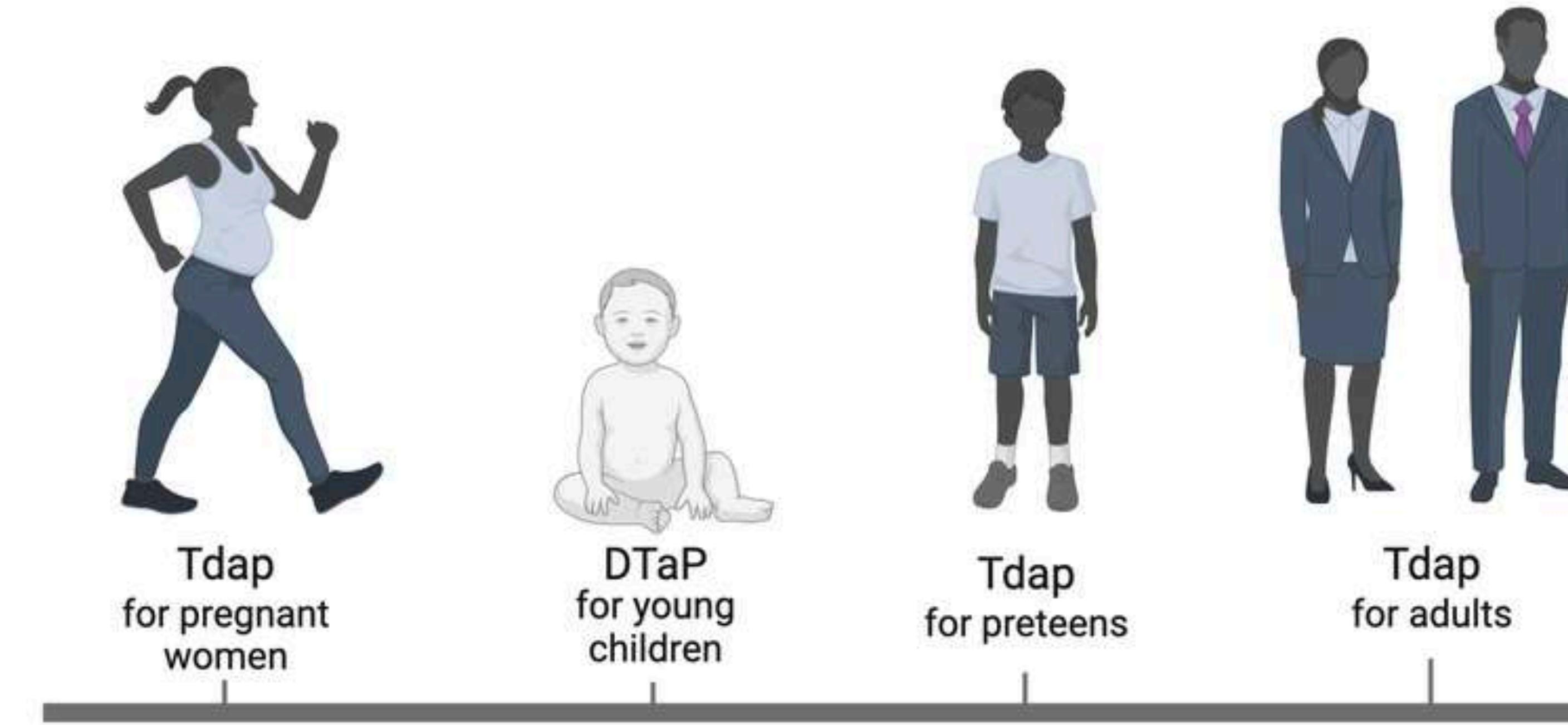
Tdap
for adults

- | | | |
|--|---|---|
| <ul style="list-style-type: none">• 2, 4 and 6 months• 15 through 18 months• 4 through 6 years | <p>• 11 through 12 years</p> <p>[From 2005]</p> | <ul style="list-style-type: none">• Anytime for those who have never received it• Subsequent boosters at 10 year intervals following initial vaccine |
|--|---|---|

Source: Centers for Disease Control

[More details >](#)

Major aP vaccines (US)



- During the 27-36th week of each pregnancy

[From 2011]

- 2, 4 and 6 months
- 15 through 18 months
- 4 through 6 years

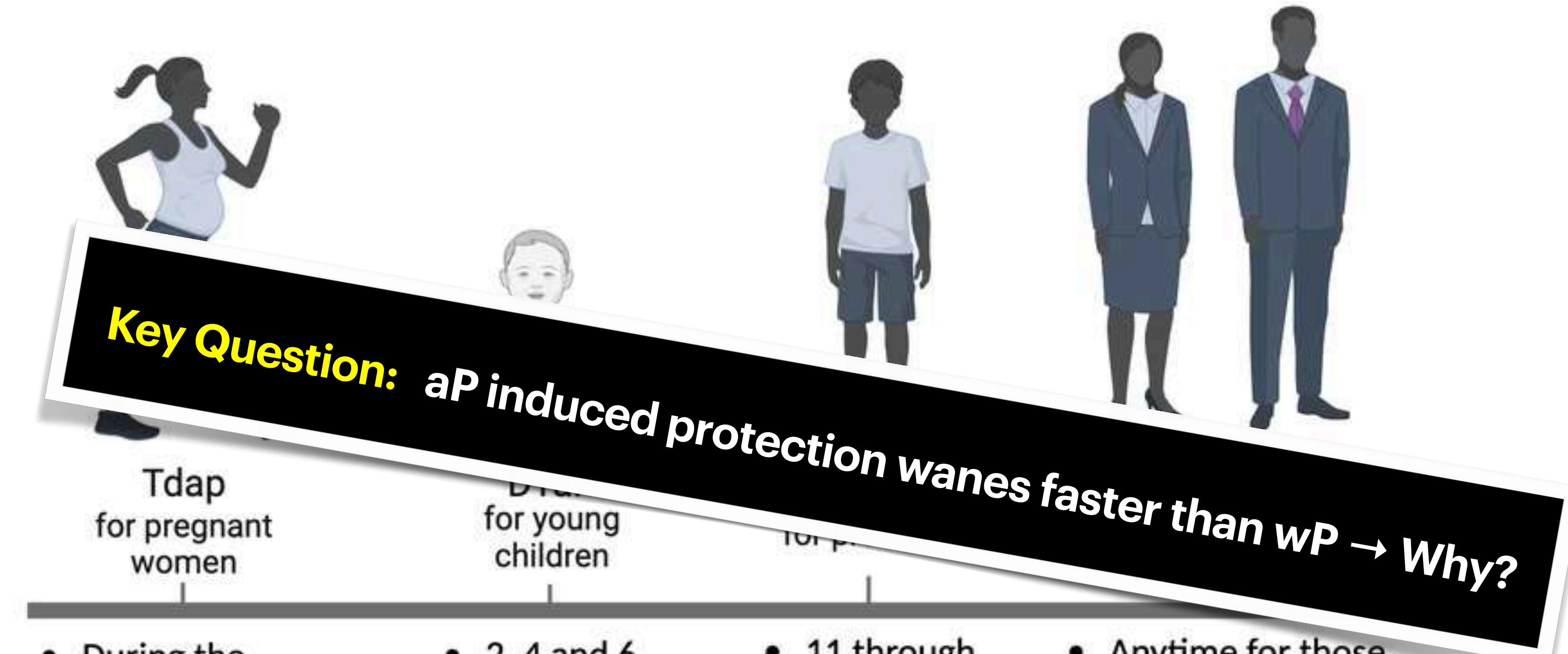
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[More details >](#)

Major aP vaccines (US)



[From 2011]

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[More details >](#)

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70+ 31

 **CMI-PB**
COMPUTATIONAL MODELS OF IMMUNITY
PERTUSSIS BOOST

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Ab titer **Search**

The mission of CMI-PB is to provide the scientific community with a comprehensive, high-quality and freely accessible resource of Pertussis booster vaccination.

LEARN ABOUT THE PROJECT



The NIH funded CMI network
What is pertussis vaccination?
What are the open scientific questions?
The CMI-PB approach: A community

UNDERSTAND THE DATA



How do we measure immune responses?
What data is available?
Our approach to data standardization
Browse our terminology

ACCESS THE DATA



Data statistics
Use the API in your programs
Download all data (SFTP)
More ...

<https://www.cmi-pb.org/>

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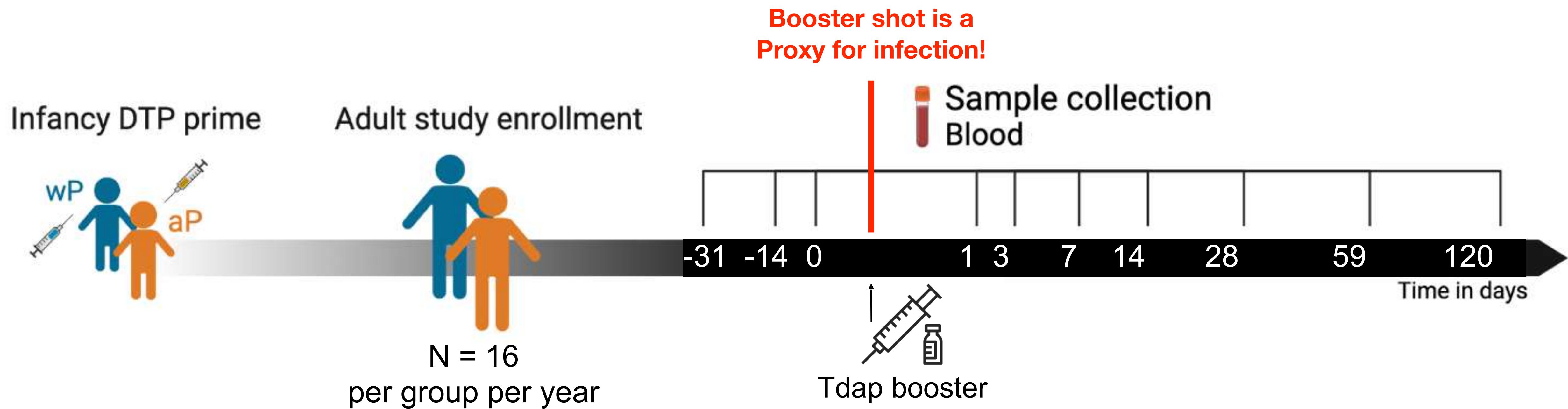
ACCESS THE DATA



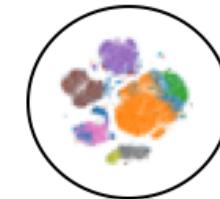
Data statistics
Use the API in your programs
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More ...

<https://www.cmi-pb.org/>

Recruitment Strategy



Characterizing immune responses - Multiomics approach



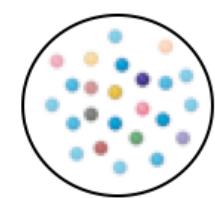
PBMC cell frequencies by flow cytometry

- Total of 37 distinct cell populations



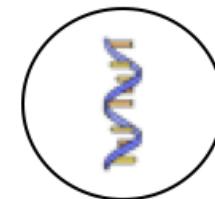
Plasma antigen-specific antibody titers by Luminex

- Antibody Isotypes: IgG, IgG1, IgG2, IgG3, IgG4
- Vaccine Antigens
 - Pertussis Toxin (PT), PRN, FHA, FIM2/3
 - Tetanus Toxoids (TT)
 - Diphtheria Toxoids (DT)
 - OVA (irrelevant control)



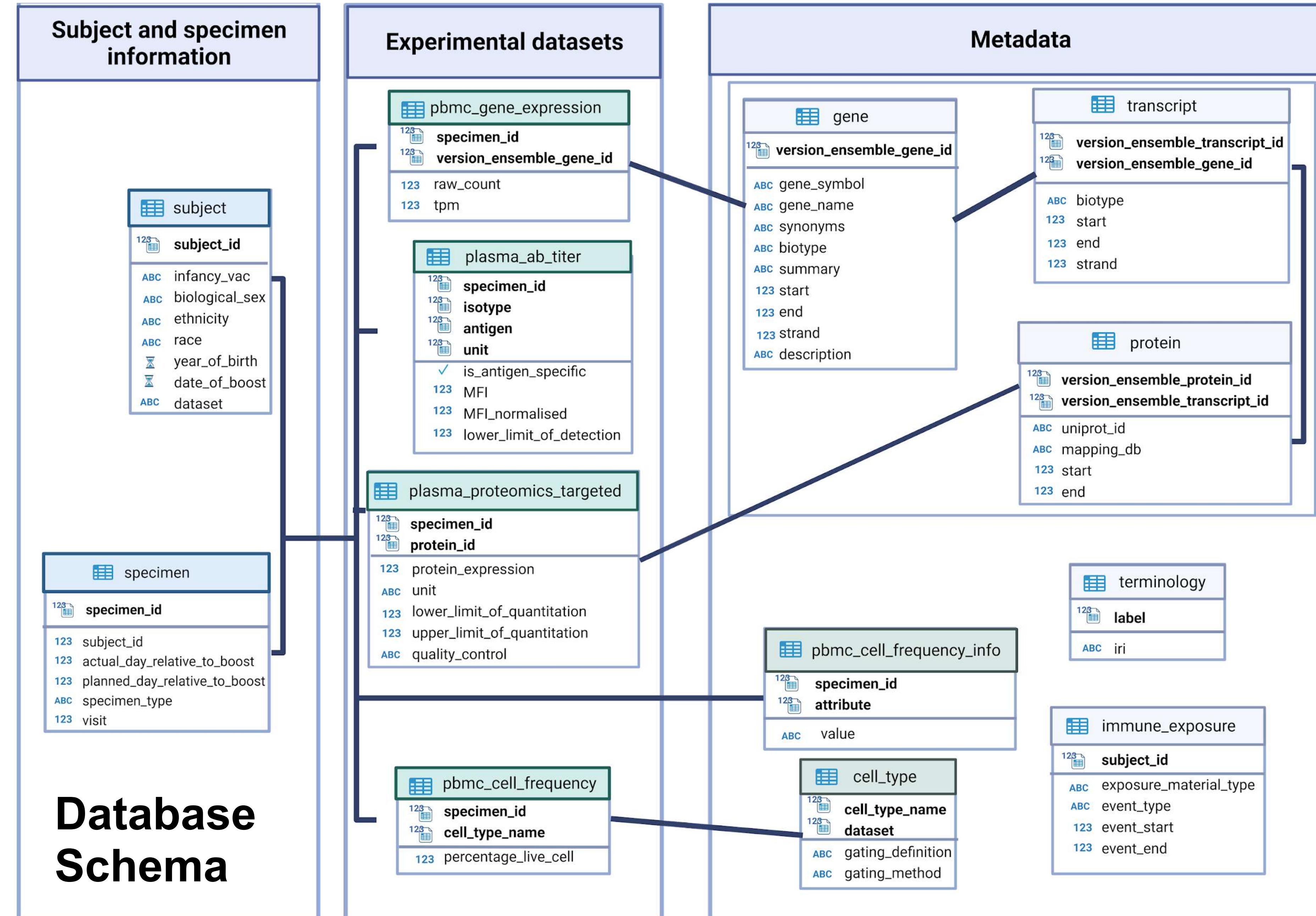
Plasma proteomics by Olink

- Concentration of 45 cytokines

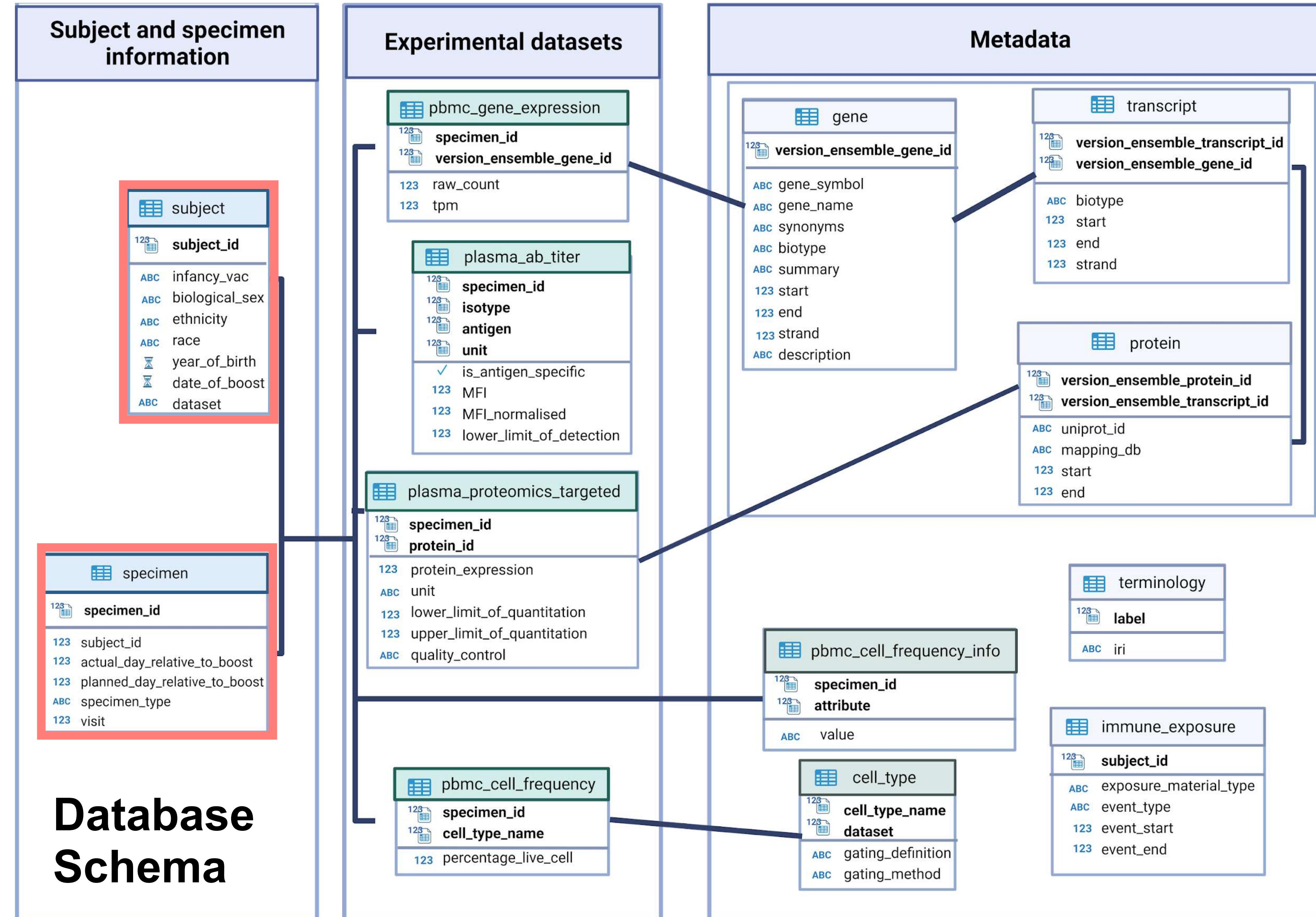


Transcriptomics by bulk RNA-Seq

CMI-PB provides access to experimental data in a standardized format



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Information Tables

SUBJECT	SPECIMEN
subject_id	specimen_id
infancy_vac	subject_id
biological_sex	actual_day_relative_to_boost
ethnicity	planned_day_relative_to_boost
race	specimen_type
year_of_birth	visit
date_of_boost	
dataset	

Dplyr *`_join()` functions...

`inner_join(x, y)`

1	x1
2	x2
3	x3

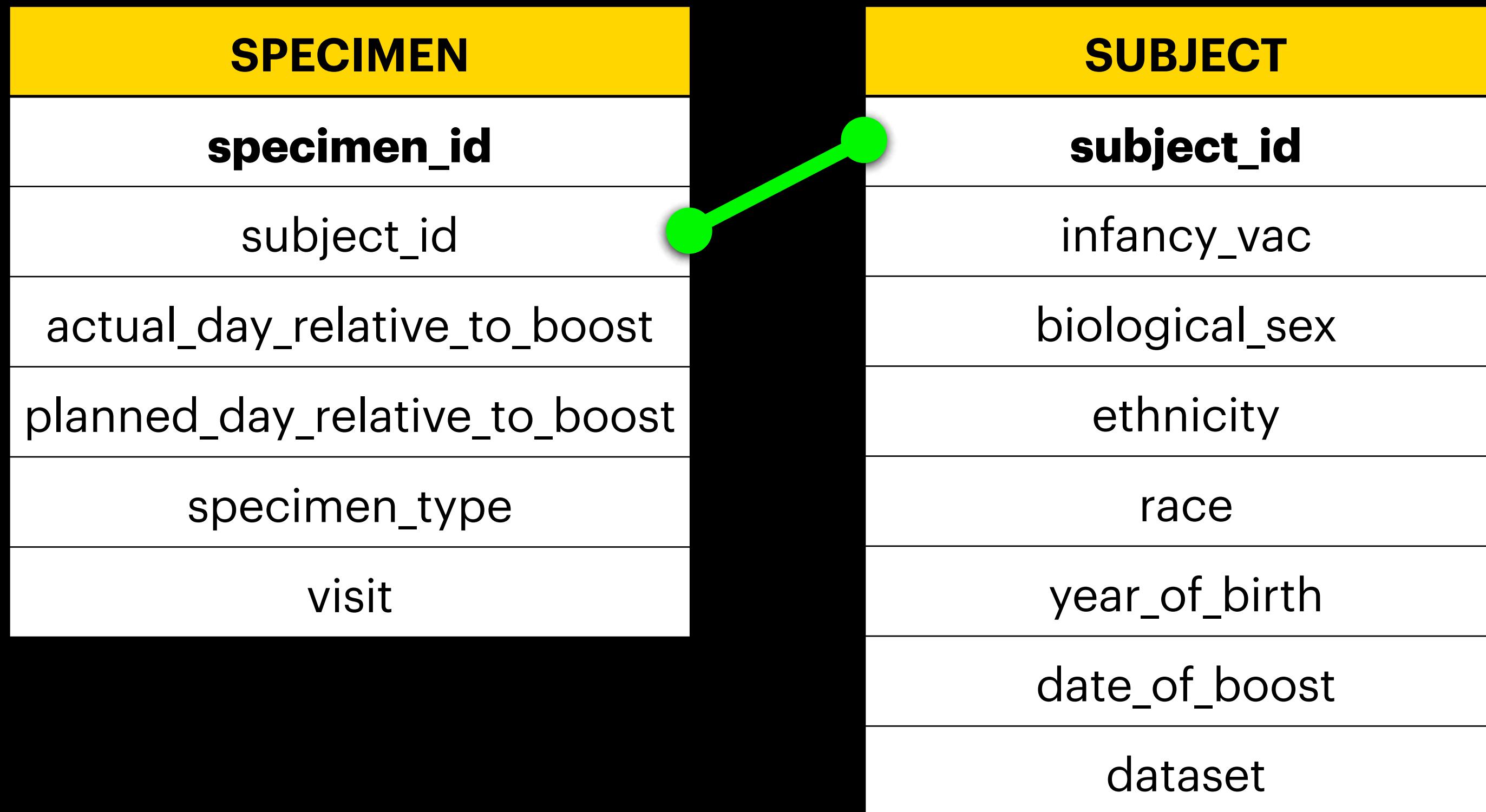
1	y1
2	y2
4	y4

`full_join(x, y)`

1	x1
2	x2
3	x3

1	y1
2	y2
4	y4

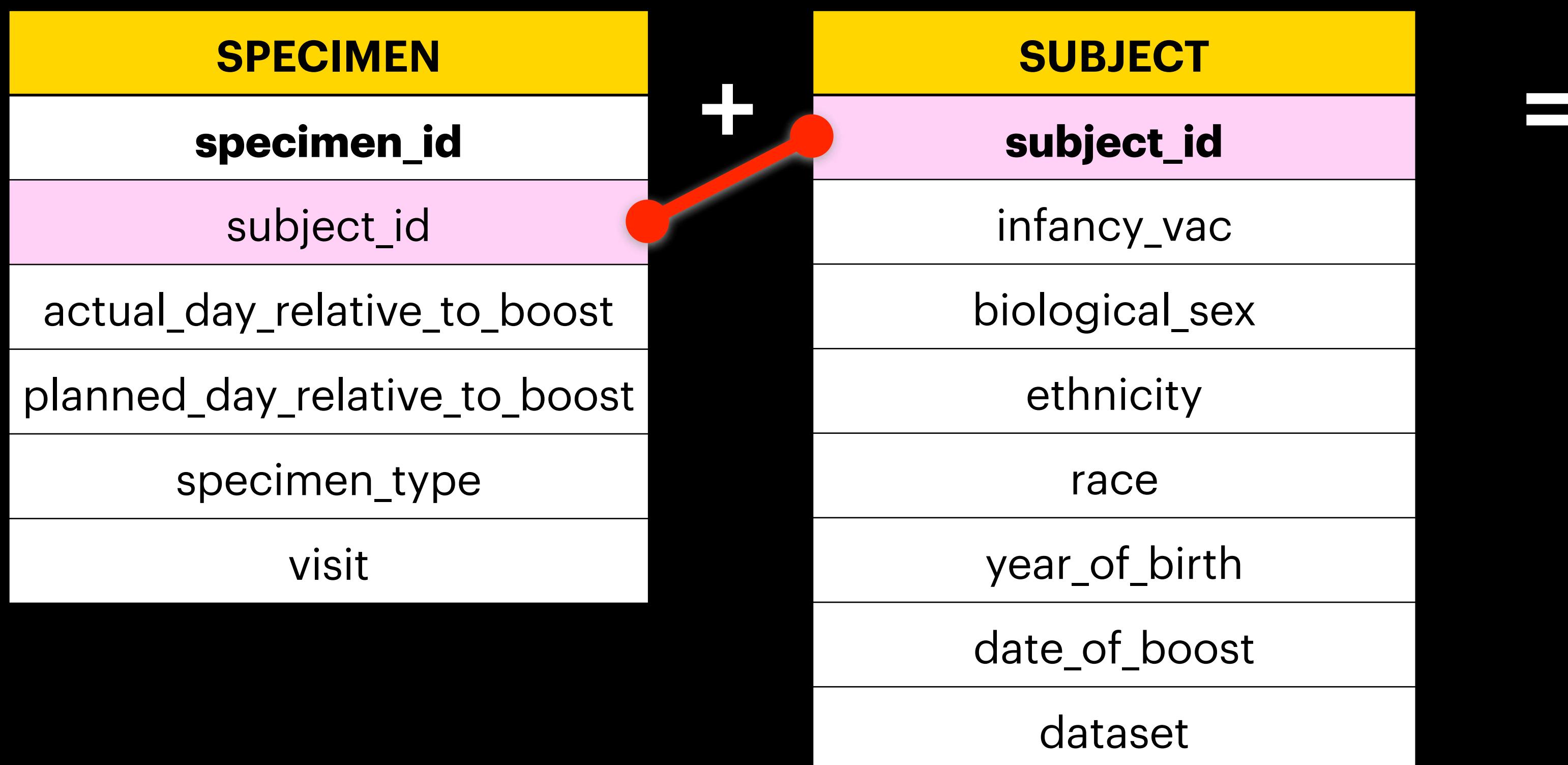
Information Tables



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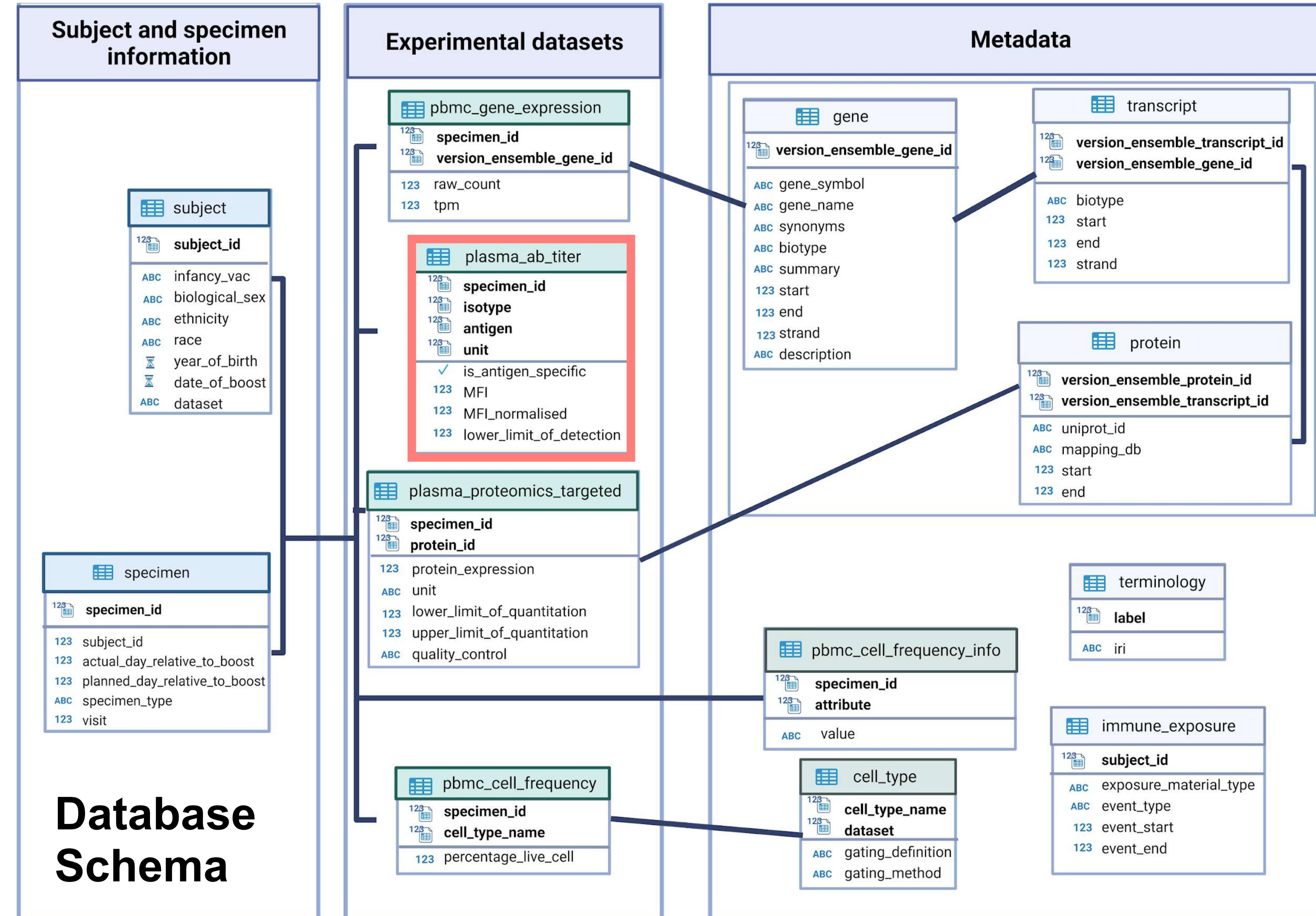
SPECIMEN	SUBJECT
specimen_id	subject_id
subject_id	
actual_day_relative_to_boost	infancy_vac
planned_day_relative_to_boost	biological_sex
specimen_type	ethnicity
visit	race
	year_of_birth
	date_of_boost
	dataset

We Want One Meta table



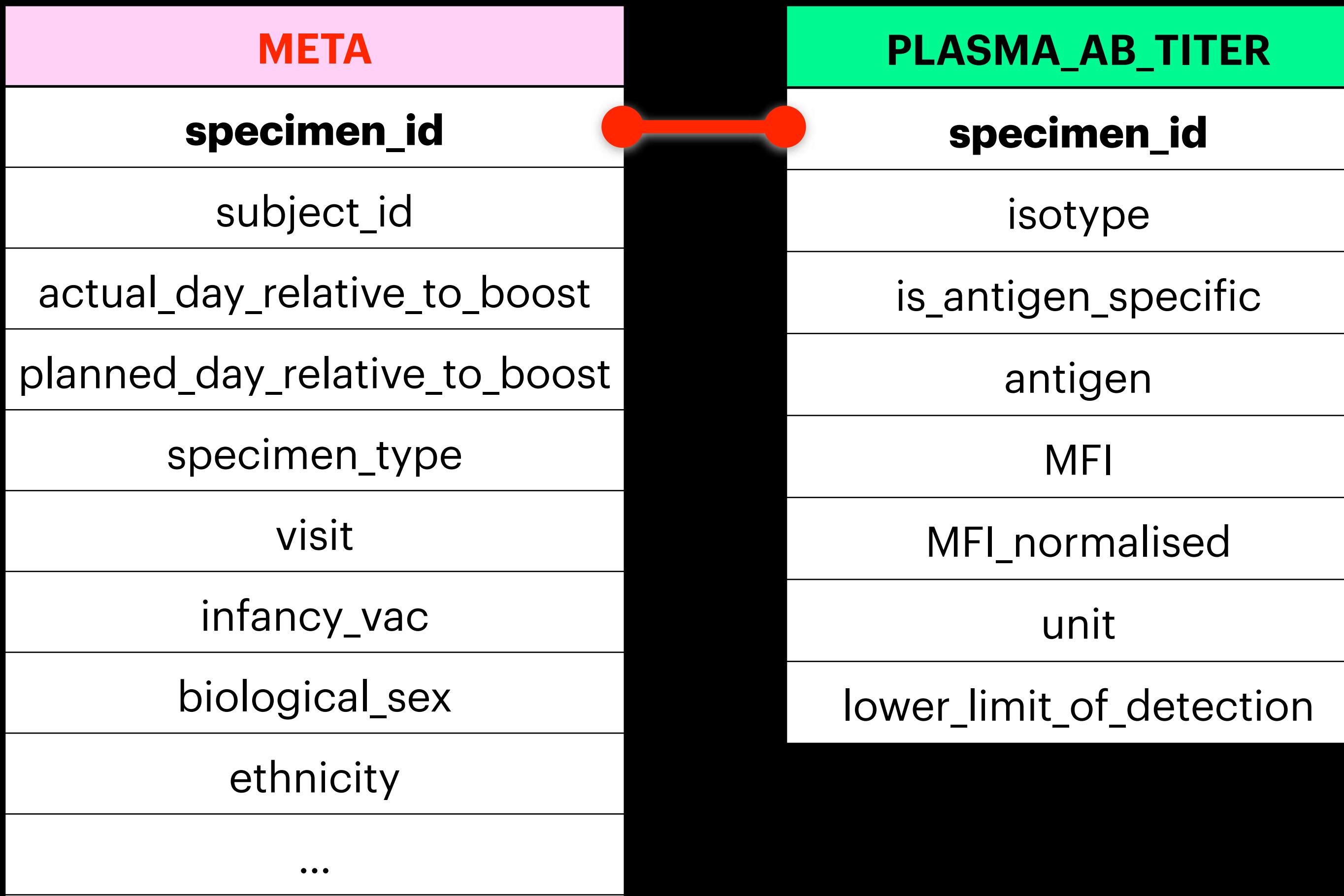
META
specimen_id
subject_id
actual_day_relative_to_boost
planned_day_relative_to_boost
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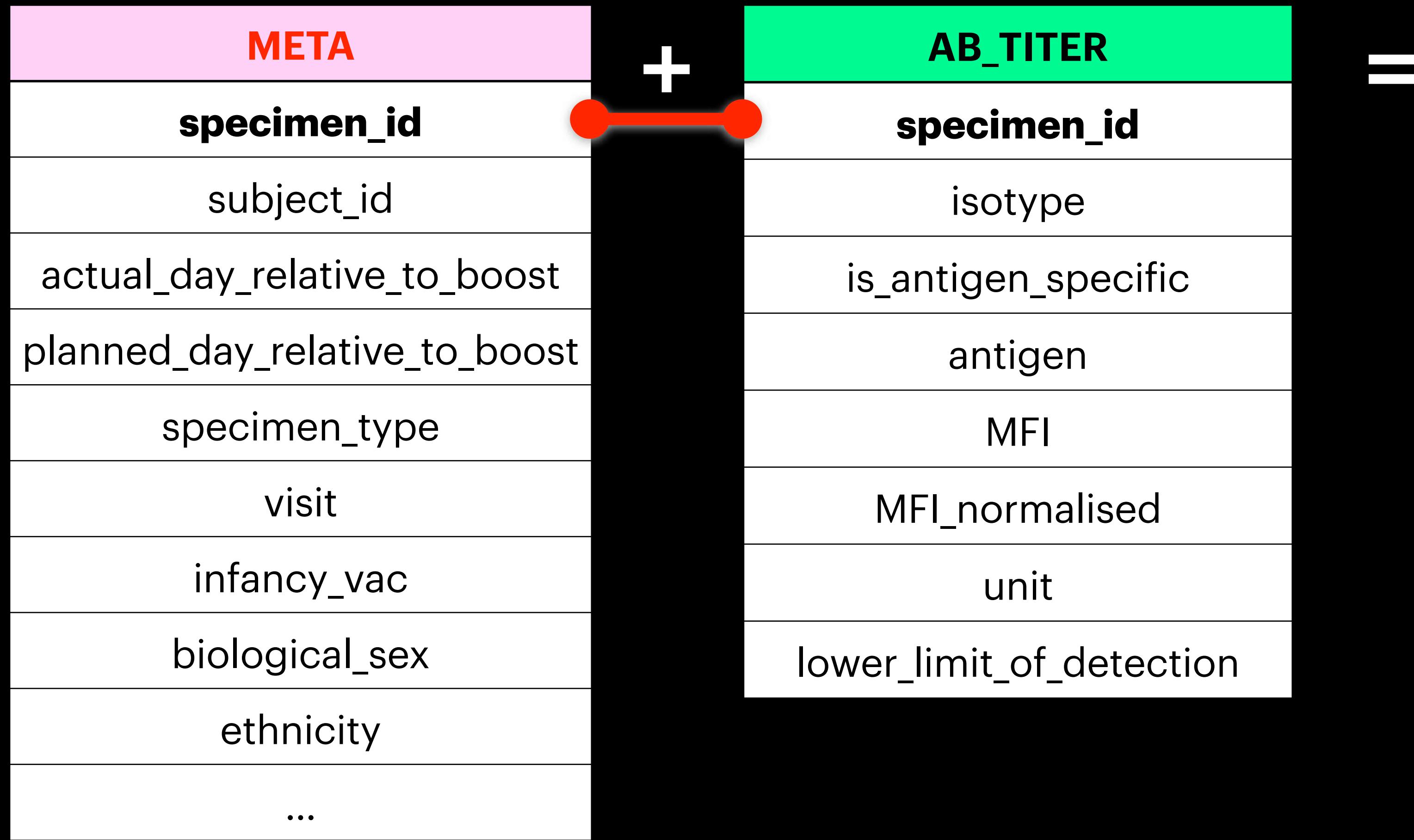


Join with Experiment Tables

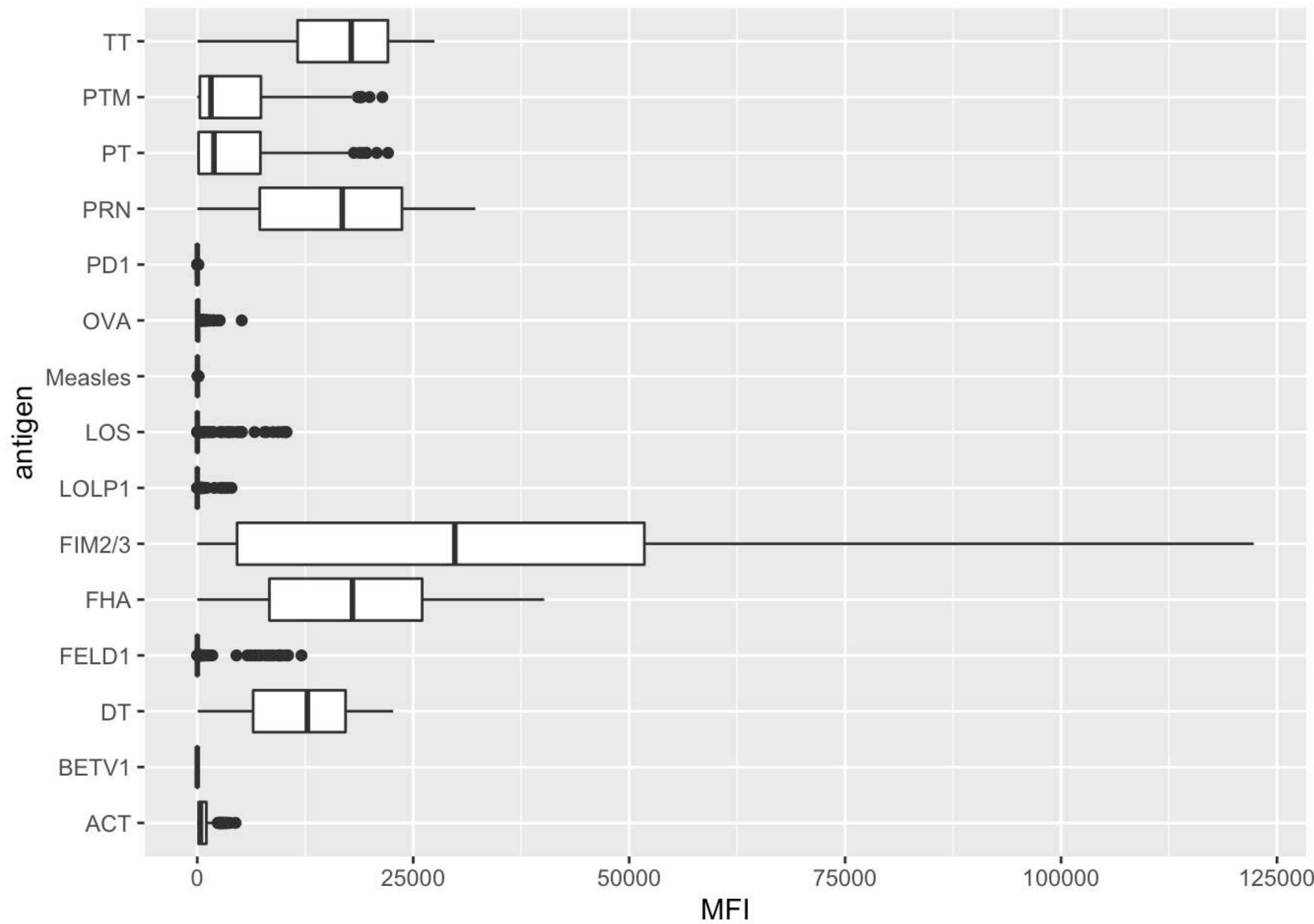
USE DPLYR ***_JOIN()** FUNCTIONS...



Meta + Experiment

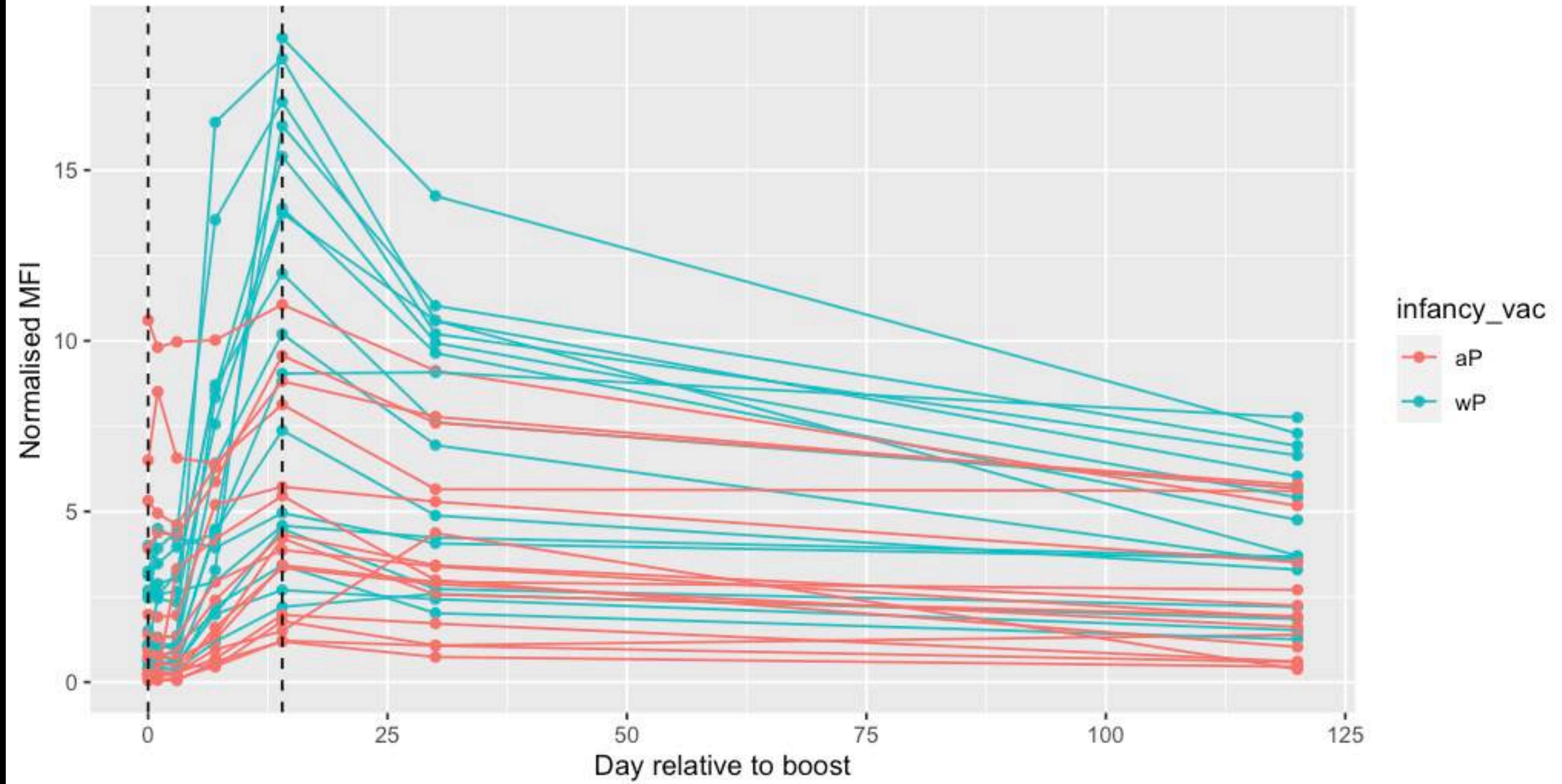


ABDATA
specimen_id
subject_id
actual_day_relative_to_boost
planned_day_relative_to_boost
specimen_type
visit
infancy_vac
biological_sex
ethnicity
race
year_of_birth
date_of_boost
dataset
isotype
is_antigen_specific
antigen
MFI
MFI_normalised
unit
lower_limit_of_detection



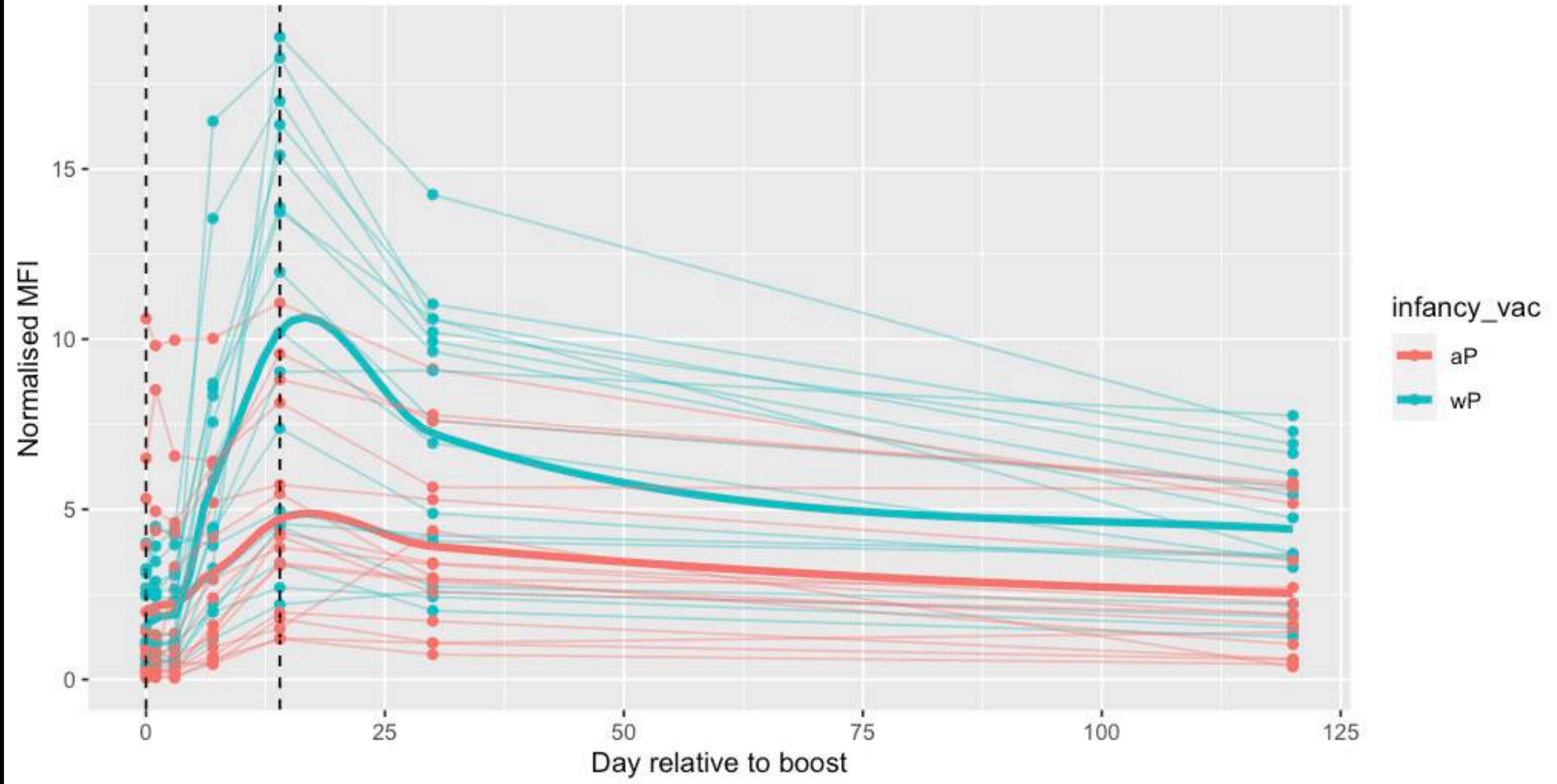
CMI-PB 2021 dataset IgG PT

Dashed lines at day 0 (pre boost) and day 14 (post boost)



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Dashed lines at day 0 (pre boost) and day 14 (post boost)



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https://www.cmi-pb.org/terminology/uniprot:Q5I8X0

fim2 - Fimbrial protein - *Bordetella pertussis* | UniProtKB | UniProt



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Terminology Browser

Fimbrial protein

Fimbrial protein Fim3

Mixture of Fim2 and Fim3

uniprot:Q5I8X0

Fimbrial prote...

<https://www.uniprot.org/uniprot/Q5I8X0>

Ontology

Class

- material entity
- molecular entity
- protein

Fimbrial protein

Annotation Property

Data Property

Object Property

Individual

Datatype

- label
 - Fimbrial protein
- CMI-PB alternative term
 - fim2
- type
 - Class
- subclass of
 - protein

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https://www.cmi-pb.org/terminology/uniprot:Q5I8X0

fim2 - Fimbrial protein - Bordetella pertussis | UniProtKB | UniProt

UniProt BLAST Align Peptide search ID mapping SPARQL UniProtKB Advanced List Search Help

Q5I8X0 · Q5I8X0_BORPT

Function

Names & Taxonomy

Proteinⁱ Fimbrial protein

Amino acids 207

Subcellular Location

Statusⁱ UniProtKB unreviewed (TrEMBL)

Protein existenceⁱ Predicted

Phenotypes & Variants

Organismⁱ Bordetella pertussis

Annotation scoreⁱ 1/5

PTM/Processing

Geneⁱ fim2

Expression

Interaction

Entry Feature viewer Publications External links History

Structure BLAST Align Download Add Add a publication Entry feedback

Family & Domains

Functionⁱ

GO Annotationsⁱ

Slimming set:

generic

Feedback Help

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Family & Domains

Sequence

Similar Proteins

Entry Feature viewer Publications External links History

BLAST Align Download Add Add a publication Entry feedback Feedback

Functionⁱ

GO Annotationsⁱ

Slimming set: generic

metabolic process
process of precursor metabolites and energy
aplication
na repair
dna recombination
chromatin organization
dna-template mediated transcription
tRNA-mediated transcription
protein folding
regulation of dna-template transcription
amino acid metabolic process
protein glycosylation
lipid metabolism
cellular compound protein transport
sulfur compound metabolic process
vitamin metabolic process
intracellular protein transport
autophagy
inflammatory response
mitochondrion organization
cytoskeleton organization
peroxisome-based movement
lysosome organization
chromosome organization
cell adhesion
establishment or maintenance of cell polarity
aging
programmed cell death
photosynthesis
mrna metabolic process
vesicle-mediated transport
reproductive system process
signaling pathway
differentiation
digestive system process
cell differentiation
rna-mediated transport
protein catabolic process
extracellular matrix organization
telomere gene silencing
cell junction organization
protein modification process
wound healing
ribosome biogenesis
cell junction organization
cilia organization
anatomical structure development
nervous system process
endocrine process
protein maturation
transmembrane transport
nucleobase-containing molecule transport
hepatocyte membrane transport
membrane transport

Cell color indicative of number of GO terms

ASPECT	TERM
Cellular Component	pilus Source:InterPro
Biological Process	cell adhesion Source:InterPro

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Similar Proteins

Subcellular Locationⁱ

UniProt Annotation GO Annotation

📍 pilus ↗

Complete GO annotation on QuickGO ↗

SIB

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UniProt Annotation GO Annotation

📍 pilus ↗

Complete GO annotation on QuickGO ↗

Fimbrium

A fimbrium or pilus is a hair-like, non-flagellar, polymeric filamentous appendage that extend from the bacterial or archaeal cell surface, such as type 1 pili, P-pili, type IV pili or curli. Pili perform a variety of functions, including surface adhesion, motility, cell-cell interactions, biofilm formation, conjugation, DNA uptake, and twitching motility.

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a. Past and future CMI-PB annual prediction challenges



	Annual prediction challenge title	Contestants	Number of subjects		Current status
			Training dataset	Test dataset	
1	First Challenge: Internal dry run	CMI-PB consortium	60 (28 aP + 32 wP)	36 (19 aP + 17 wP)	May 2022
2	Second Challenge: Invited challenge	Invited contestants	96 (47 aP + 49 wP)	22 (13 aP + 9 wP)	Announced on September 12, 2023
3	Third Challenge: Open Challenge 1	Public	118 (60 aP + 58 wP)	32 (16 aP + 16 wP)	Will be announced in April 2024
4	Fourth Challenge: Open Challenge 2	Public	150 (76 aP + 74 wP)	32 (16 aP + 16 wP)*	Will be announced in December 2024

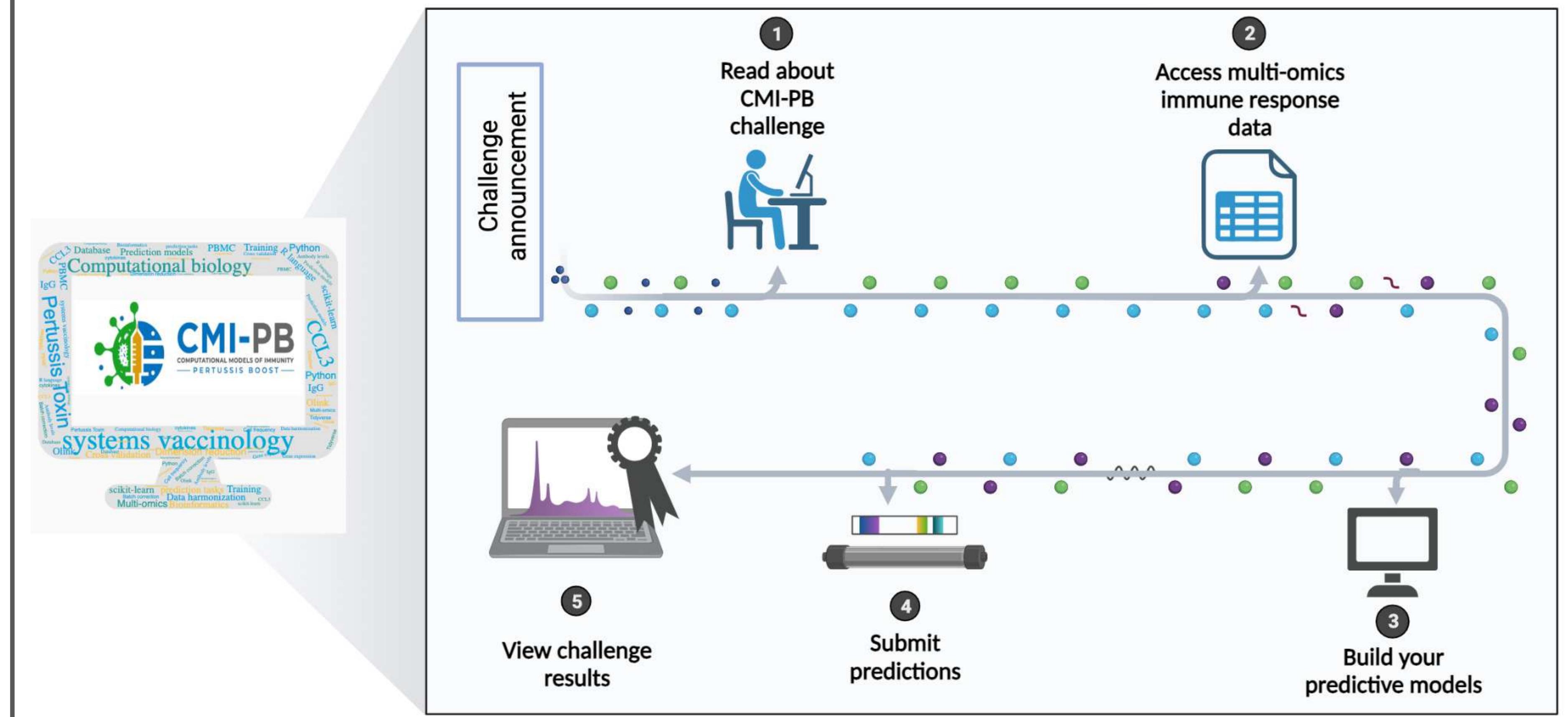
b. Prediction challenge outline



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PERTUSSIS BOOST

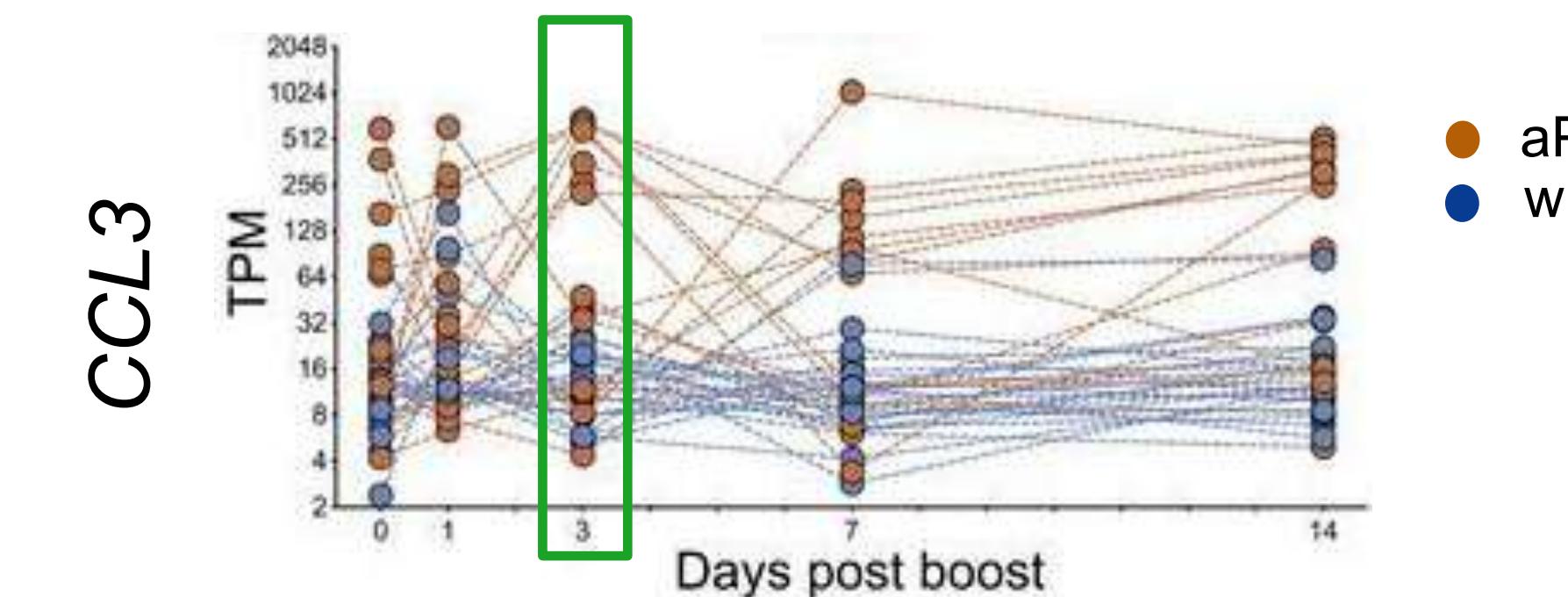
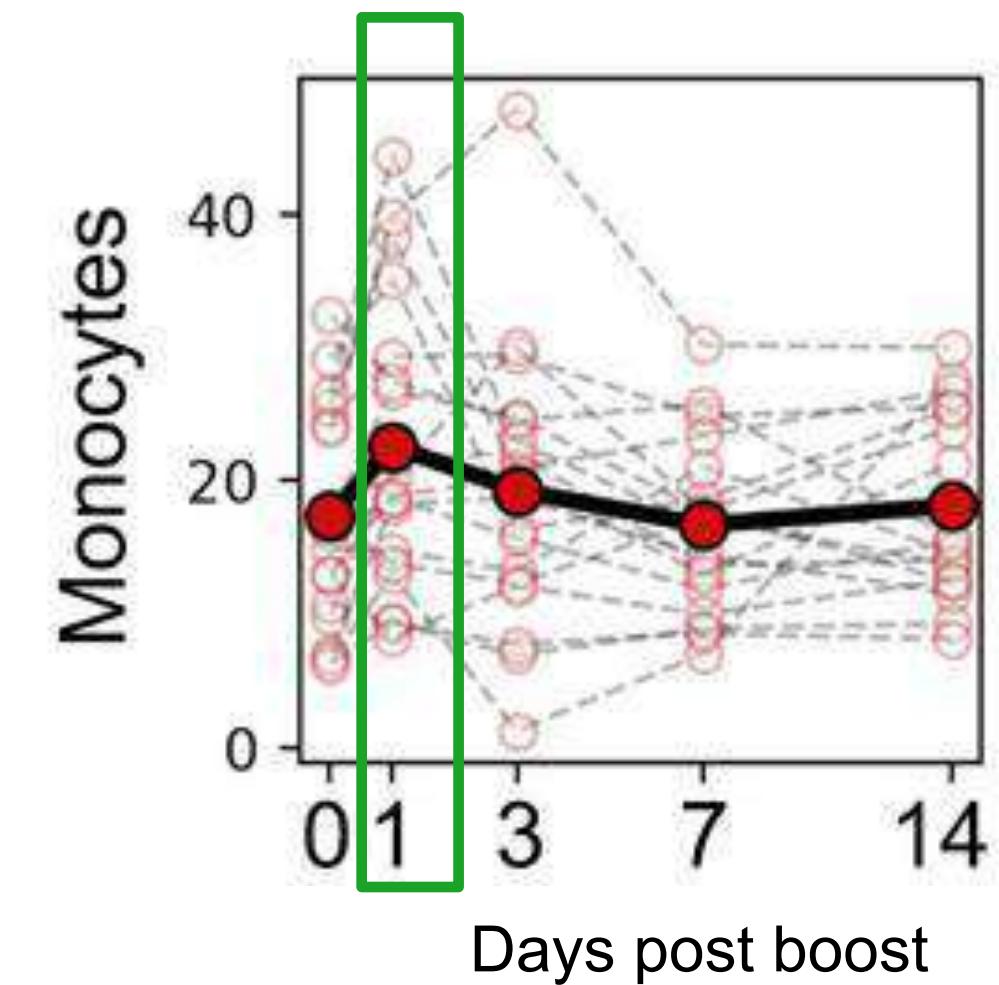
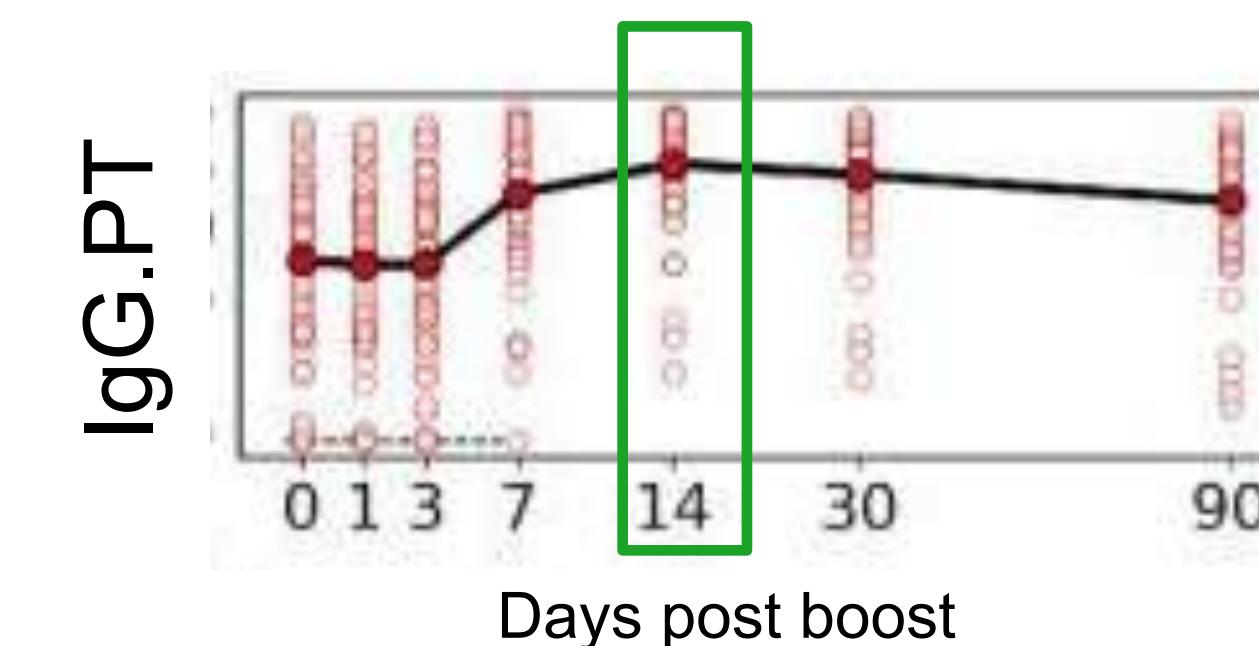
2nd CMI-PB Prediction Challenge Outline



c. Formulating prediction tasks for CMI-PB Challenge



- Previously identified **vaccine responses** are formulated as prediction tasks*
- General vaccine responses:**
 - Plasma IgG levels increased at day 14 post-booster vaccination compared to baseline
 - Increase in the percentage of monocytes on day 1 post-booster than baseline
- aP/wP specific vaccine responses:**
 - A subset of aP-primed individuals showed an increased expression of proinflammatory genes, including CCL3 at day 3 post-booster vaccination



* A system-view of *Bordetella pertussis* booster vaccine responses in adults primed with whole-cell versus acellular vaccine in infancy

c. Formulating prediction tasks for CMI-PB Challenge



List of tasks

1) Antibody titer tasks

1.1) Rank the individuals by IgG antibody titers against pertussis toxin (PT) that we detect in plasma 14 days post booster vaccinations.

predicted values

1.2) Rank the individuals by fold change of IgG antibody titers against pertussis toxin (PT) that we detect in plasma 14 days post booster vaccinations compared to titer values at day 0.

predicted fold-change values

2) Cell frequencies tasks

2.1) Rank the individuals by predicted frequency of Monocytes on day 1 post boost after vaccination.

2.2) Rank the individuals by fold change of predicted frequency of Monocytes on day 1 post booster vaccination compared to cell frequency values at day 0.

3) Gene expression tasks

3.1) Rank the individuals by predicted gene expression of CCL3 on day 3 post-booster vaccination.

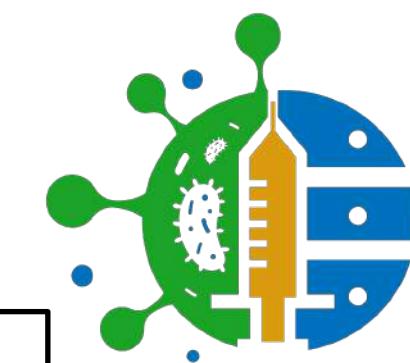
3.2) Rank the individuals by fold change of predicted gene expression of CCL3 on day 3 post booster vaccination compared to gene expression values at day 0.

Example of Rankings

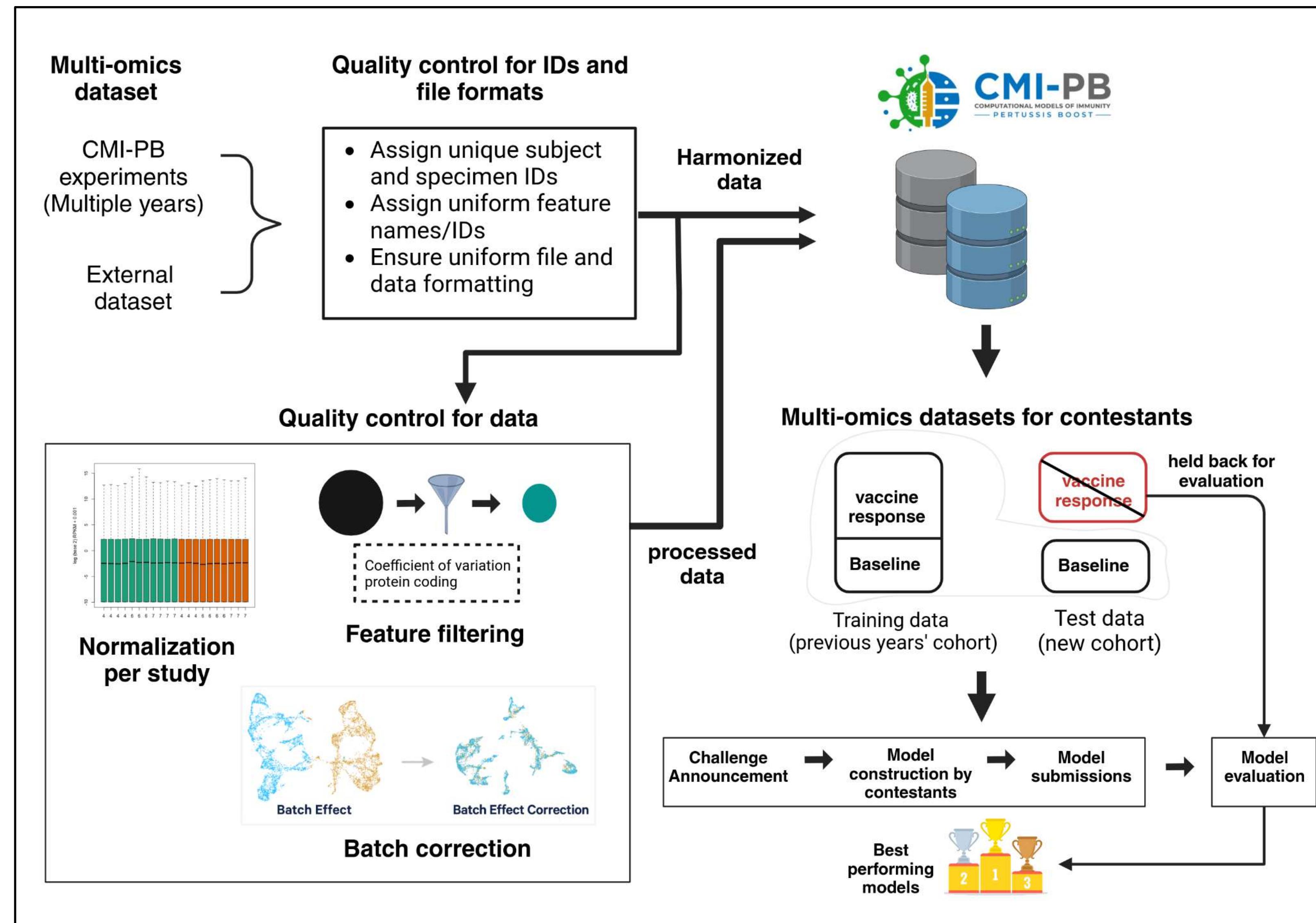
Subject ID	Predicted value	Rank
101	2.9	4
102	9.1	1
103	1.2	5
104	4.5	3
105	4.7	2

The ultimate goal is to model as many of the tasks as possible. However, contestants are not required to submit answers for all tasks.

d. Overview of the CMI-PB Challenge data



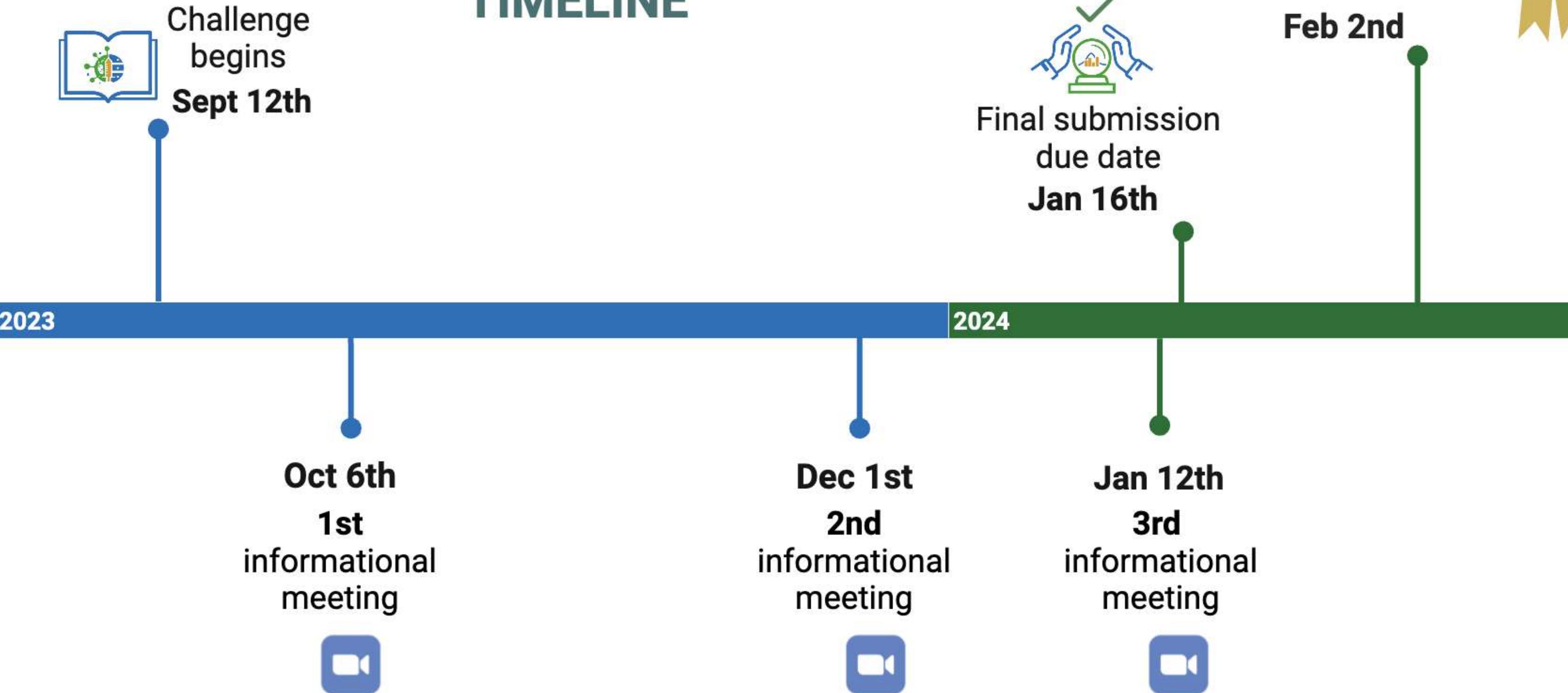
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Challenge related information and Data access is provided via the CMI-PB website



CMI-PB PREDICTION CHALLENGE TIMELINE



The CMI-PB team



Kleinstein Lab (Yale)



- Expertise: A combination of "big data" analysis and immunology domain.
- Collaborating on data and models being released to the community to support reproducibility and the prediction contest, and also participate in the prediction challenge.

Steven Kleinstein
Jeremy Gygi
Leying Guan
Anna Konstorum

Grant Lab (UCSD)



- Expertise: the use of computational approaches, based on both biophysics and bioinformatics, to study the structure, function and evolution of key biological macromolecules.
- Dr. Grant will engage and advise over 40 biology graduate students in the CMI-PB Prediction Challenge.

Barry Grant

Ay Lab (LJI)



- Expertise: Development of bioinformatics tools that utilize high-dimensional and high-throughput datasets to deduce insights into chromatin conformation, genetic variation, and the regulation of gene expression.
- The Ay lab is focused on developing predictive machine learning models, which will serve as examples and baselines for participants in the CMI-PB challenge.

Ferhat Ay
Joaquin Reyna

Peters Lab (LJI)



- Expertise: Both experimental and computational studies to better understand human immune responses in the context of infectious diseases, allergy, cancer and vaccines.
- The team is responsible for the generation of experimental data, making it accessible in a central and standardized fashion, and coordinating the creation and coordination of the prediction contest.

Bjoern Peters
Jason Greenbaum
James Overton
Brendan Ha

Pramod Shinde
Mari Kojima
Rasteh Haji Kazem Nili

Jiyeun Lee
Lisa Willemsen
Shelby Orfield

And thank you to the Sette Lab, Crotty lab, LJI Clinical Core, LJI Bioinformatics Core

The CMI-PB team members



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Bjoern Peters



Steven Kleinstein



Ferhat Ay



Barry Grant



Shane Crotty



Alessandro Sette



Pramod Shinde



Shelby Orfield



Lisa Willemsen



Leying Guan



Joaquin Reyna



Mari Kojima



Ferran Soldevila



Rasteh Nili



Jason Greenbaum



Brendan Ha



Jiyeun Lee



Ricardo De Silva Antunes



Jeremy Gygi



Anna Konstorum