CMI Pertussis Boost

Class 18: Mini Project

Barry Grant

UC San Diego

http://thegrantlab.org

Exploring Pertussis Vaccination Through Systems Vaccinology

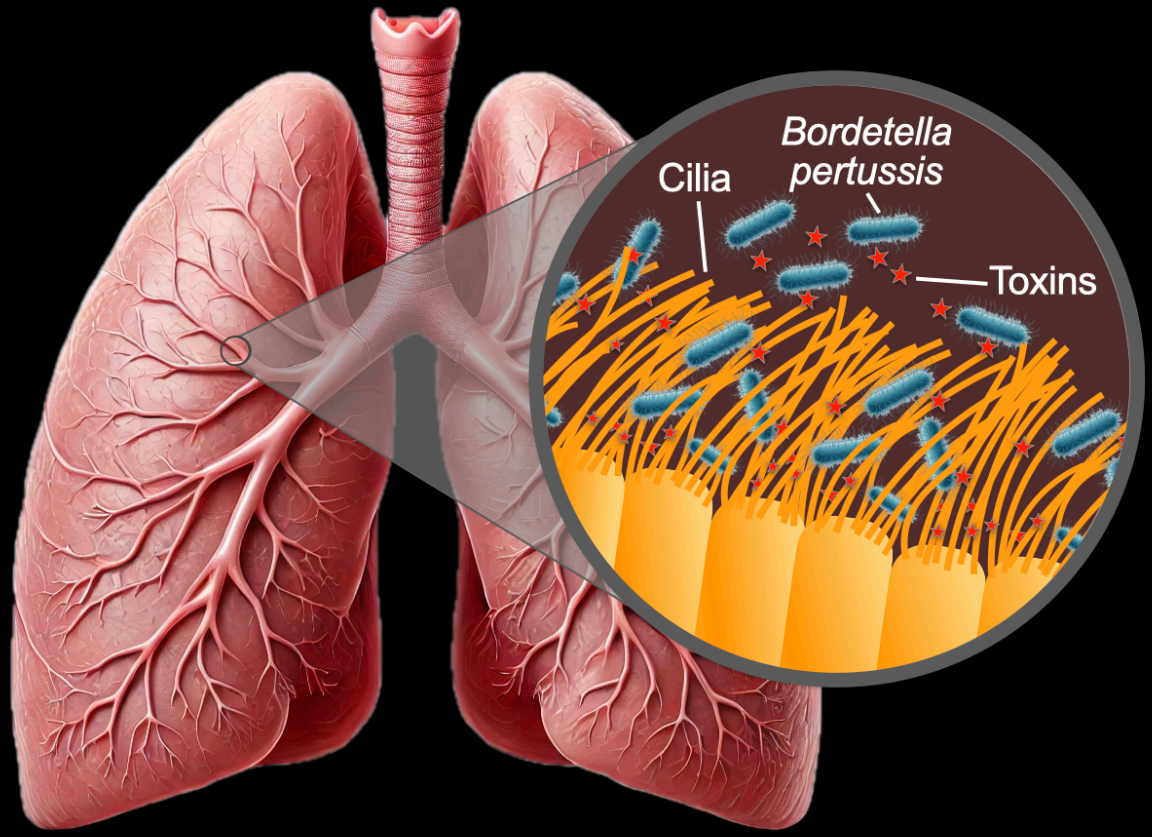
Pertussis is a leading causes of vaccine-preventable deaths

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

- Over 16 million cases & 200,000 associated infant deaths annually. (Blake *et al.* 2016)
- Can infect people of all ages but is most severe and life threatening for infants under a year old. (Video link)
- Transmission occurs primarily through bacteria laden respiratory droplets produced when an infected individual coughs and sneezes.

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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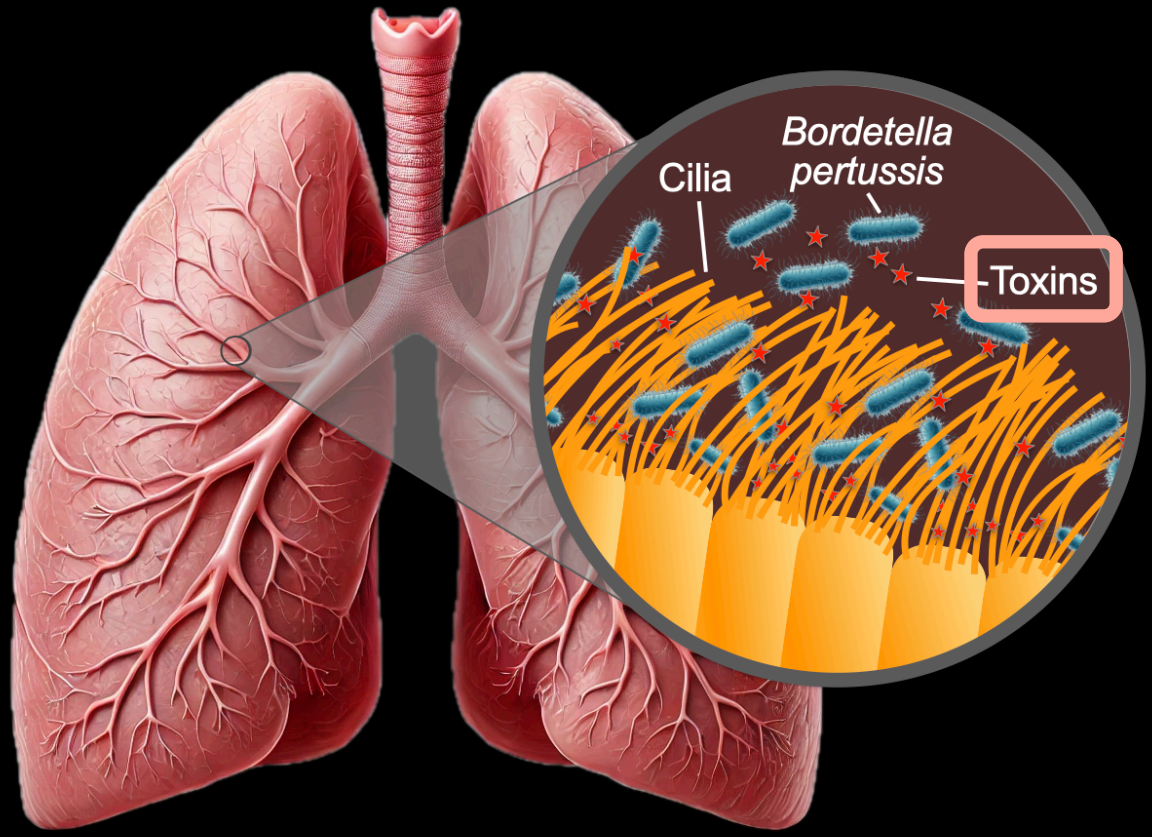
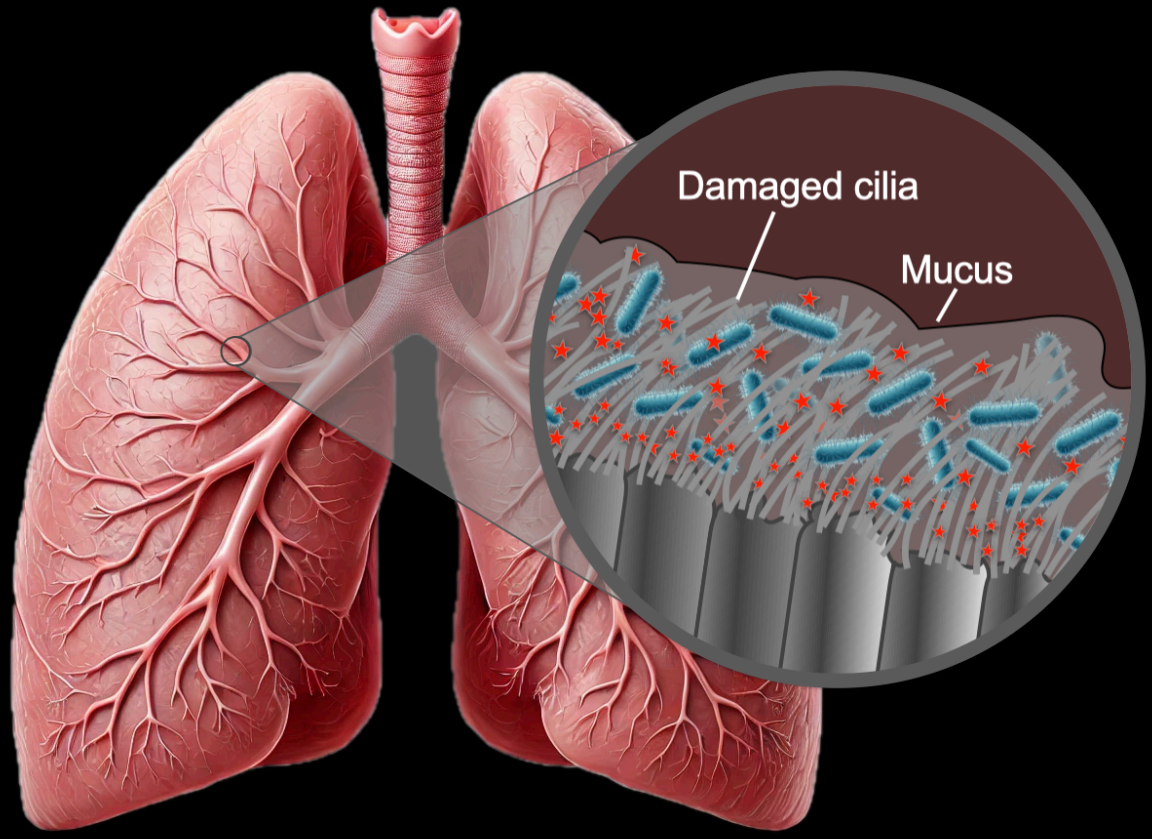


More details >

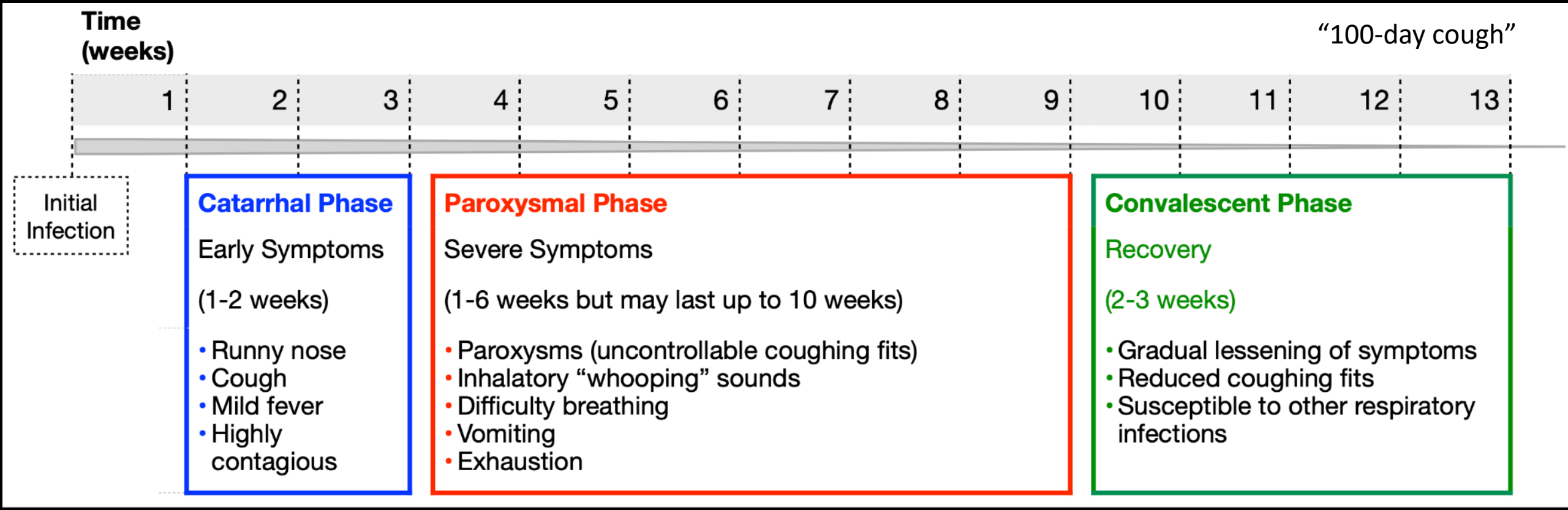
Pertussis is primarily a toxin-mediated disease

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



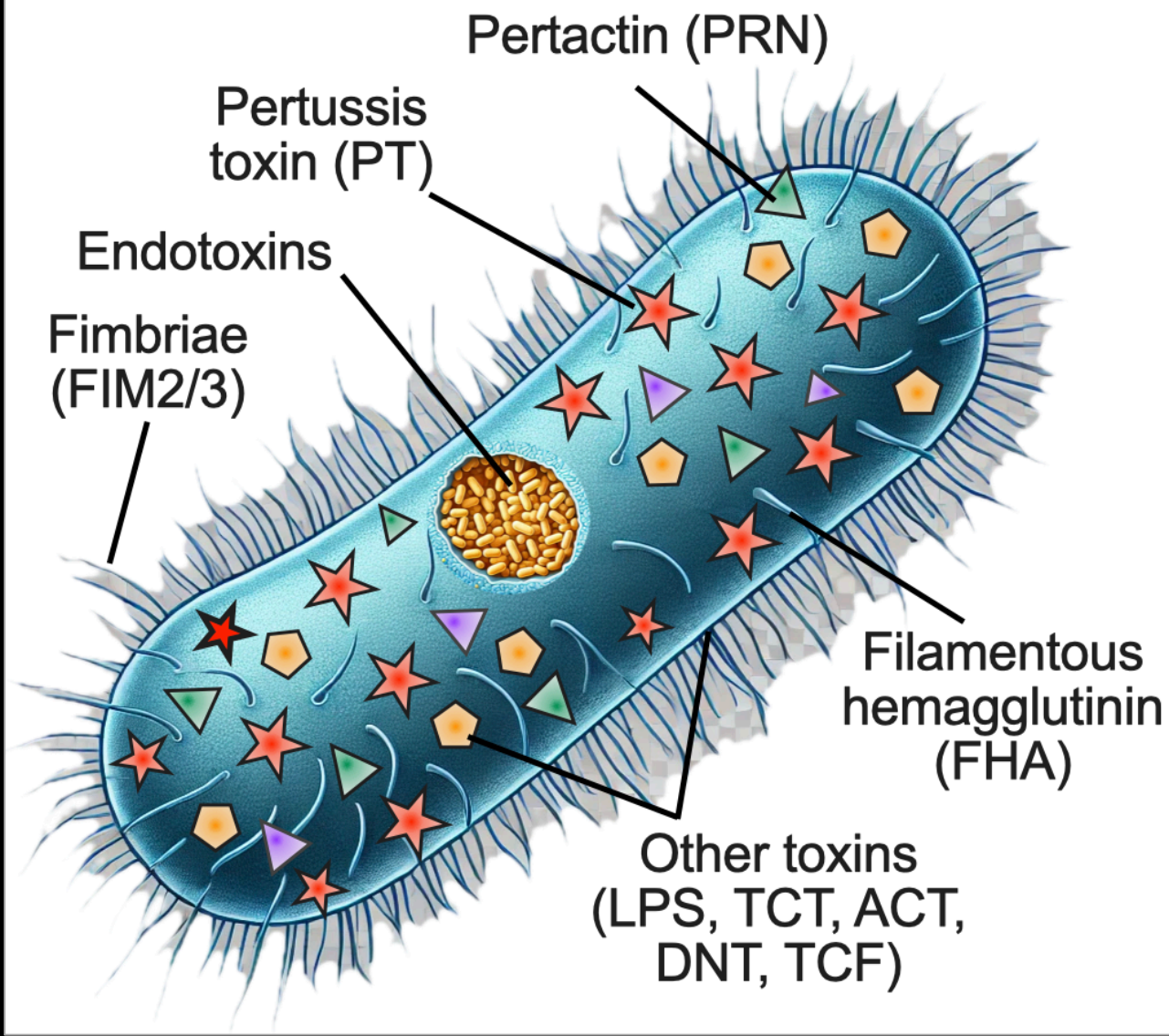
More details >

Pertussis develops in three main phases

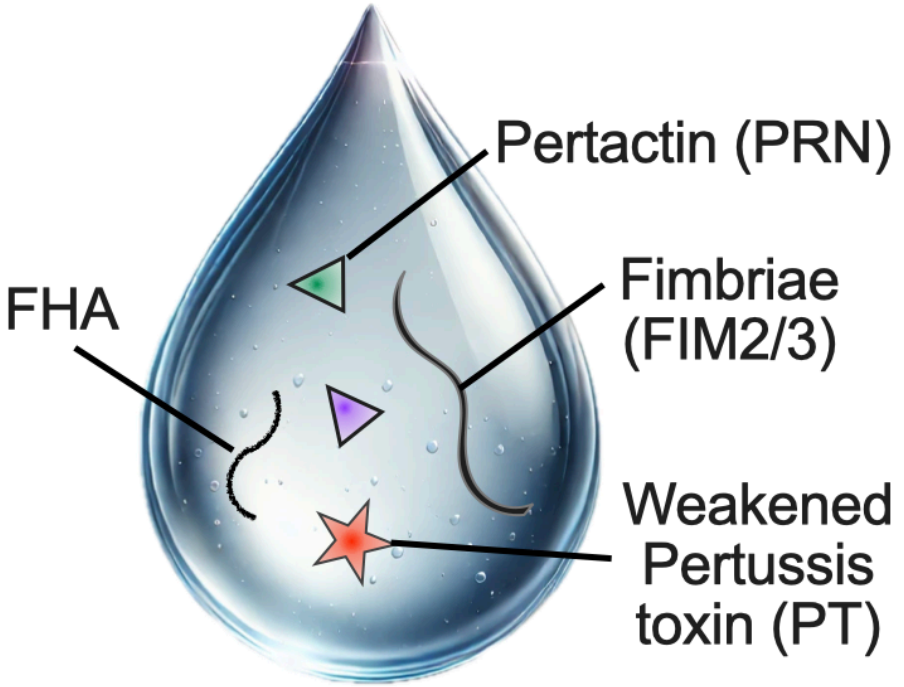


Disease progression details >

Whole-cell (wP) vaccine



Acellular (aP) vaccine



Fascinating history

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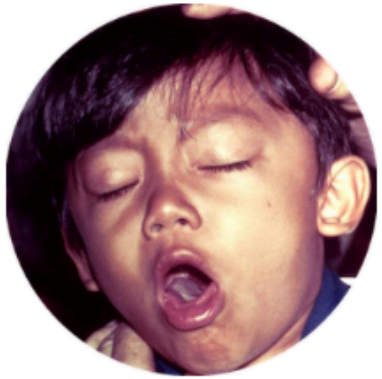
1578

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

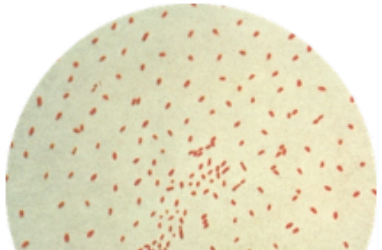


The Name "Pertussis" First Appears

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, tusis perennis, tussis epidemica infantum, and tusis quinta.

Read more

1900

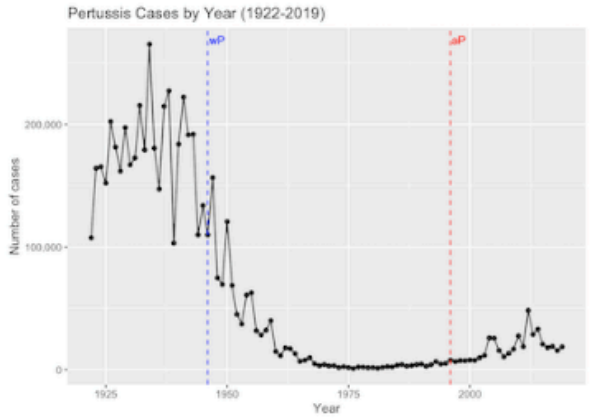


[Interactive Timeline >]

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.



1970

Decline of Whooping Cough

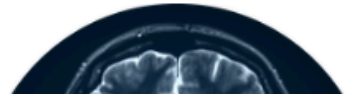
First Whole-cell Pertussis Vaccine Tested on a Wide Scale

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 made compulsory in some states by the end of the decade.



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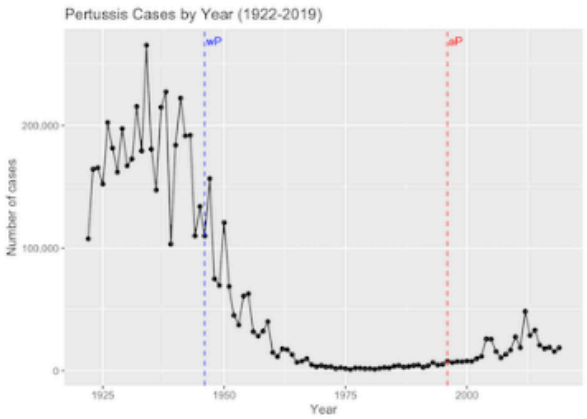

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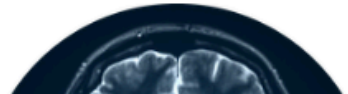
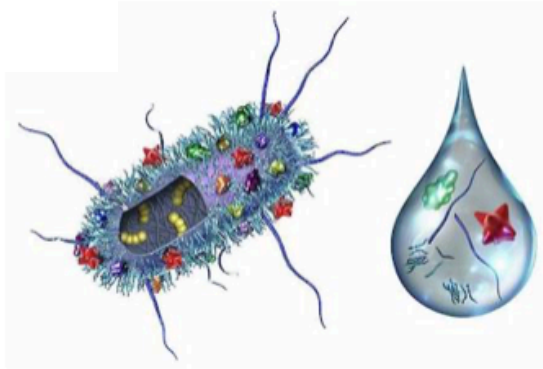


Interactive Timeline >

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.

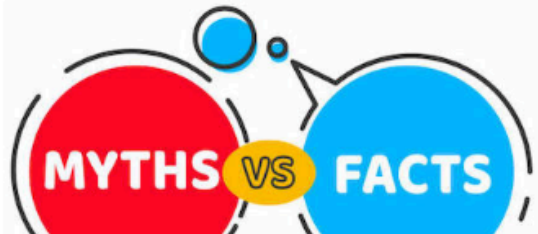
Read more

1984

Liability

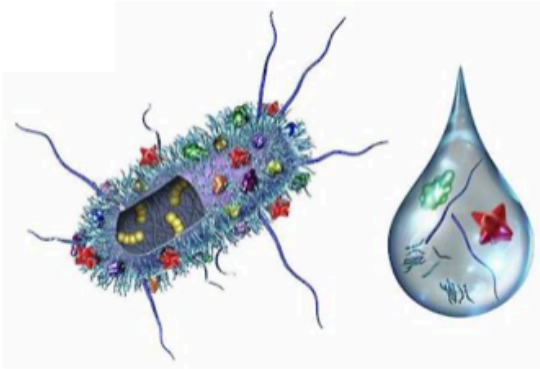
By 1984 DPT vaccine manufacturers had a hard time obtaining liability insurance. By the end of the year, only one DPT manufacturer remained. Scientists respond by ramping up development and testing of safer new acellular pertussis vaccines. These would replace the older whole cell vaccine in many countries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

1985



Timeline >

1981



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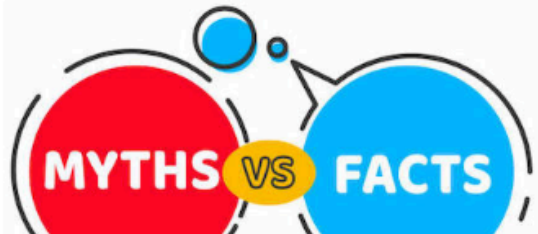
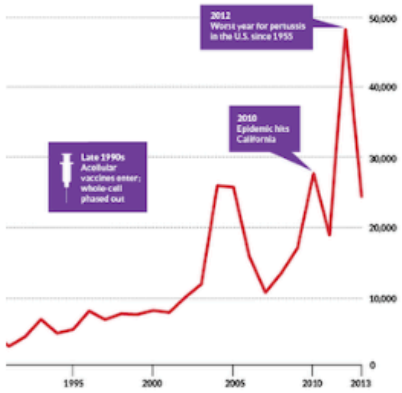


Timeline >

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

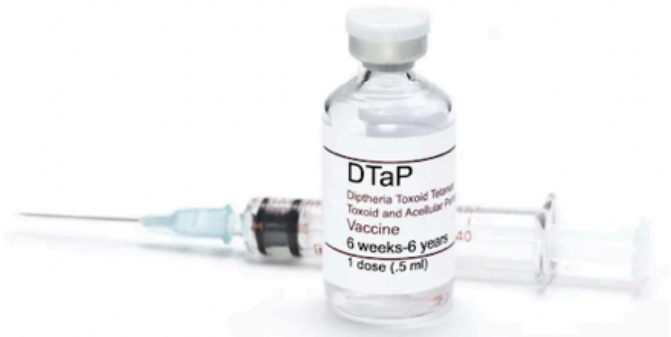


Pertussis Outbreaks

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

1992



aP Vaccine Approved in the U.S.

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

2020

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PERTUSSIS BOOST

CMI-PB Project

A new systems vaccinology project is launced 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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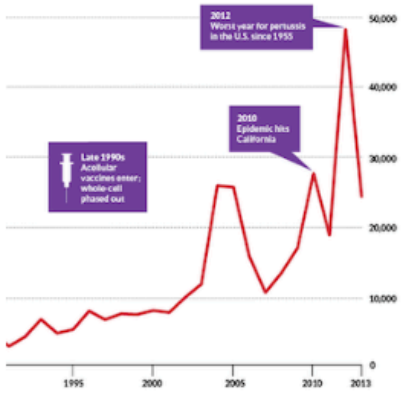

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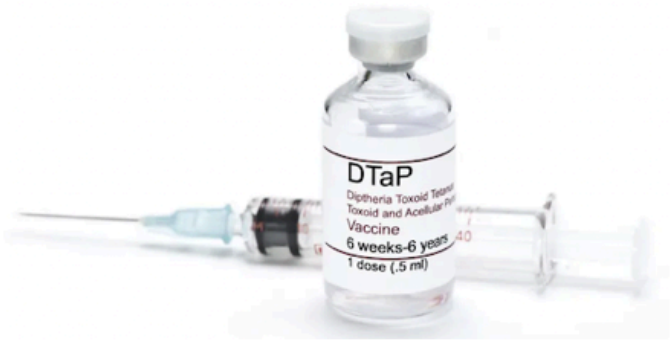

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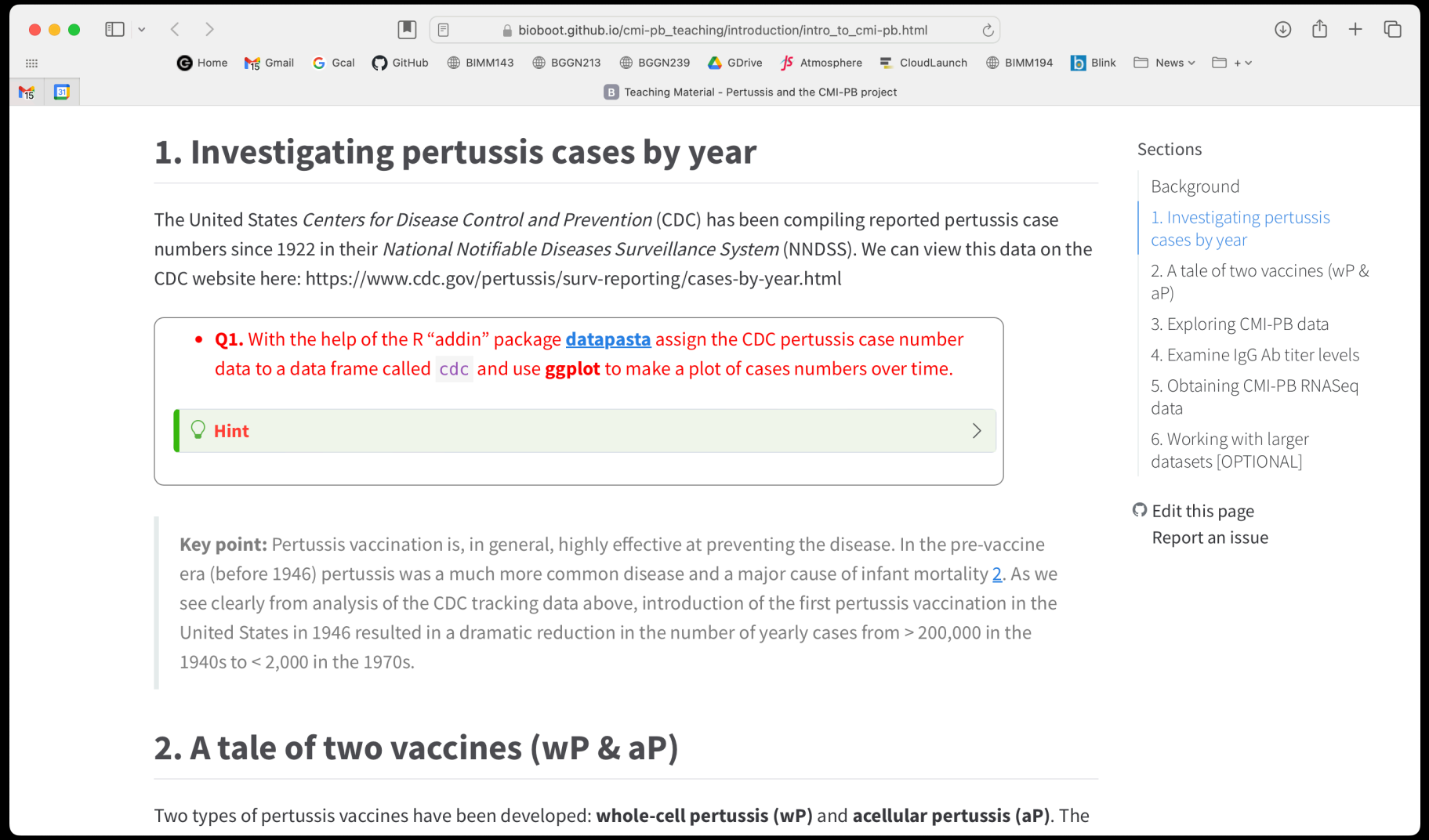
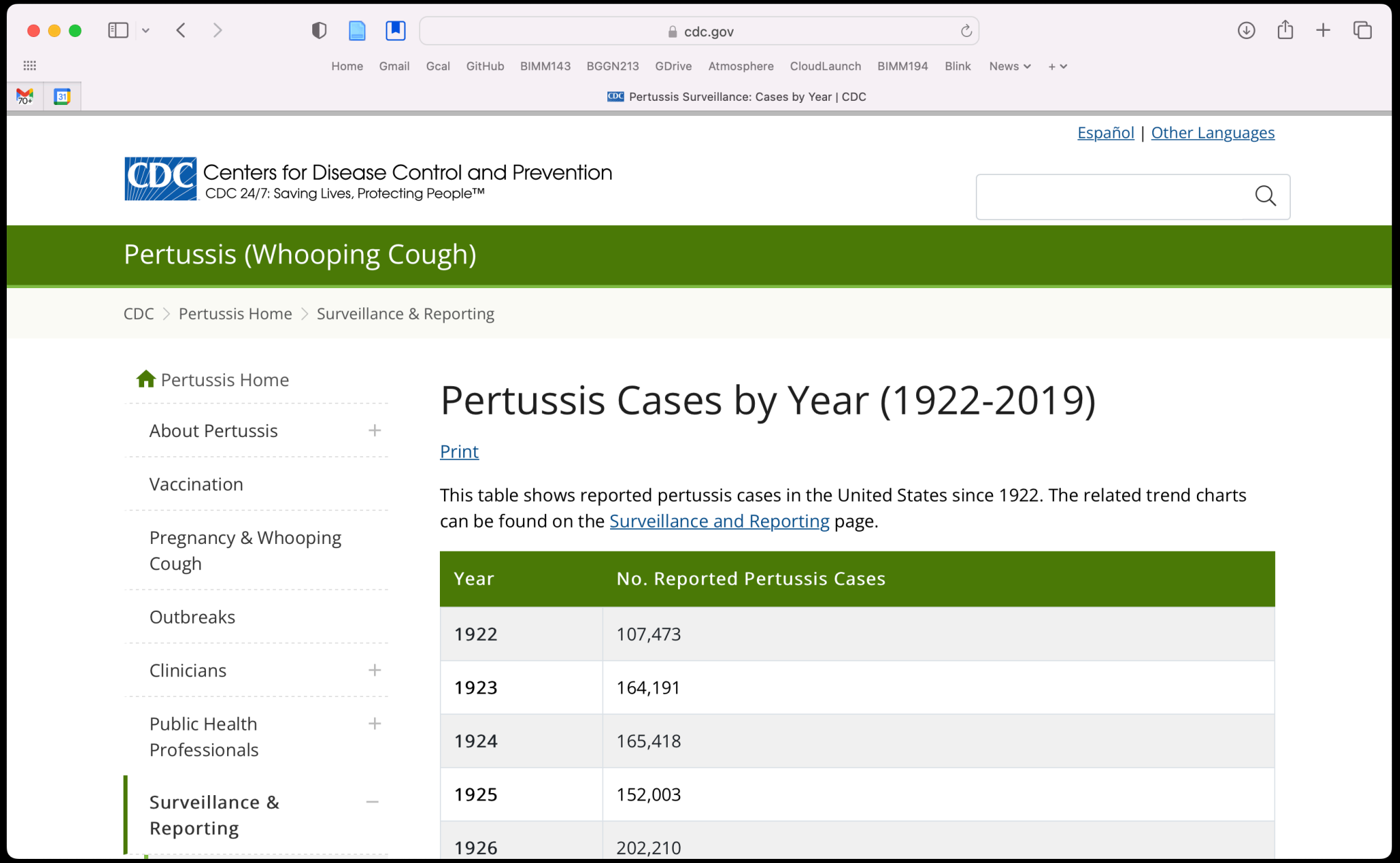
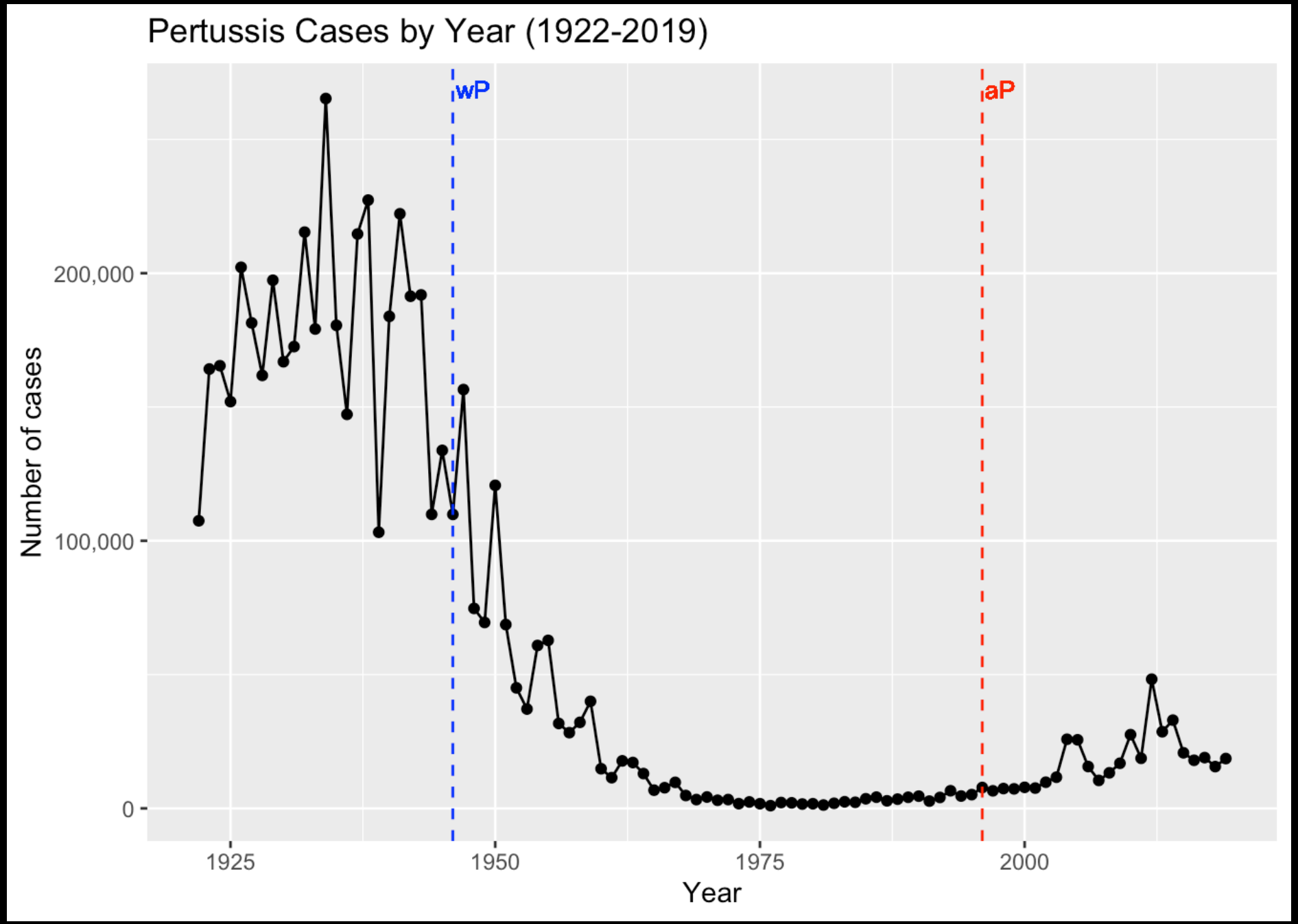
Hands-On Student Worksheet



https://tinyurl.com/pertussiscdc




Pertussis Cases by Year (1922-2019)
wP
aP
200,000
100,000
0
Number of cases
1925
1950
1975
2000
Year

Side-Note: Using ggplot with custom y-axis scale

```
library(ggplot2)

base <- ggplot(cdc) +
  aes(Year, Cases) +
  geom_point() +
  geom_line() +
  labs(title="Pertussis Cases by Year (1922-2019)", y="Number of cases") +
  scale_y_continuous(labels = scales::label_comma())

print(base)
```

2024 numbers: **35,493**

Weekly cases* of notifiable diseases, United States, U.S. Territories, and Non-U.S. Residents week ending December 28, 2024 (Week 52)

(Accessible Version: https://wonder.cdc.gov//nndss/static/2024/52/2024-52-table990.html)

Reporting Area	Pertussis			
	Current week	Previous 52 weeks Max †	Cum YTD 2024 †	Cum YTD 2023 †
New Mexico	-	9	101	41
Utah	1	13	263	238
Wyoming	-	0	-	-
Pacific	16	254	5,508	799
Alaska	5	48	595	26
California	4	68	1,775	643
Hawaii	-	7	70	3
Oregon	5	50	1,039	40
Washington	2	139	2,029	87
U.S. Territories	-	3	57	36
American Samoa	-	0	-	-
Commonwealth of Northern Mariana Islands	-	0	-	-
Guam	-	1	5	-
Puerto Rico	-	3	52	36
U.S. Virgin Islands	-	0	-	-
Non-U.S. Residents	-	1	1	-
Total	212	1,619	35,493	7,099

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 detals >

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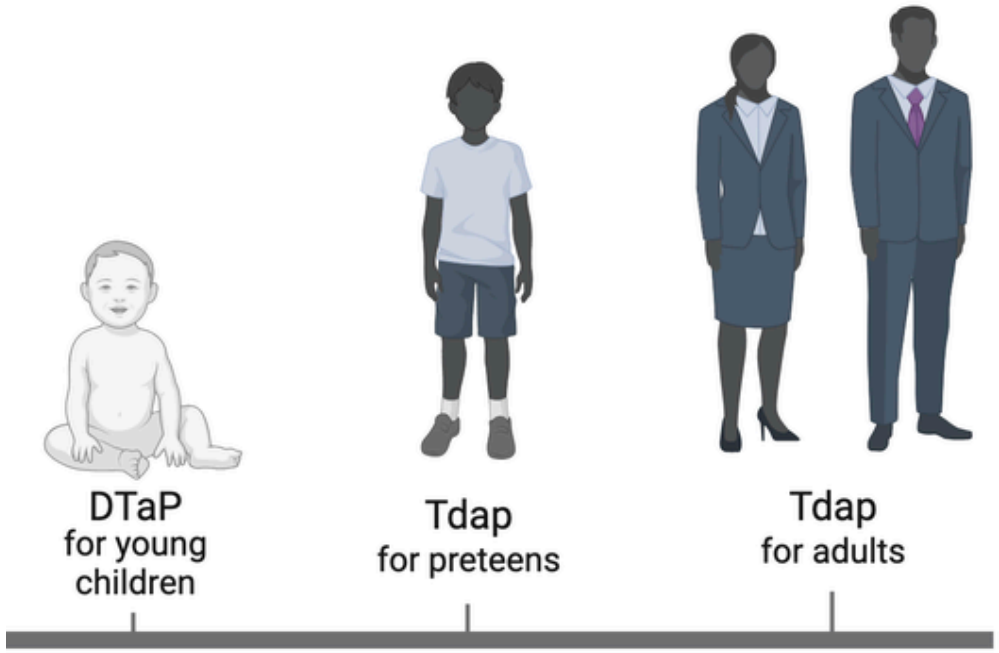
The two aP vaccine formulations (DTaP and Tdap) differ in their concentrations of Pertussis derived antigens.

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

More detals >

Major **aP** vaccines (US)



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

- 11 through 12 years

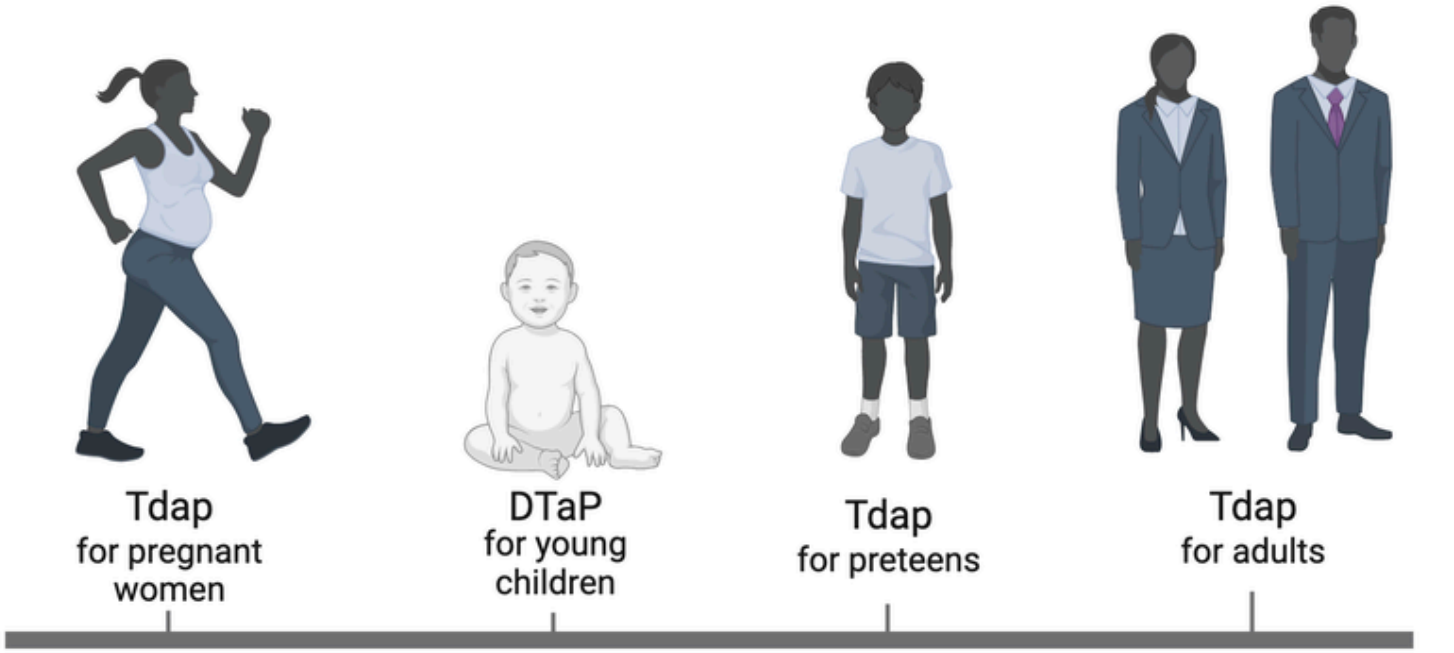
[From **2005**]

- Anytime for those who have never received it
- Subsequent boosters at 10 year intervals following initial vaccine

Source: Centers for Disease Control

More detals >

Major **aP** vaccines (US)



Tdap
for pregnant women

- During the 27-36th week of each pregnancy

[From **2011**]

DTaP
for young children

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

Tdap
for preteens

- 11 through 12 years

Tdap
for adults

- Anytime for those who have never received it
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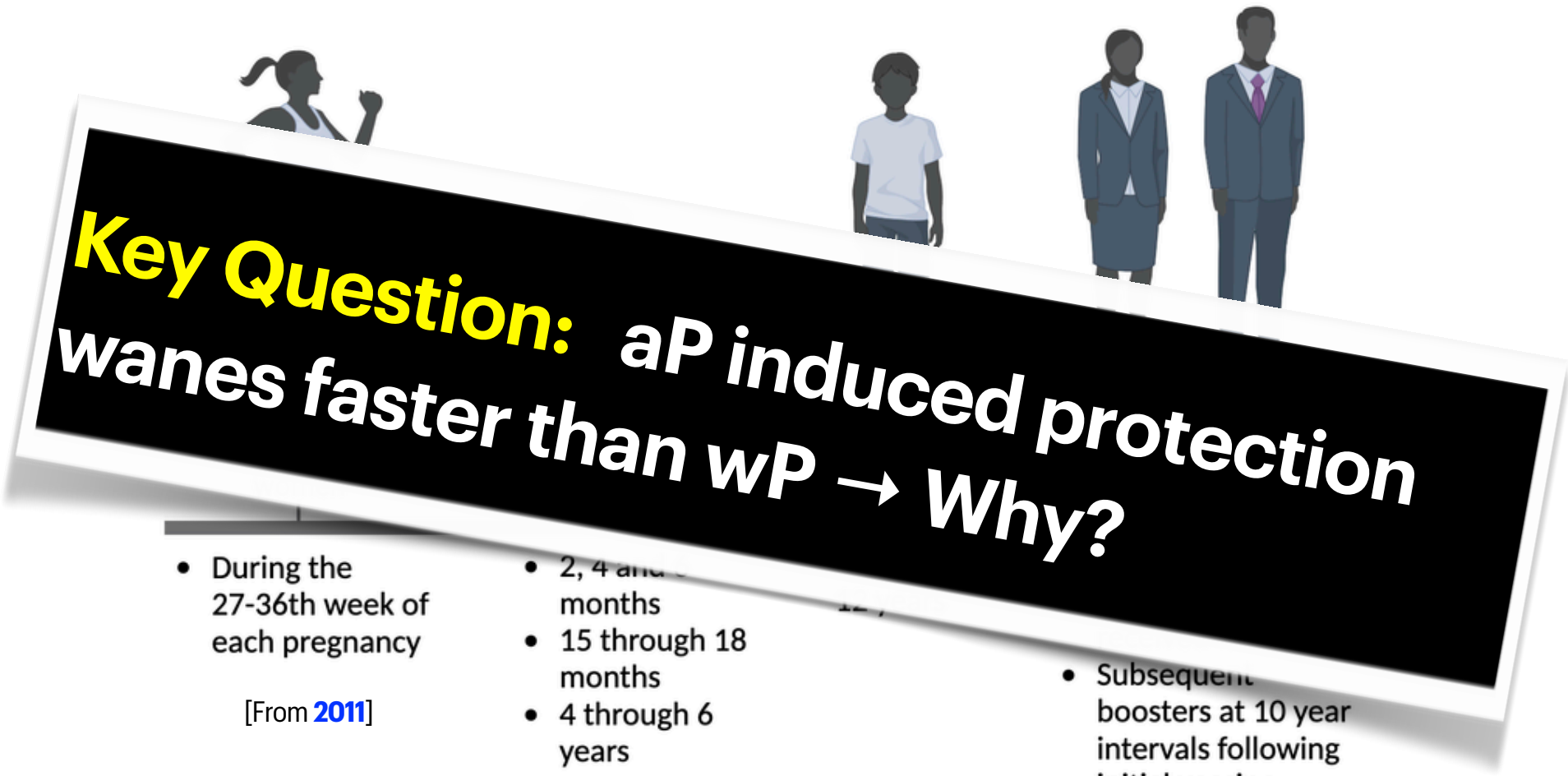
More detals >

Major **aP** vaccines (US)



Key Question: aP induced protection wanes faster than wP → Why?

- During the 27-36th week of each pregnancy

[From **2011**]

- 2, 4 and [illegible] months
- 15 through 18 months
- 4 through 6 years

- Subsequent boosters at 10 year intervals following initial vaccine

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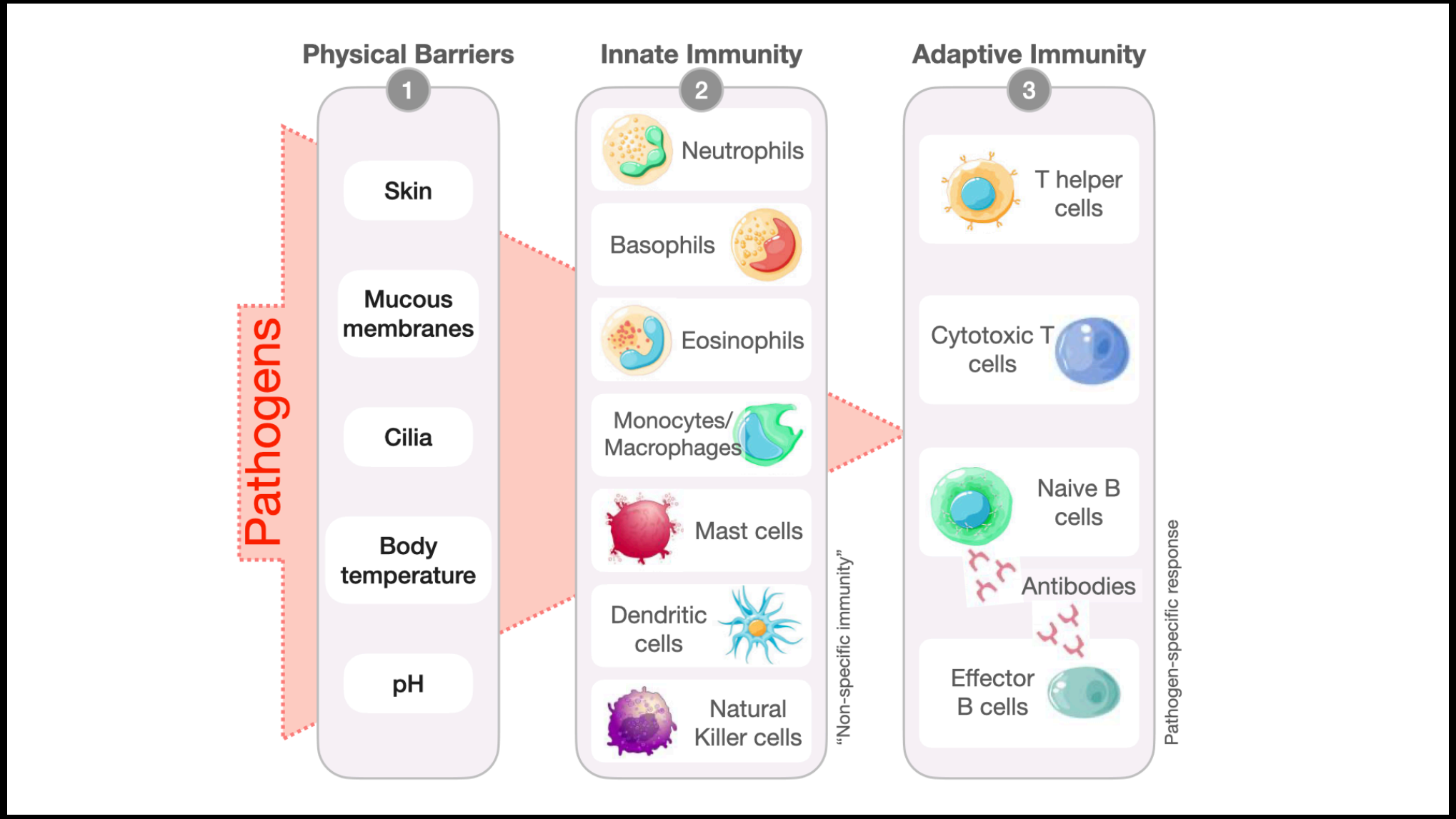
More detals >

Vaccine development exploits adaptive immunity



The adaptive immune response is antigen specific & can be long lasting

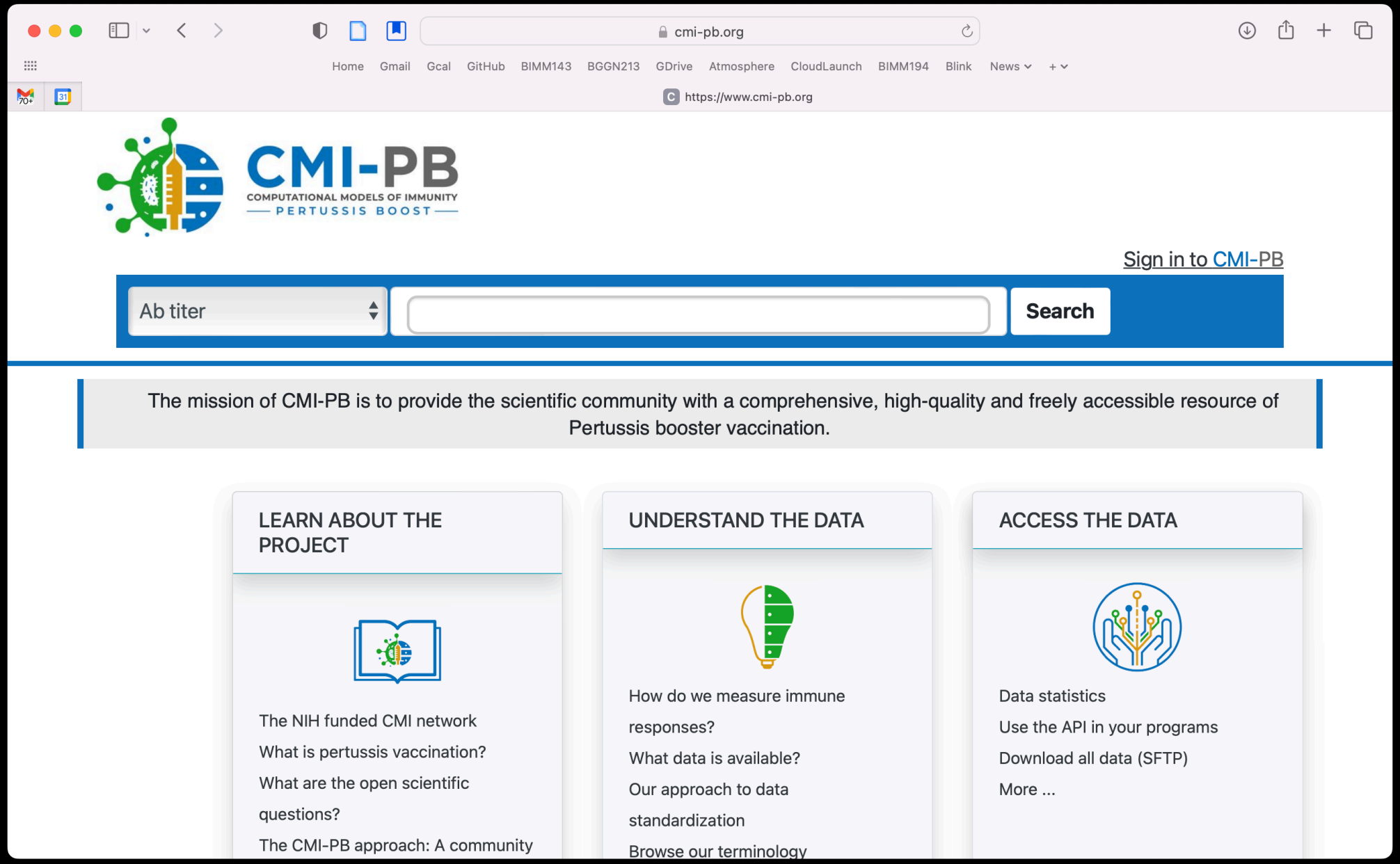
- Adaptive immune defenses are:
  - Mediated primarily by **T cells**, **B cells** and **antibodies**.
  - Specific for particular **antigens** (foreign substance or molecule) and are specialized to provide the best protection.
  - Diverse in their specificity.
  - Enhance with each repeated exposure (express **Immunologic memory**) providing lasting protection from future challenges).
  - Capable of self/non-self recognition.

Antibodies

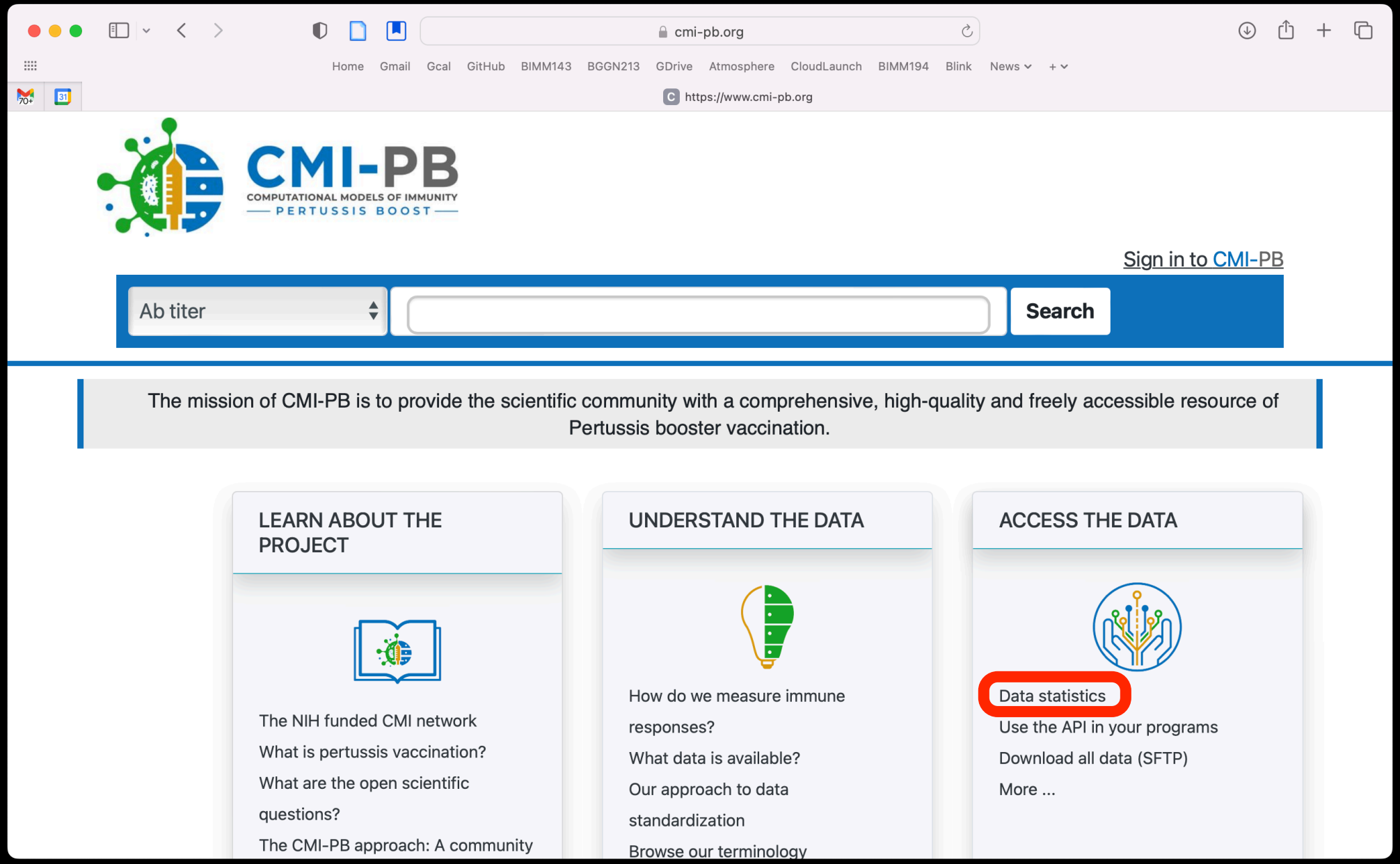
Y shaped proteins, made by B cells, that bind specific antigens to sequester & neutralize germs & activate other immune cells.

Major types include:

- **IgG**: The most abundant antibody in blood. With four sub-classes (IgG1 to IgG4) crucial for long-term immunity and responding to bacterial & viral infections.
- IgA: Found primarily in mucous membranes and body secretions like saliva and breast milk.
- IgM: The first antibody produced in response to an infection, important in early immune responses.
- IgE: Involved in allergic reactions and defense against parasitic infections.

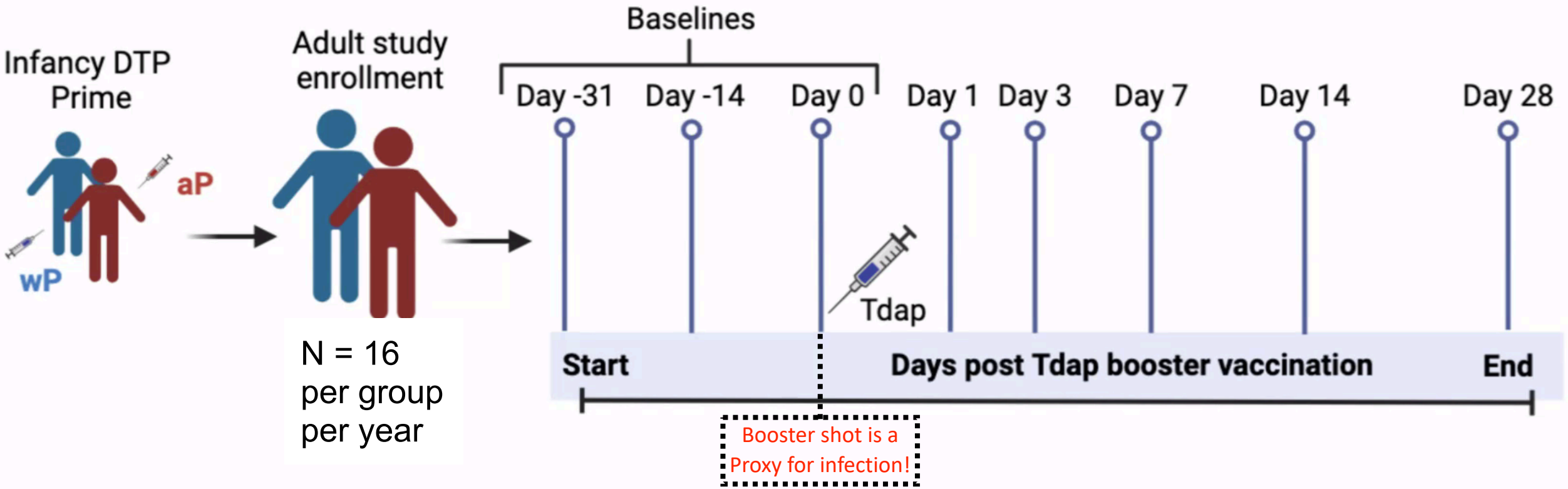


https://www.cmi-pb.org/

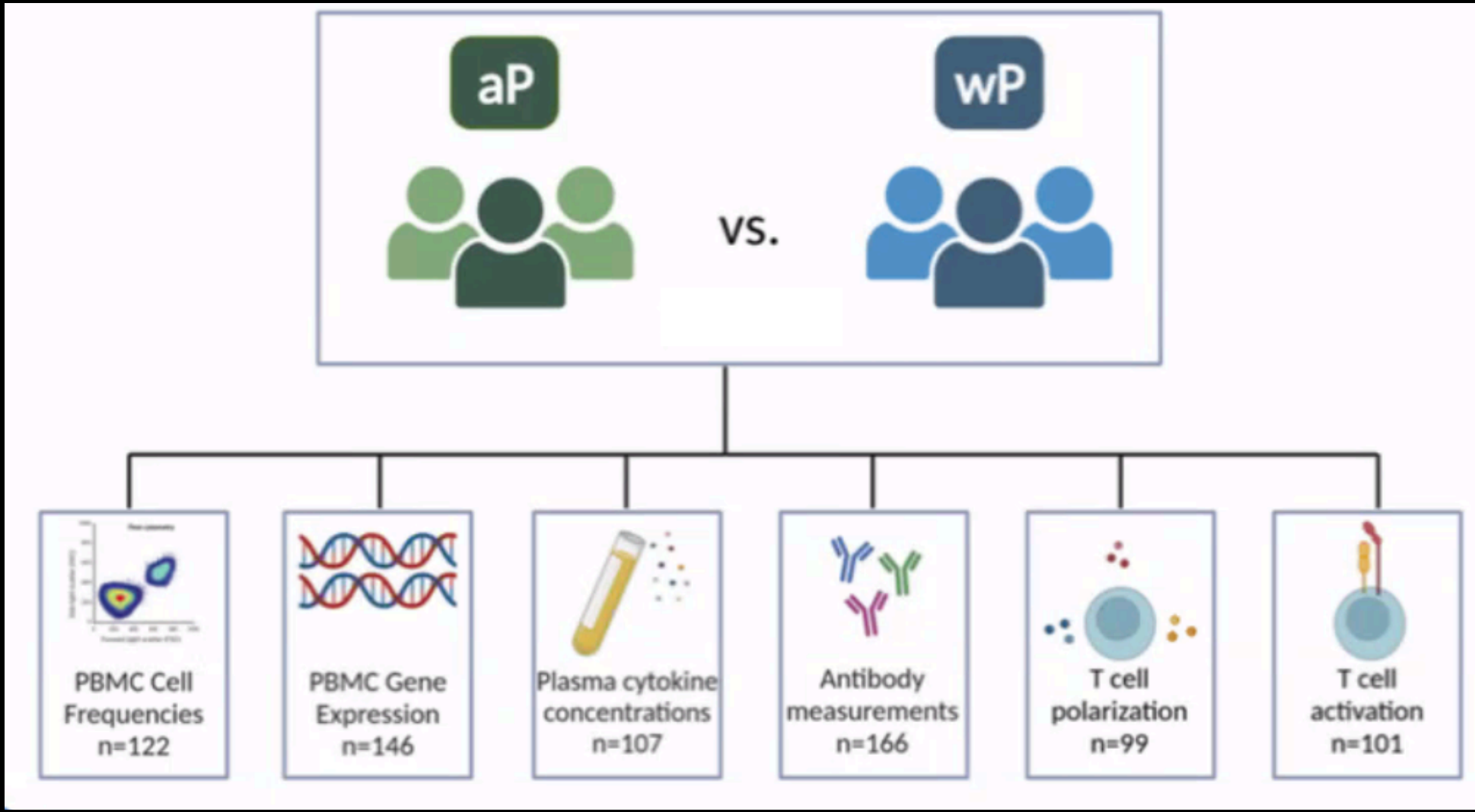


https://www.cmi-pb.org/

Blood samples are taken at different time-points both pre- and post booster vaccination



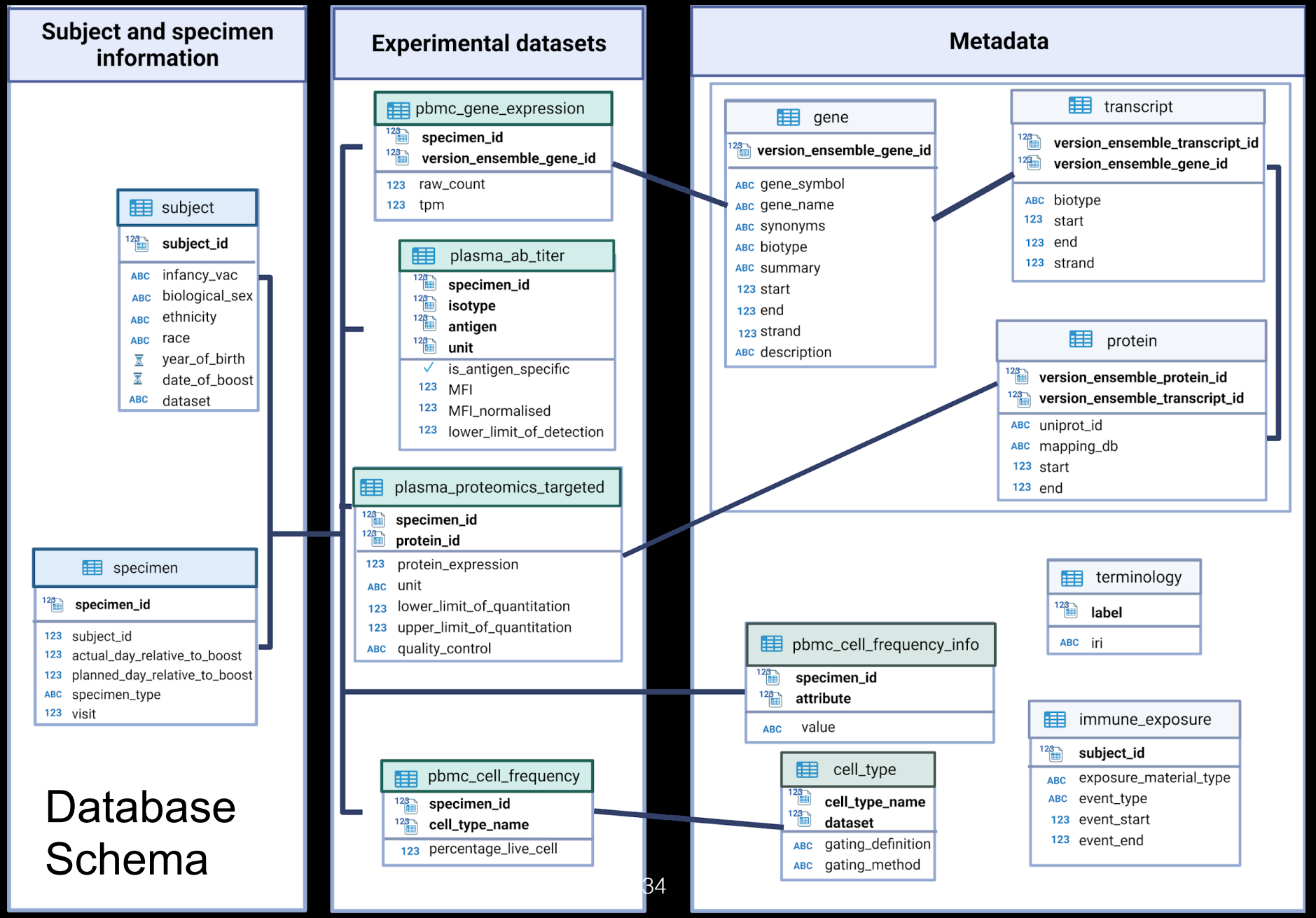
These samples undergo multi-omics characterization



This includes:

- PBMC cell frequencies by flow cytometry
  - Total of 37 distinct cell populations
- Plasma antigen-specific antibody titers
  - 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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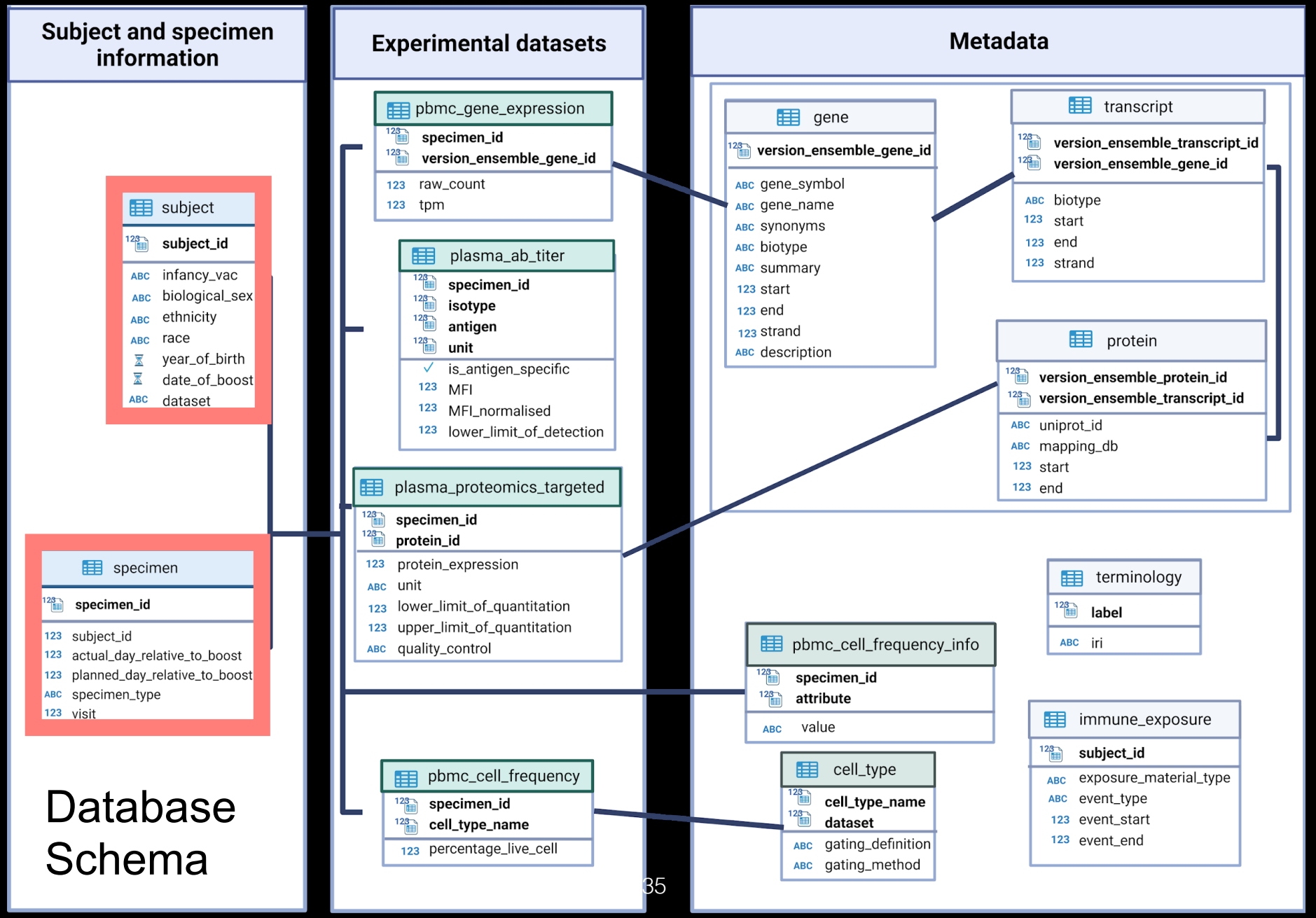

Database Information Tables

SUBJECT
subject_id
infancy_vac
biological_sex
ethnicity
race
year_of_birth
date_of_boost
dataset

SPECIMEN
specimen_id
subject_id
actual_day_relative_to_boost
planned_day_relative_to_boost
specimen_type
visit

Side Note: Dates and times…

Image credit: XKCD https://xkcd.com/1179/

Database Information Tables

SUBJECT
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race
year_of_birth
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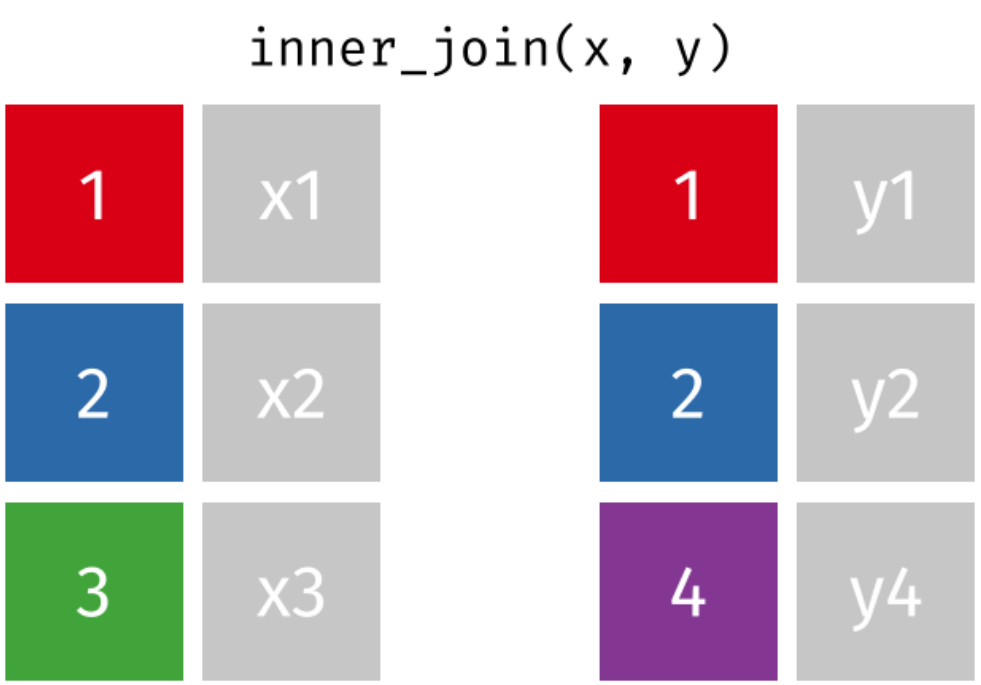
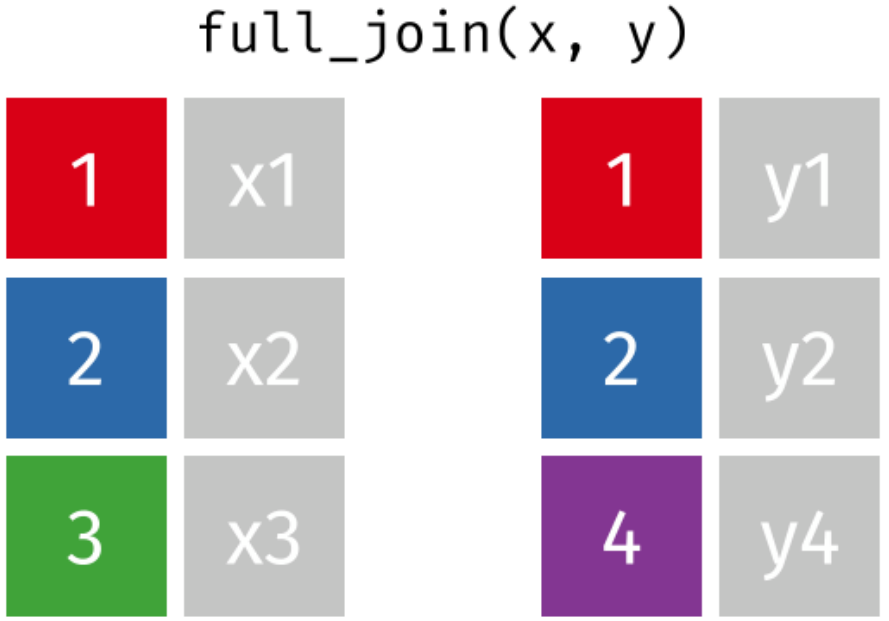
dataset

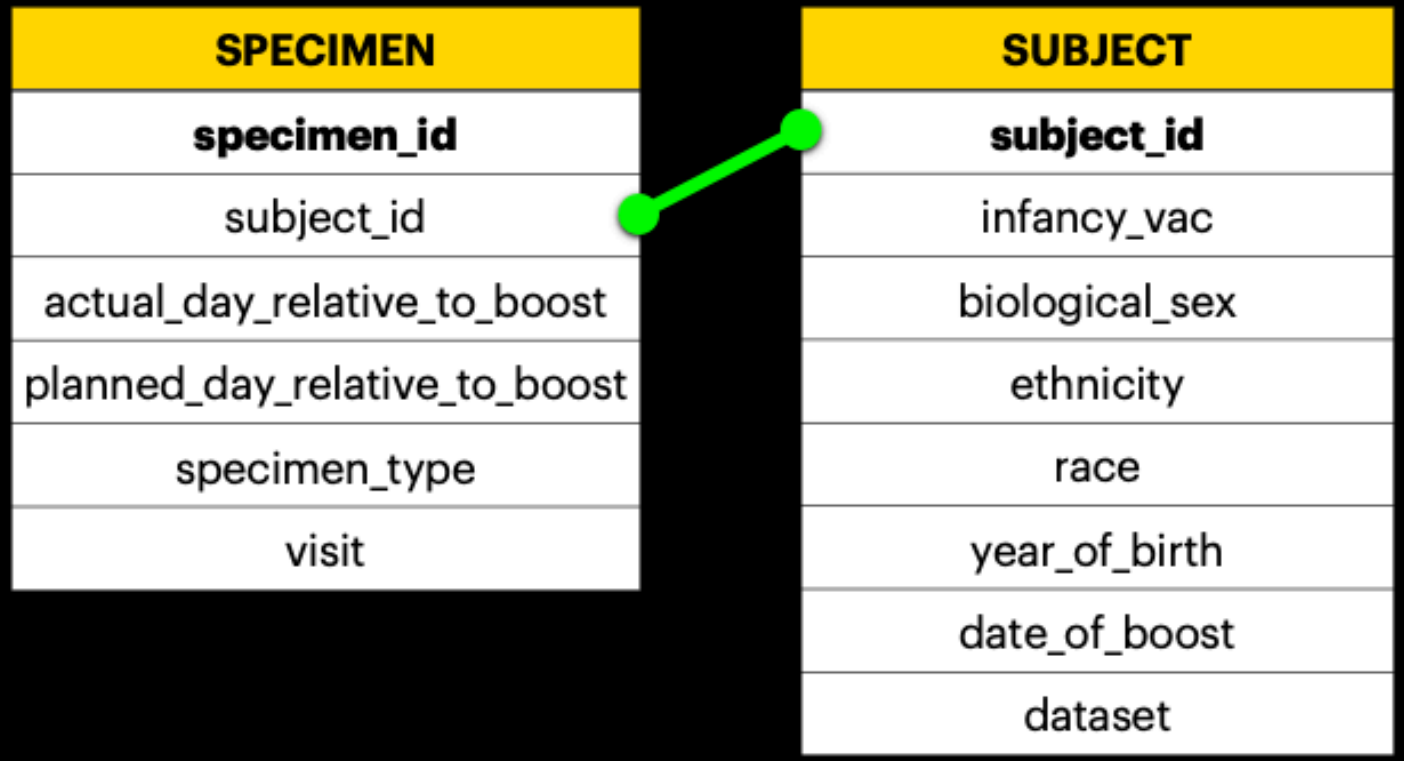
SPECIMEN
specimen_id
subject_id
actual_day_relative_to_boost
planned_day_relative_to_boost
specimen_type
visit

Dplyr *_join() functions...





Information Tables



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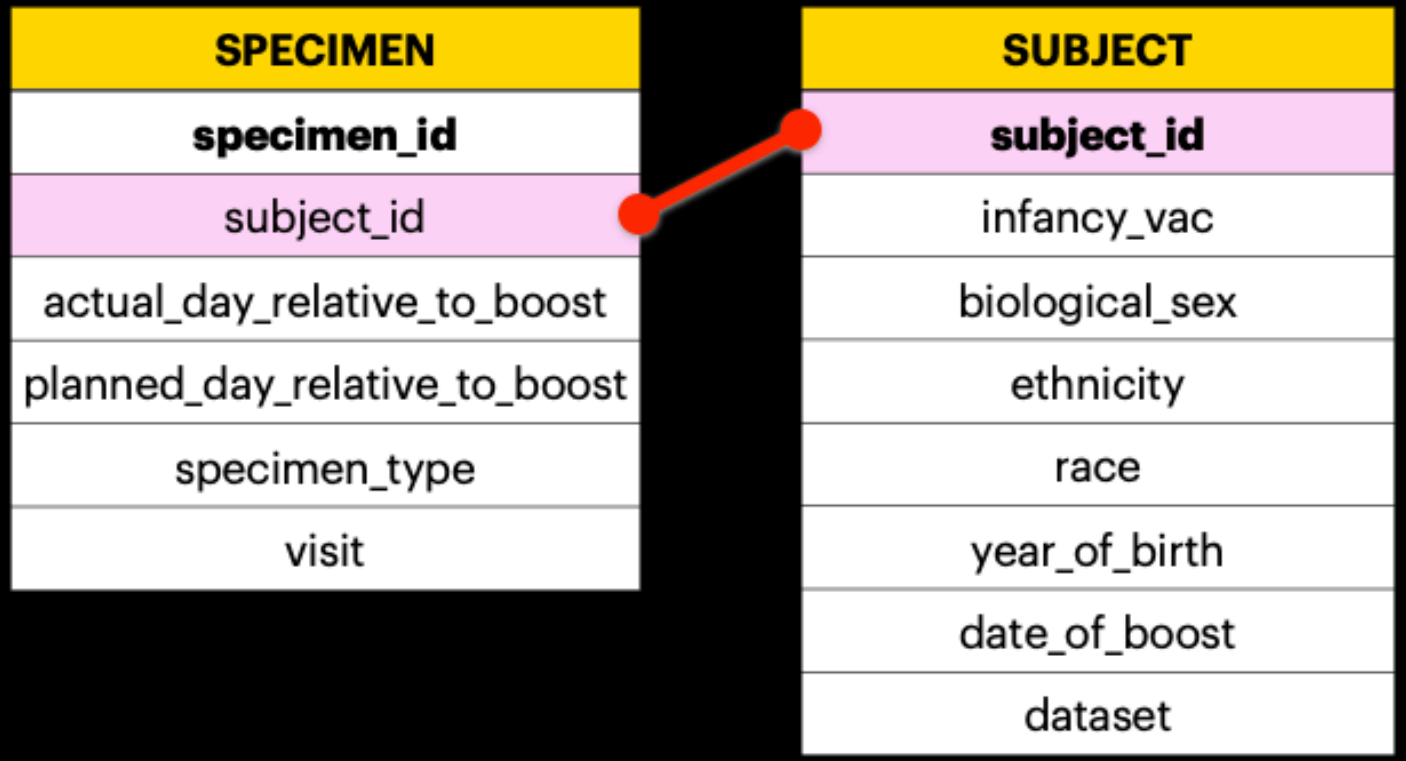

We Want One Meta table

SPECIMEN
specimen_id
subject_id
actual_day_relative_to_boost
planned_day_relative_to_boost
specimen_type
visit

+

SUBJECT
subject_id
infancy_vac
biological_sex
ethnicity
race
year_of_birth
date_of_boost
dataset

=

META
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

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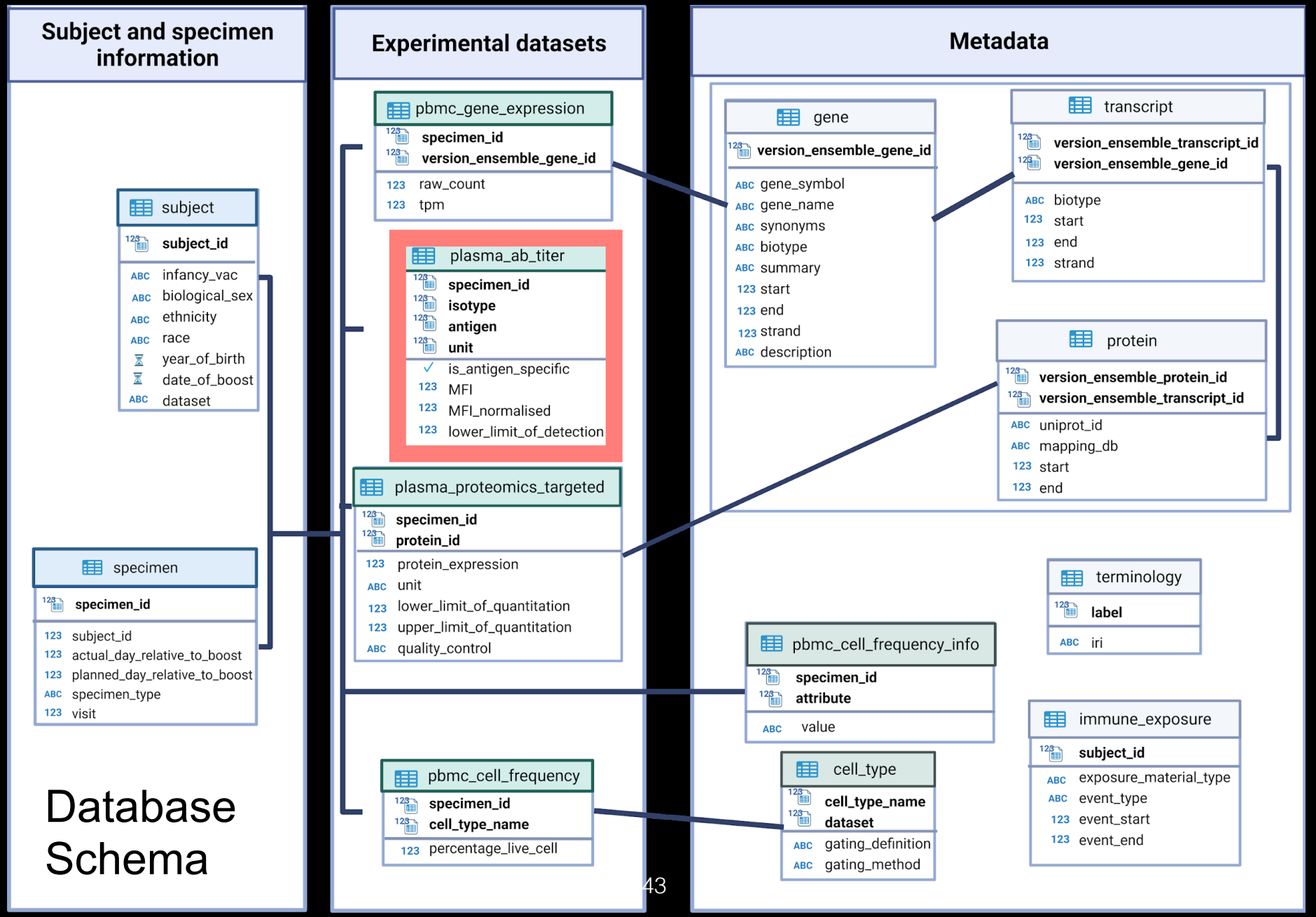
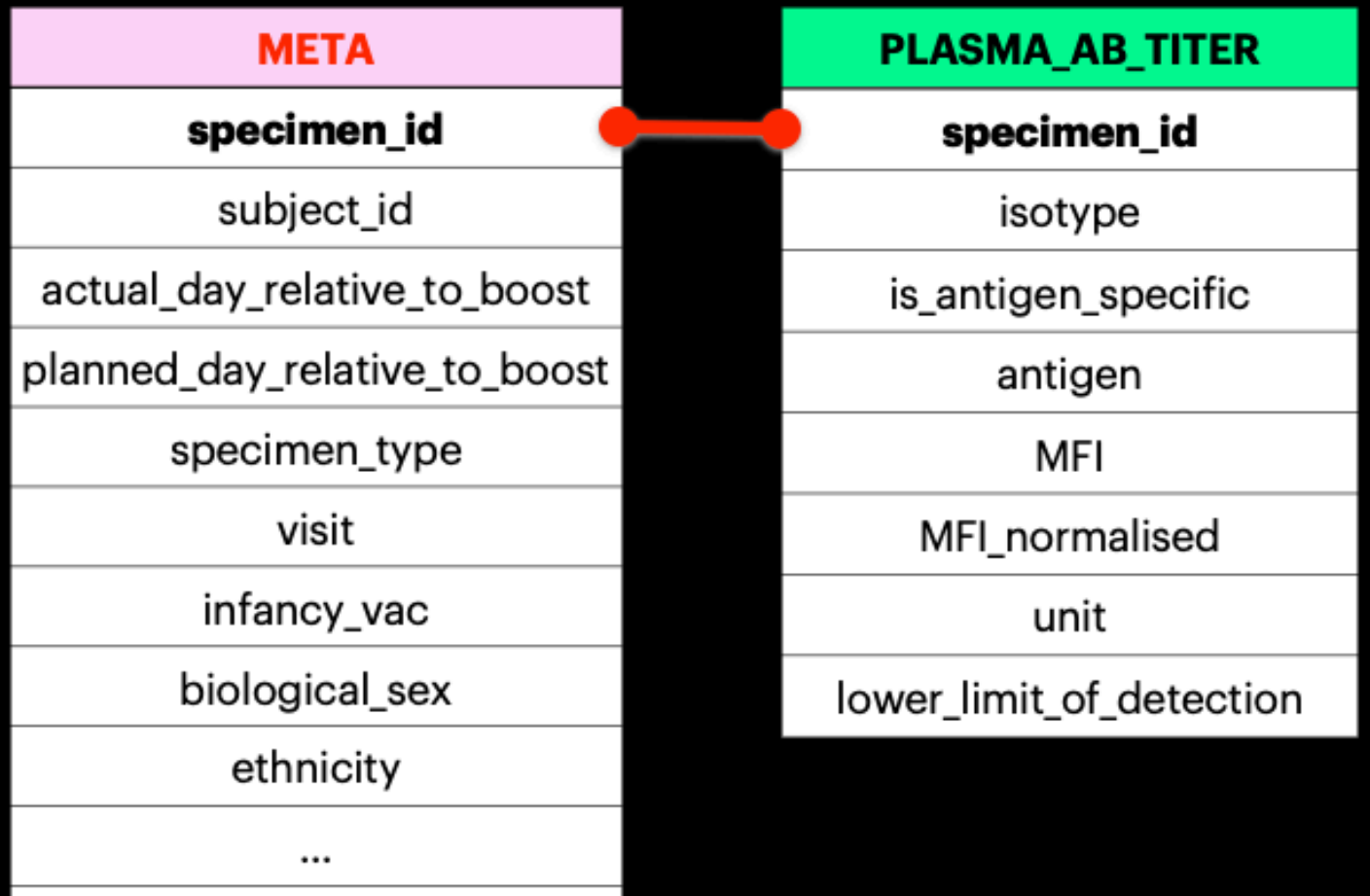


Join with Experement Tables

USE DPLYR *_JOIN() FUNCTIONS...



Meta + Experiment

META
specimen_id
subject_id
actual_day_relative_to_boost
planned_day_relative_to_boost
specimen_type
visit
infancy_vac
biological_sex
ethnicity
...

+

AB_TITER
specimen_id
isotype
is_antigen_specific
antigen
MFI
MFI_normalised
unit
lower_limit_of_detection

=

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
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isotype
is_antigen_specific
antigen
MFI
MFI_normalised
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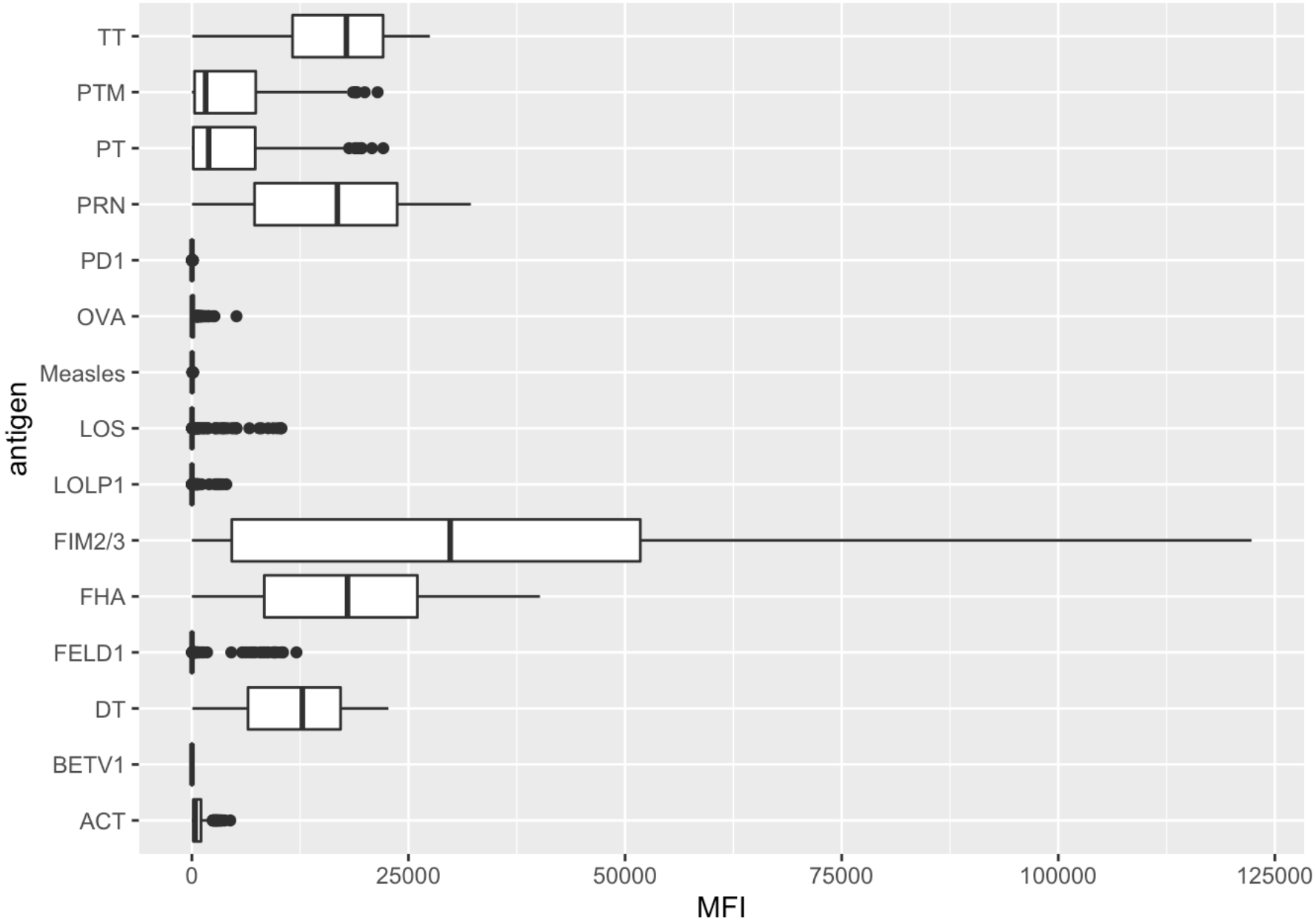
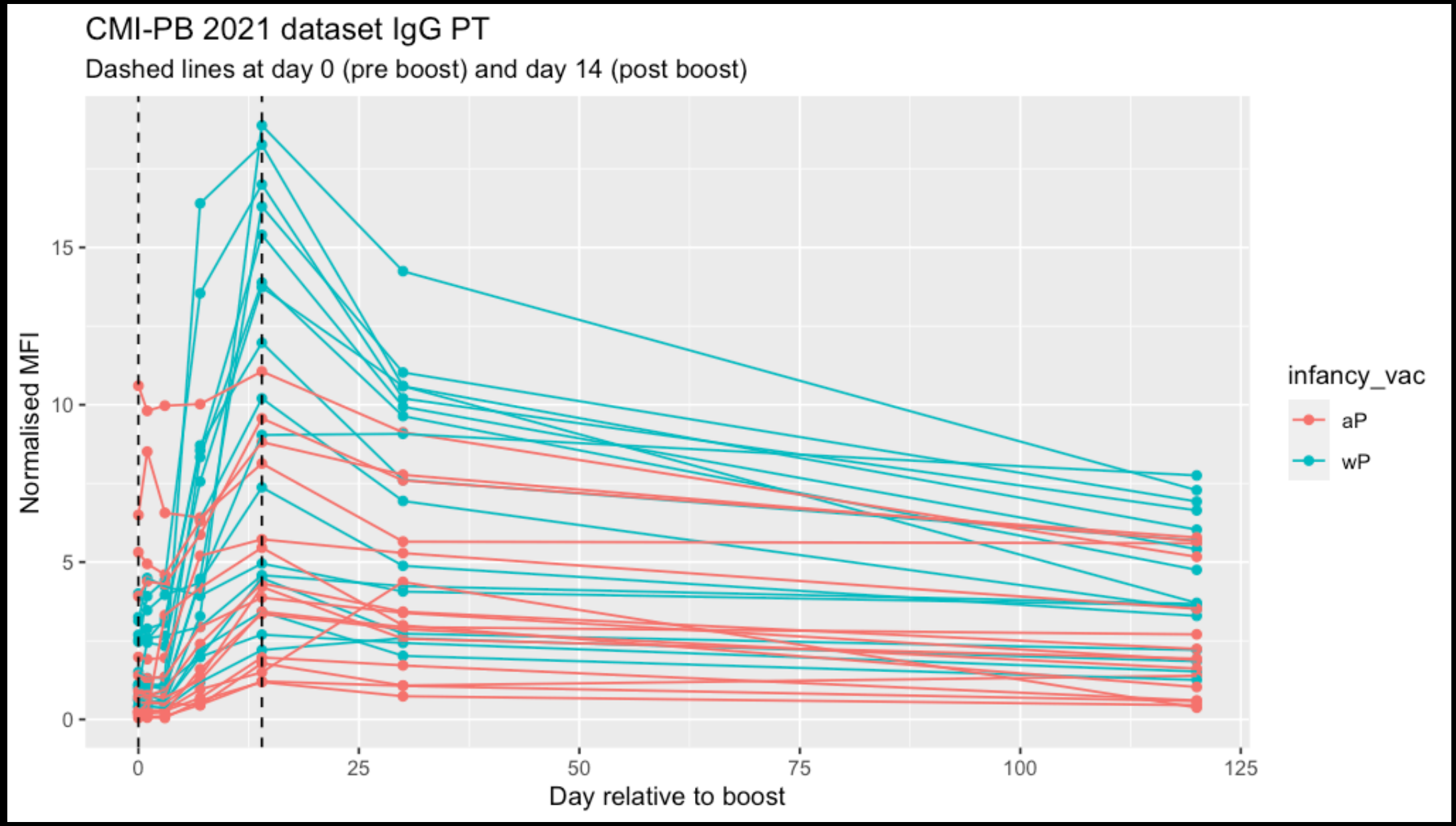
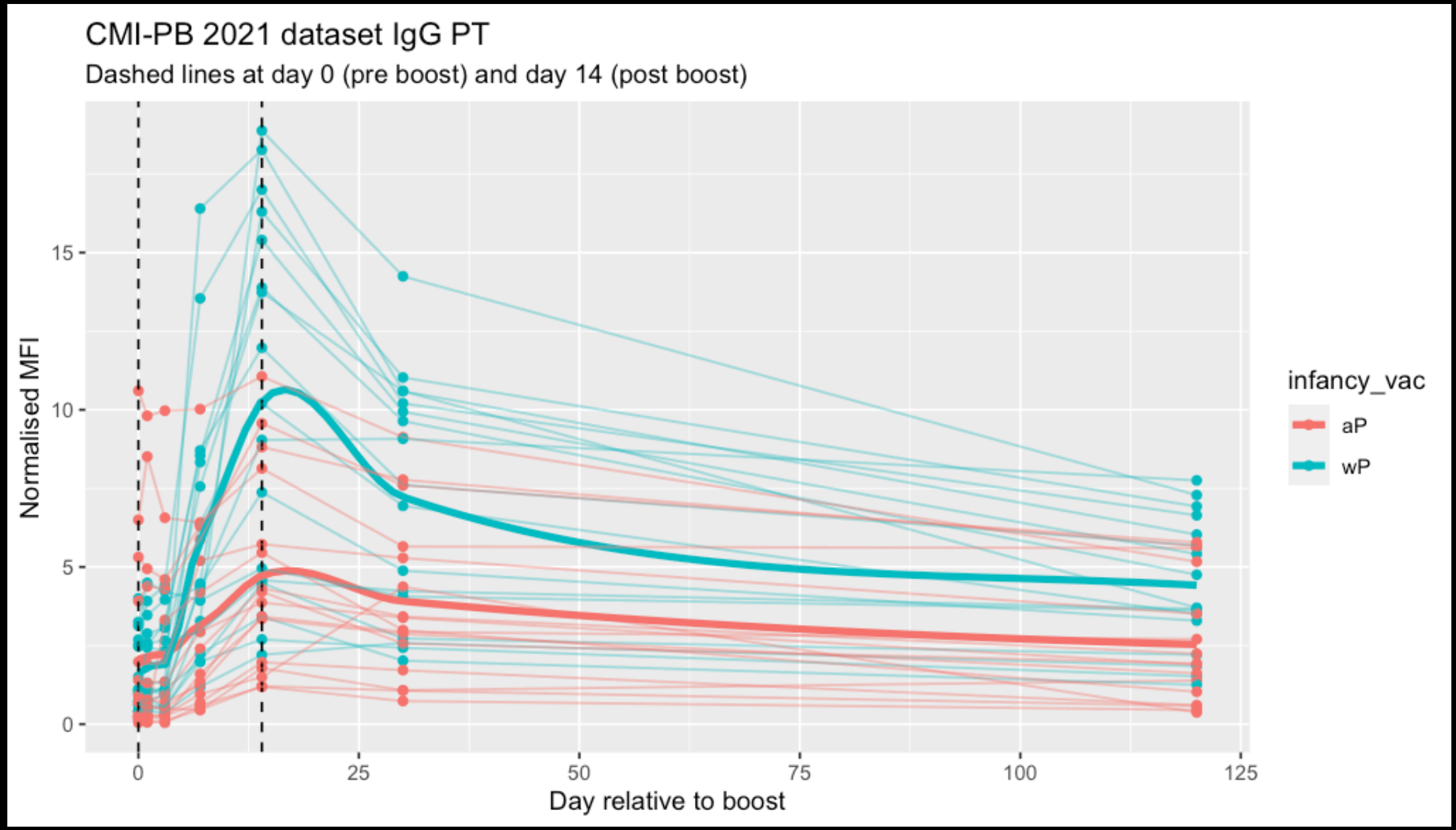

antigen
TT
PTM
PT
PRN
PD1
OVA
Measles
LOS
LOLP1
FIM2/3
FHA
FELD1
DT
BETV1
ACT
0
25000
50000
75000
100000
125000
MFI


CMI-PB 2021 dataset IgG PT
Dashed lines at day 0 (pre boost) and day 14 (post boost)
Normalised MFI
15
10
5
0
0
25
50
75
100
125
Day relative to boost
infancy_vac
aP
wP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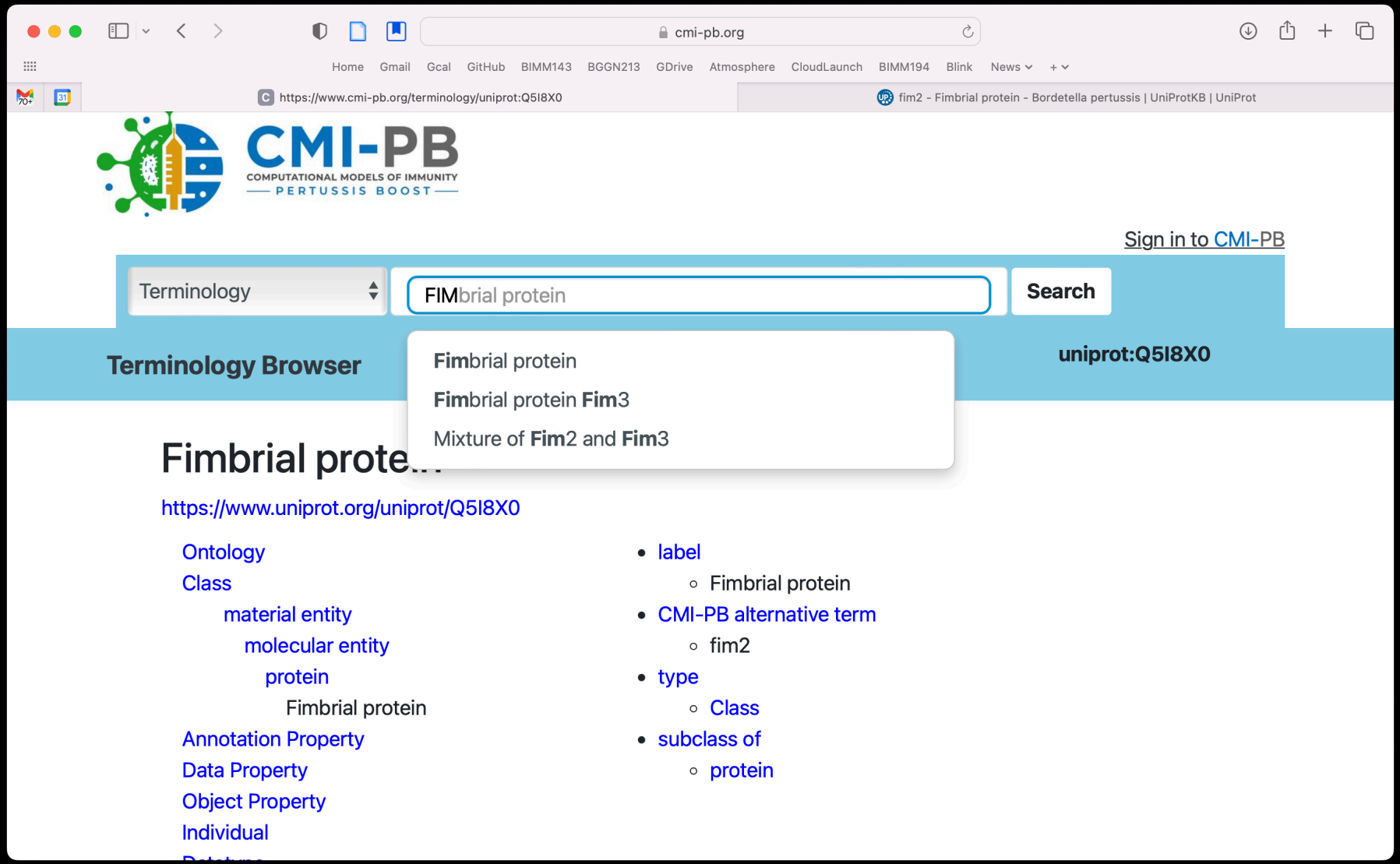
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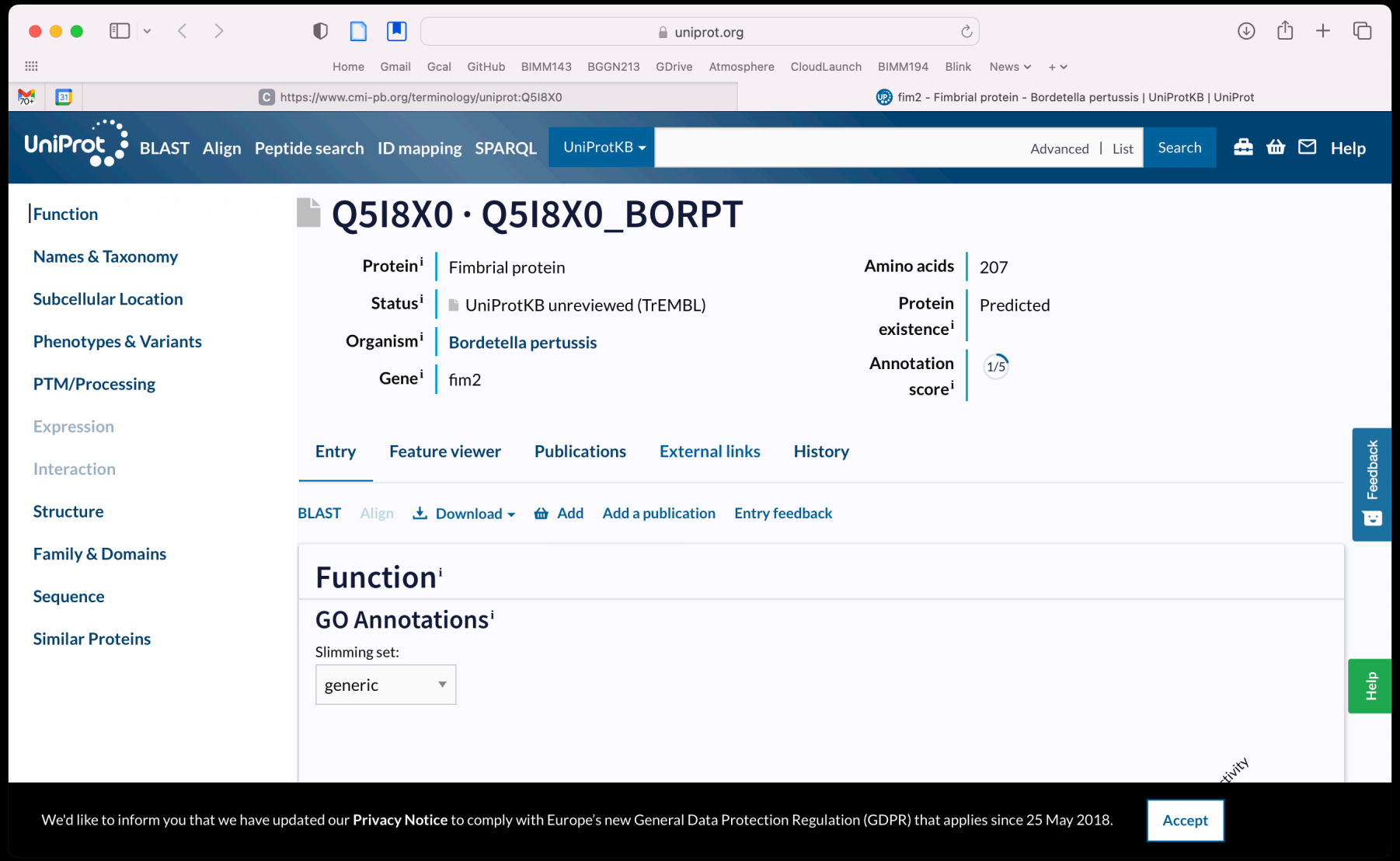
Sign in to CMI-PB
Terminology
FIMbrial protein
Search
Fimbrial protein
Fimbrial protein Fim3
Mixture of Fim2 and Fim3
Terminology Browser
uniprot:Q5I8X0
Fimbrial prote
https://www.uniprot.org/uniprot/Q5I8X0
Ontology
Class
material entity
molecular entity
protein
Fimbrial protein
Annotation Property
Data Property
Object Property
Individual
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
Function
Names & Taxonomy
Subcellular Location
Phenotypes & Variants
PTM/Processing
Expression
Interaction
Structure
Family & Domains
Sequence
Similar Proteins
Q5I8X0 · Q5I8X0_BORPT
Protein Fimbrial protein
Status UniProtKB unreviewed (TrEMBL)
Organism Bordetella pertussis
Gene fim2
Amino acids 207
Protein existence Predicted
Annotation score 1/5
Entry Feature viewer Publications External links History
BLAST Align Download Add Add a publication Entry feedback
Function
GO Annotations
Slimming set:
generic
Feedback
Help
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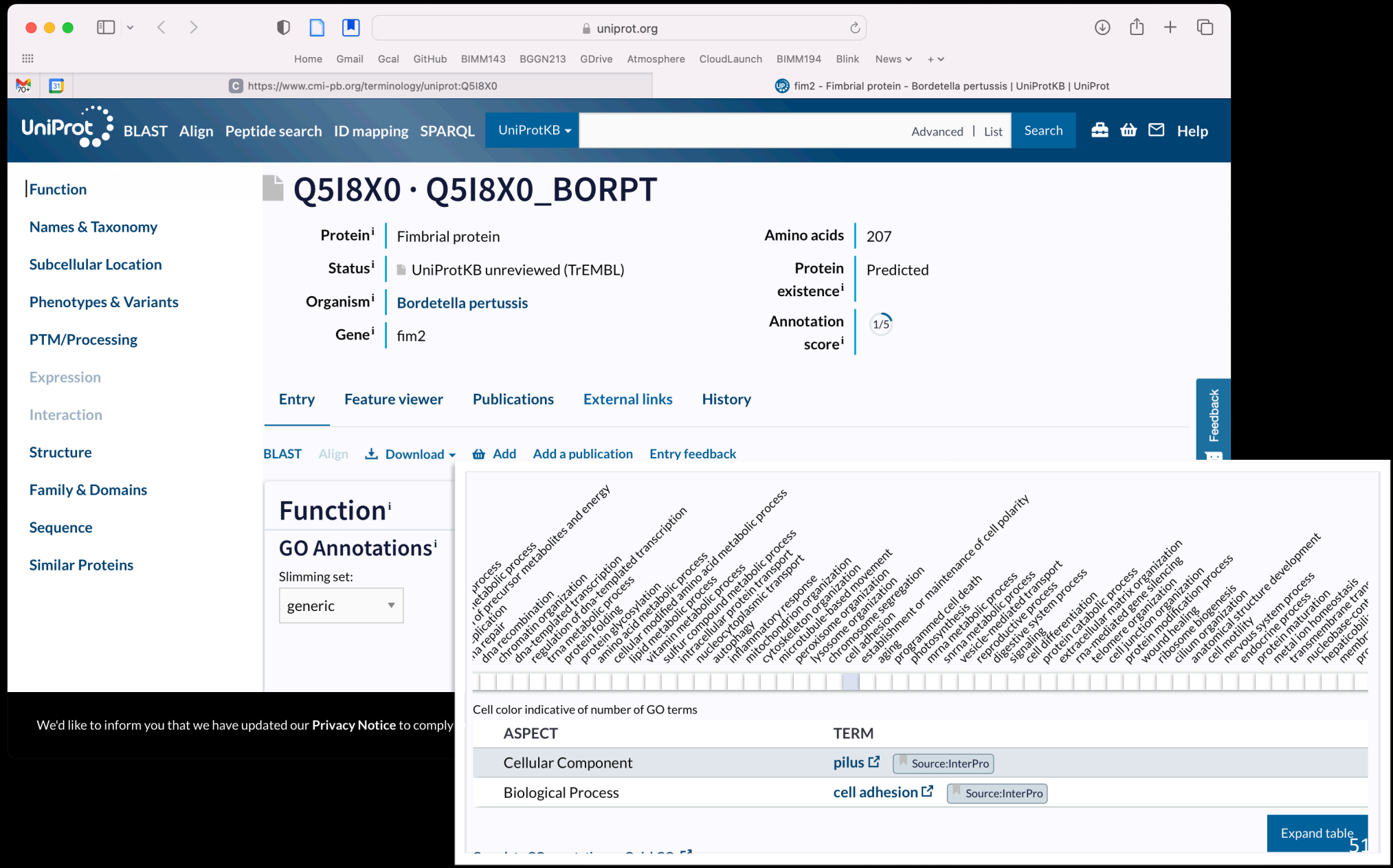
Accept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fim2 - Fimbrial protein - Bordetella pertussis | UniProtKB | UniProt
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Protein Fimbrial protein
Status UniProtKB unreviewed (TrEMBL)
Organism Bordetella pertussis
Gene fim2
Amino acids 207
Protein existence Predicted
Annotation score 1/5
Entry Feature viewer Publications External links History
BLAST Align Download Add Add a publication Entry feedback
Feedback
Function
GO Annotations
Slimming set:
generic
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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https://www.cmi-pb.org/terminology/uniprot:Q5I8X0

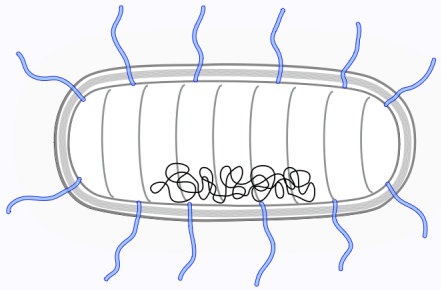
fim2 - Fimbrial protein - Bordetella pertussis | UniProtKB | UniProt

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

- Function
- Names & Taxonomy
- Subcellular Location
- Phenotypes & Variants
- PTM/Processing
- Expression
- Interaction
- Structure
- Family & Domains
- Sequence
- Similar Proteins

Subcellular Location[i]

UniProt Annotation | GO Annotation



pilus

Complete GO annotation on QuickGO

Feedback

Help

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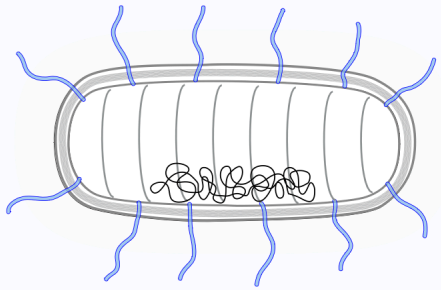

pilus

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.

Feedback

Help

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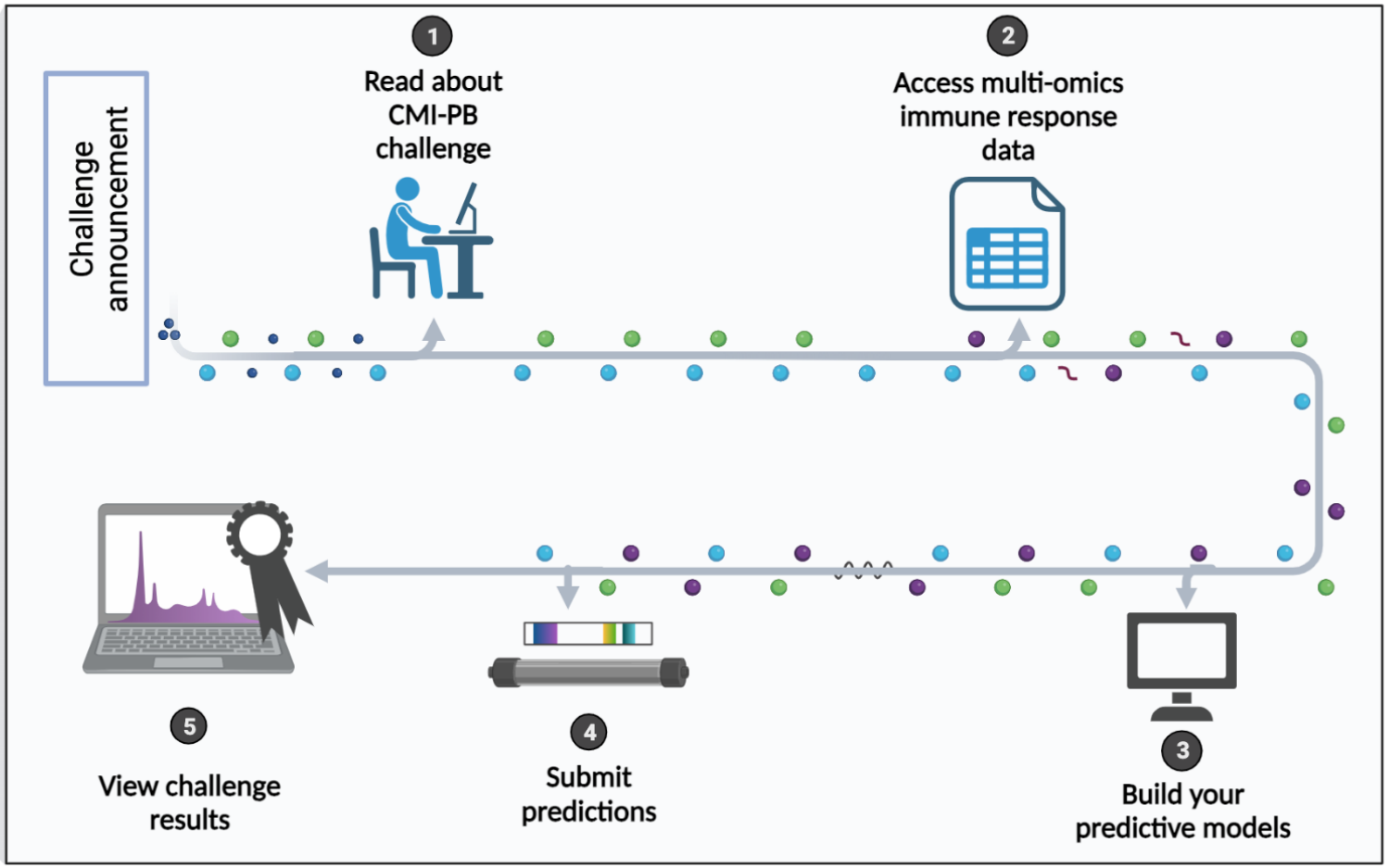
Prediction challenges

	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

2nd CMI-PB Prediction Challenge Outline

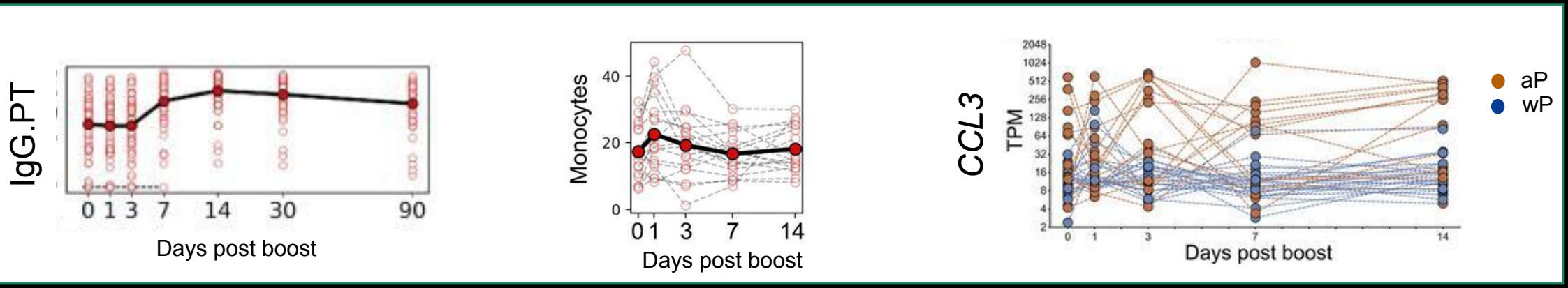
Revolutionizing computational modelling approaches for immune response prediction



Previously identified vaccine responses are formulated as prediction tasks

These include:

- Plasma IgG levels are increased at day 14 post-booster vaccination compared to baseline
- Increase in the percentage of monocytes on day 1 post-booster over baseline
- A subset of aP-primed individuals showed an increased expression of proinflammatory genes, including CCL3, at day 3 post-booster vaccination when compared to wP primed individuals.



Prediction tasks

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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.

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.

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 CMI-PB team:

CMI-PB
COMPUTATIONAL MODELS OF IMMUNITY
PERTUSSIS BOOST

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(Yale)

Steven Kleinstein
Jeremy Gygi
Leying Guan
Anna Konstorum

Grant Lab
(UCSD)

Barry Grant
Jason Hsiao

Ay Lab
(LJI)

Ferhat Ay
Joaquin Reyna

Peters Lab
(LJI)

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