Class 19

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Pertussis is a severe lung infection also known as whooping cough.

We will begin by investigating the number of Pertussis cases per year in the US.

This data is available on the CDC website here

```
#/ echo = FALSE
cdc <- data.frame(
year = c(1922L,1923L,1924L,1925L,
                                        1926L,1927L,1928L,1929L,1930L,1931L,
                                        1932L,1933L,1934L,1935L,1936L,
                                        1937L,1938L,1939L,1940L,1941L,1942L,
                                        1943L,1944L,1945L,1946L,1947L,
                                        1948L,1949L,1950L,1951L,1952L,
                                        1953L,1954L,1955L,1956L,1957L,1958L,
                                        1959L,1960L,1961L,1962L,1963L,
                                        1964L,1965L,1966L,1967L,1968L,1969L,
                                        1970L,1971L,1972L,1973L,1974L,
                                        1975L,1976L,1977L,1978L,1979L,1980L,
                                        1981L,1982L,1983L,1984L,1985L,
                                        1986L,1987L,1988L,1989L,1990L,
                                        1991L,1992L,1993L,1994L,1995L,1996L,
                                        1997L,1998L,1999L,2000L,2001L,
                                        2002L,2003L,2004L,2005L,2006L,2007L,
                                        2008L,2009L,2010L,2011L,2012L,
                                        2013L,2014L,2015L,2016L,2017L,2018L,
                                        2019L,2020L,2021L),
cases = c(107473,164191,165418,152003,
                                        202210,181411,161799,197371,
                                        166914,172559,215343,179135,265269,
                                        180518,147237,214652,227319,103188,
                                        183866,222202,191383,191890,109873,
```

```
                                        133792,109860,156517,74715,69479,
                                        120718,68687,45030,37129,60886,
                                        62786,31732,28295,32148,40005,
                                        14809,11468,17749,17135,13005,6799,
                                        7717,9718,4810,3285,4249,3036,
                                        3287,1759,2402,1738,1010,2177,2063,
                                        1623,1730,1248,1895,2463,2276,
                                        3589,4195,2823,3450,4157,4570,
                                        2719,4083,6586,4617,5137,7796,6564,
                                        7405,7298,7867,7580,9771,11647,
                                        25827,25616,15632,10454,13278,
                                        16858,27550,18719,48277,28639,32971,
                                        20762,17972,18975,15609,18617,
                                        6124,2116)
        )
```

Lets havwe a look at this data.frame

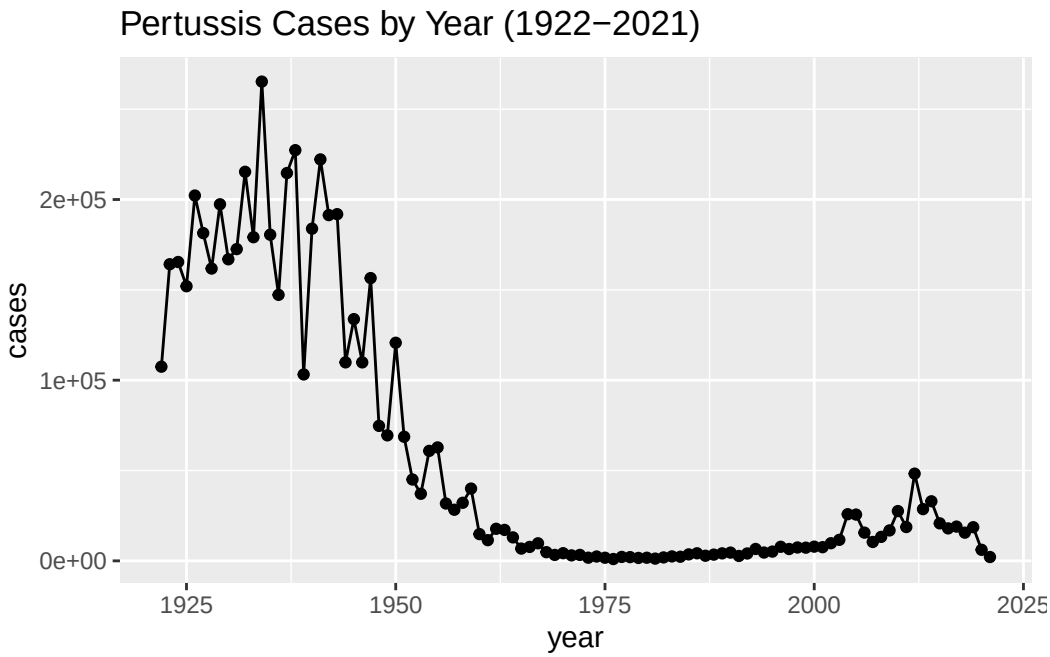
```
head(cdc)
```

```
  year  cases
1 1922 107473
2 1923 164191
3 1924 165418
4 1925 152003
5 1926 202210
6 1927 181411
```

I want a nice plot of the number of cases per year

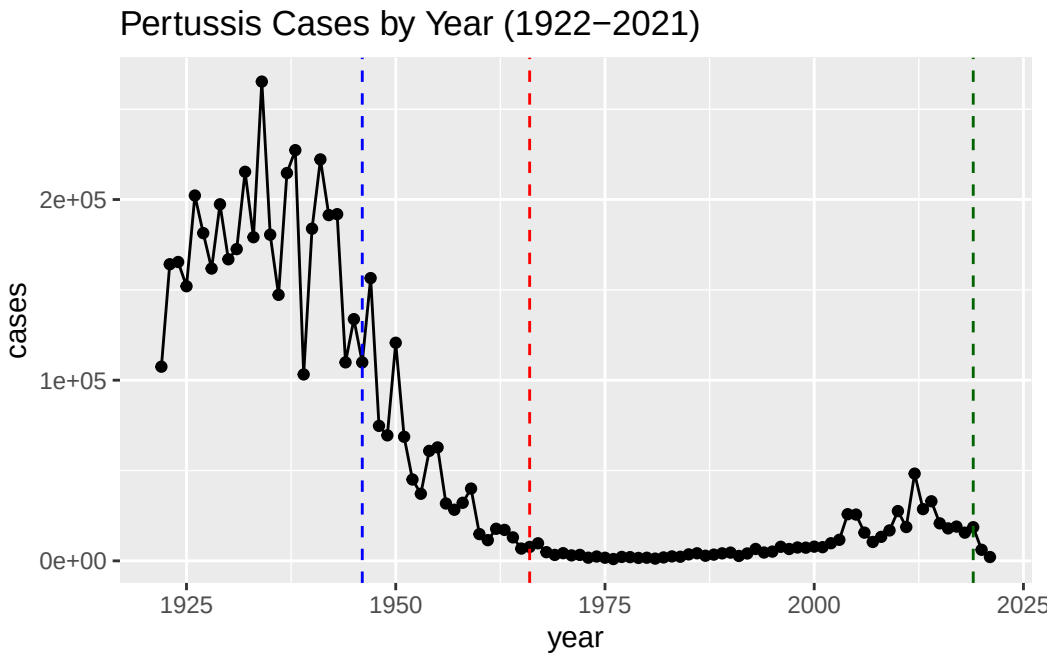
> Q1. With the help of the R "addin" package datapasta assign the CDC pertussis case number data to a data frame called cdc and use ggplot to make a plot of cases numbers over time.

```
library(ggplot2)

ggplot(cdc) + aes(x=year, y=cases) + geom_point() + geom_line() +labs(title= "Pertussis Ca
```



Q2. Using the ggplot geom_vline() function add lines to your previous plot for the 1946 introduction of the wP vaccine and the 1996 switch to aP vaccine (see example in the hint below). What do you notice?

```
library(ggplot2)

ggplot(cdc) + aes(x=year, y=cases) +
  geom_point() +
  geom_line() +
  geom_vline(xintercept=1946, col="BLUE", linetype= "dashed") +
  geom_vline(xintercept = 1966, col="RED", linetype= "dashed") +
  geom_vline(xintercept = 2019, col="DARKGREEN", linetype= "dashed") +
  labs(title= "Pertussis Cases by Year (1922-2021)")
```



Q3. Describe what happened after the introduction of the aP vaccine? Do you have a possible explanation for the observed trend?

There is a lag and then cases rise within a ~3 year cycle perhaps similar to that observed before to the first wP vaccine introduction.

Exploring CMI-PB Data

Why is this vaccine-preventable disease on the upswing? To answer this question we need to investigate the mechanisms underlying waning protection against pertussis. This requires evaluation of pertussis-specific immune responses over time in wP and aP vaccinated individuals.

This is the goals of the CMI-PB project: https://www.cmi-pb.org/

The CMI-PB project makes its data available via "API-endpoint" that return JSON format.

We will use the **jsonlite** package to access this data. The main function in this package is called `read_json()`

```
library(jsonlite)

#Subject Table
```

```
subject <- read_json("https://www.cmi-pb.org/api/subject", simplifyVector = TRUE)
#Specimen Table
specimen <-  read_json("https://www.cmi-pb.org/api/specimen", simplifyVector = TRUE)
#Titer Table
titer <- read_json("https://www.cmi-pb.org/api/v4/plasma_ab_titer", simplifyVector = TRUE)
```

Have a little peek at these new objects

```
head(subject, 3)
```

```
  subject_id infancy_vac biological_sex              ethnicity  race
1          1          wP         Female Not Hispanic or Latino White
2          2          wP         Female Not Hispanic or Latino White
3          3          wP         Female                 Unknown White
  year_of_birth date_of_boost      dataset
1    1986-01-01    2016-09-12 2020_dataset
2    1968-01-01    2019-01-28 2020_dataset
3    1983-01-01    2016-10-10 2020_dataset
```

```
head(specimen, 3)
```

```
  specimen_id subject_id actual_day_relative_to_boost
1           1          1                           -3
2           2          1                            1
3           3          1                            3
  planned_day_relative_to_boost specimen_type visit
1                             0         Blood     1
2                             1         Blood     2
3                             3         Blood     3
```

```
head(titer, 3)
```

```
  specimen_id isotype is_antigen_specific antigen        MFI MFI_normalised
1           1     IgE               FALSE   Total 1110.21154       2.493425
2           1     IgE               FALSE   Total 2708.91616       2.493425
3           1     IgG                TRUE      PT   68.56614       3.736992
   unit lower_limit_of_detection
1 UG/ML                 2.096133
2 IU/ML                29.170000
3 IU/ML                 0.530000
```

Q4. How many aP and wP infancy vaccinated subjects are in the dataset?

60 infants with aP vaccine and 58 infants with wP vaccine

```
table(subject$infancy_vac)
```

```
aP wP
60 58
```

Q5. How many Male and Female subjects/patients are in the dataset?

79 female subjects and 39 male subjects are in the data set

```
table(subject$biological_sex)
```

```
Female   Male
    79     39
```

Q6. What is the breakdown of race and biological sex (e.g. number of Asian females, White males etc…)?

```
table(subject$race, subject$biological_sex)
```

```
                                        Female Male
  American Indian/Alaska Native              0    1
  Asian                                     21   11
  Black or African American                  2    0
  More Than One Race                         9    2
  Native Hawaiian or Other Pacific Islander  1    1
  Unknown or Not Reported                   11    4
  White                                     35   20
```

Working with dates

Dates can really suck to work with and do math. The lubridate package makes this much easier. It is part of the **tidyverse** that included deplyr, ggplot2, etc.

```
  library(tidyverse)
```

```
-- Attaching core tidyverse packages ------------------------ tidyverse 2.0.0 --
v dplyr     1.1.3     v readr     2.1.4
v forcats   1.0.0     v stringr   1.5.0
v lubridate 1.9.3     v tibble    3.2.1
v purrr     1.0.2     v tidyr     1.3.0
-- Conflicts ------------------------------------------ tidyverse_conflicts() --
x dplyr::filter()  masks stats::filter()
x purrr::flatten() masks jsonlite::flatten()
x dplyr::lag()     masks stats::lag()
i Use the conflicted package (<http://conflicted.r-lib.org/>) to force all conflicts to beco
```

```
  today()
```

```
[1] "2023-12-05"
```

```
  today() - mdy("11-28-2001")
```

```
Time difference of 8042 days
```

```
  today() - mdy("03-09-2002")
```

```
Time difference of 7941 days
```

```
  time_length( today() - mdy("03-09-2002"),  "years")
```

```
[1] 21.74127
```

Now add the age of each subject to the subject table

> Q7. Using this approach determine (i) the average age of wP individuals, (ii) the average age of aP individuals; and (iii) are they significantly different?

```
# Use today's date to calculate age in days
subject$age <- ymd(subject$date_of_boost) - ymd(subject$year_of_birth)

subject$age_years <- time_length(subject$age, "years")

head(subject)
```

```
  subject_id infancy_vac biological_sex              ethnicity  race
1          1          wP         Female Not Hispanic or Latino White
2          2          wP         Female Not Hispanic or Latino White
3          3          wP         Female                 Unknown White
4          4          wP           Male Not Hispanic or Latino Asian
5          5          wP           Male Not Hispanic or Latino Asian
6          6          wP         Female Not Hispanic or Latino White
  year_of_birth date_of_boost      dataset        age age_years
1    1986-01-01    2016-09-12 2020_dataset 11212 days  30.69678
2    1968-01-01    2019-01-28 2020_dataset 18655 days  51.07461
3    1983-01-01    2016-10-10 2020_dataset 12336 days  33.77413
4    1988-01-01    2016-08-29 2020_dataset 10468 days  28.65982
5    1991-01-01    2016-08-29 2020_dataset  9372 days  25.65914
6    1988-01-01    2016-10-10 2020_dataset 10510 days  28.77481
```

```
library(dplyr)

ap <- subject %>% filter(infancy_vac == "aP")

round( summary( time_length( ap$age, "years" ) ) )
```

```
 Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
   19      20      20      21      21      28
```

```
# wP
wp <- subject %>% filter(infancy_vac == "wP")
round( summary( time_length( wp$age, "years" ) ) )
```

```
 Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
   23      26      29      31      34      51
```

Q8. Determine the age of all individuals at time of boost?

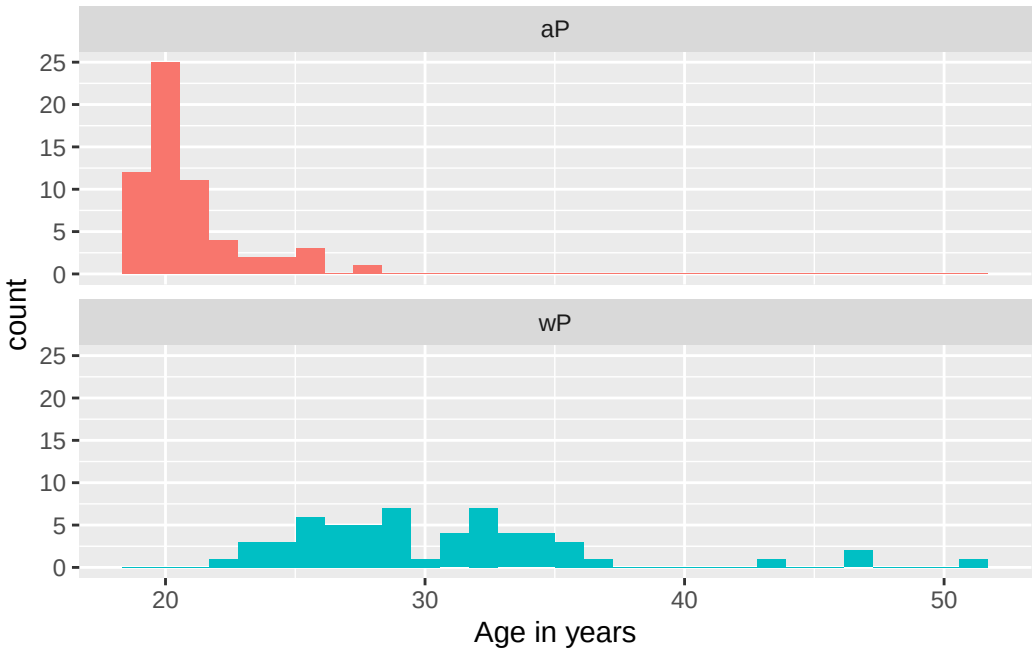
```
int <- ymd(subject$date_of_boost) - ymd(subject$year_of_birth)
age_at_boost <- time_length(int, "year")
head(age_at_boost)
```

```
[1] 30.69678 51.07461 33.77413 28.65982 25.65914 28.77481
```

Q9. With the help of a faceted boxplot or histogram (see below), do you think these two groups are significantly different?

```
library(ggplot2)

ggplot(subject) +
  aes(time_length(age, "year"),
      fill=as.factor(infancy_vac)) +
  geom_histogram(show.legend=FALSE) +
  facet_wrap(vars(infancy_vac), nrow=2) +
  xlab("Age in years")
```

```
`stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
```



```
# Or use wilcox.test()
x <- t.test(time_length( wp$age, "years" ),
       time_length( ap$age, "years" ))

x$p.value
```

```
[1] 9.121472e-19
```

#Joining

Q9. Complete the code to join specimen and subject tables to make a new merged data frame containing all specimen records along with their associated subject details:

```
library(dplyr)
meta <- inner_join(specimen, subject)
```

```
Joining with `by = join_by(subject_id)`
```

```
dim(meta)
```

```
[1] 939  15
```

```
head(meta)
```

```
  specimen_id subject_id actual_day_relative_to_boost
1           1          1                           -3
2           2          1                            1
3           3          1                            3
4           4          1                            7
5           5          1                           11
6           6          1                           32
  planned_day_relative_to_boost specimen_type visit infancy_vac biological_sex
1                             0         Blood     1          wP         Female
2                             1         Blood     2          wP         Female
3                             3         Blood     3          wP         Female
4                             7         Blood     4          wP         Female
5                            14         Blood     5          wP         Female
```

```
6                            30         Blood     6          wP         Female
                ethnicity  race year_of_birth date_of_boost      dataset
1 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
2 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
3 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
4 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
5 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
6 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
         age age_years
1 11212 days  30.69678
2 11212 days  30.69678
3 11212 days  30.69678
4 11212 days  30.69678
5 11212 days  30.69678
6 11212 days  30.69678
```

Q10. Now using the same procedure join meta with titer data so we can further analyze this data in terms of time of visit aP/wP, male/female etc.

```
abdata <- inner_join(titer, meta)
```

```
Joining with `by = join_by(specimen_id)`
```

```
dim(abdata)
```

```
[1] 41810    22
```

Q. How many isotopes are we measuring for all these individuals

```
table(abdata$isotype)
```

```
 IgE  IgG IgG1 IgG2 IgG3 IgG4
6698 3240 7968 7968 7968 7968
```

Lets focus on one of these IgG

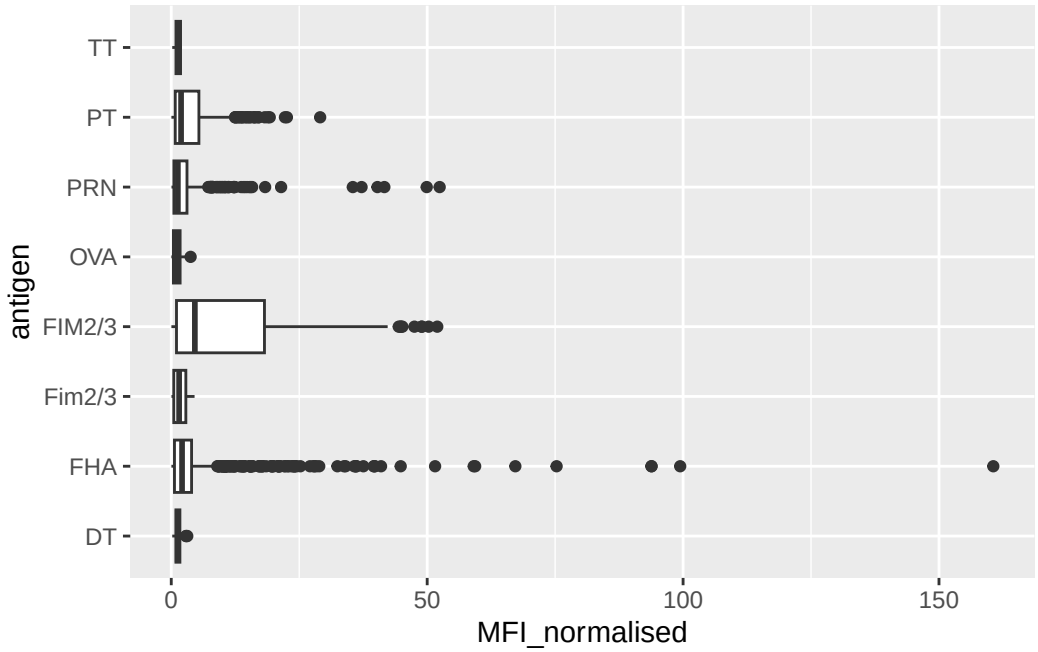
#Examine IgG Ab titer levels

```r
igg <- abdata %>% filter(isotype == "IgG")
head(igg)
```

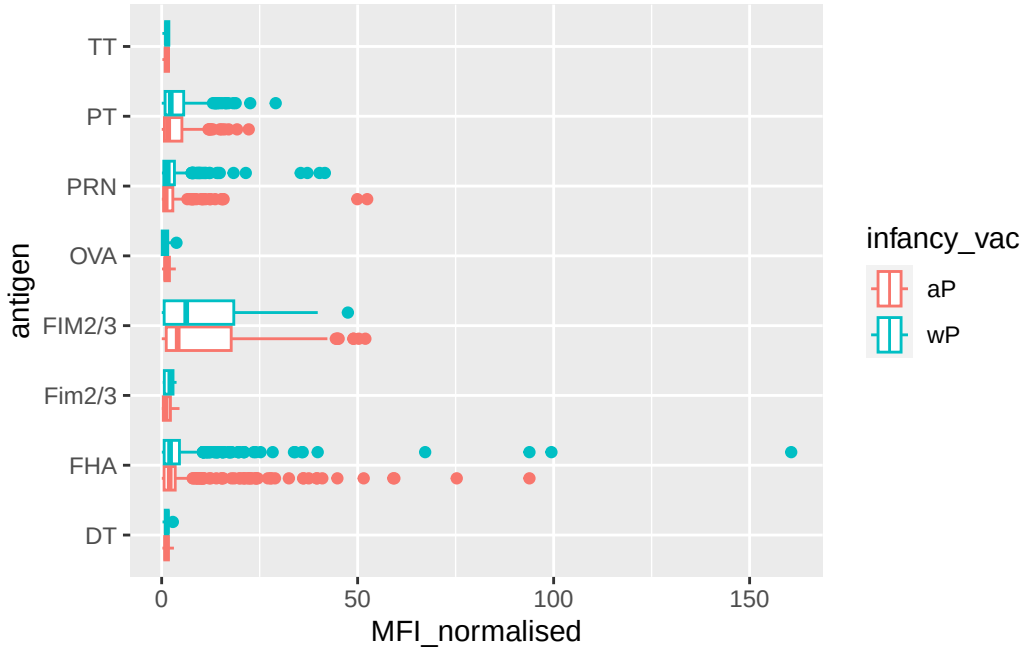
```
  specimen_id isotype is_antigen_specific antigen        MFI MFI_normalised
1           1     IgG                TRUE      PT   68.56614       3.736992
2           1     IgG                TRUE     PRN  332.12718       2.602350
3           1     IgG                TRUE     FHA 1887.12263      34.050956
4          19     IgG                TRUE      PT   20.11607       1.096366
5          19     IgG                TRUE     PRN  976.67419       7.652635
6          19     IgG                TRUE     FHA   60.76626       1.096457
   unit lower_limit_of_detection subject_id actual_day_relative_to_boost
1 IU/ML                 0.530000          1                           -3
2 IU/ML                 6.205949          1                           -3
3 IU/ML                 4.679535          1                           -3
4 IU/ML                 0.530000          3                           -3
5 IU/ML                 6.205949          3                           -3
6 IU/ML                 4.679535          3                           -3
  planned_day_relative_to_boost specimen_type visit infancy_vac biological_sex
1                             0         Blood     1          wP         Female
2                             0         Blood     1          wP         Female
3                             0         Blood     1          wP         Female
4                             0         Blood     1          wP         Female
5                             0         Blood     1          wP         Female
6                             0         Blood     1          wP         Female
              ethnicity  race year_of_birth date_of_boost      dataset
1 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
2 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
3 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
4               Unknown White    1983-01-01    2016-10-10 2020_dataset
5               Unknown White    1983-01-01    2016-10-10 2020_dataset
6               Unknown White    1983-01-01    2016-10-10 2020_dataset
        age age_years
1 11212 days  30.69678
2 11212 days  30.69678
3 11212 days  30.69678
4 12336 days  33.77413
5 12336 days  33.77413
6 12336 days  33.77413
```

Box plot of the MFI_normalised vs antigen

```
ggplot(igg) +
  aes(x=MFI_normalised, y=antigen) +
  geom_boxplot()
```




```
ggplot(igg) +
  aes(x=MFI_normalised, y=antigen, col=infancy_vac) +
  geom_boxplot()
```




```
head(igg)
```

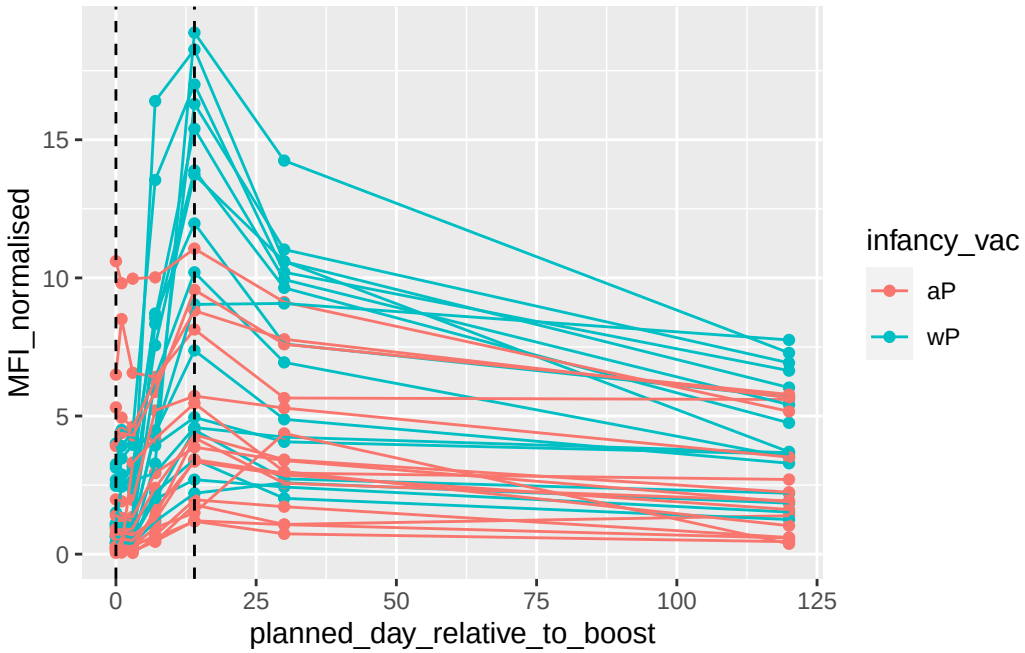
```
  specimen_id isotype is_antigen_specific antigen        MFI MFI_normalised
1           1     IgG                TRUE      PT   68.56614       3.736992
2           1     IgG                TRUE     PRN  332.12718       2.602350
3           1     IgG                TRUE     FHA 1887.12263      34.050956
4          19     IgG                TRUE      PT   20.11607       1.096366
5          19     IgG                TRUE     PRN  976.67419       7.652635
6          19     IgG                TRUE     FHA   60.76626       1.096457
   unit lower_limit_of_detection subject_id actual_day_relative_to_boost
1 IU/ML                 0.530000          1                           -3
2 IU/ML                 6.205949          1                           -3
3 IU/ML                 4.679535          1                           -3
4 IU/ML                 0.530000          3                           -3
5 IU/ML                 6.205949          3                           -3
6 IU/ML                 4.679535          3                           -3
  planned_day_relative_to_boost specimen_type visit infancy_vac biological_sex
1                             0         Blood     1          wP         Female
2                             0         Blood     1          wP         Female
3                             0         Blood     1          wP         Female
4                             0         Blood     1          wP         Female
5                             0         Blood     1          wP         Female
```

```
6                              0         Blood     1           wP         Female
                ethnicity  race year_of_birth date_of_boost      dataset
1 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
2 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
3 Not Hispanic or Latino White    1986-01-01    2016-09-12 2020_dataset
4                 Unknown White    1983-01-01    2016-10-10 2020_dataset
5                 Unknown White    1983-01-01    2016-10-10 2020_dataset
6                 Unknown White    1983-01-01    2016-10-10 2020_dataset
          age age_years
1 11212 days  30.69678
2 11212 days  30.69678
3 11212 days  30.69678
4 12336 days  33.77413
5 12336 days  33.77413
6 12336 days  33.77413
```

Focus on IgG to the Pertussis Toxin (PT) antigen in the 2021 data set

```
igg.pt<- igg %>% filter(antigen=="PT", dataset=="2021_dataset")
```

```
ggplot(igg.pt) +
aes(x=planned_day_relative_to_boost, y=MFI_normalised, col=infancy_vac, group=subject_id)
geom_point() +
geom_line()+
geom_vline(xintercept=0, linetype= "dashed", col="BLACK")+
geom_vline(xintercept=14, linetype= "dashed", col="BLACK")
```


MFI_normalised
15
10
5
0
0
25
50
75
100
125
planned_day_relative_to_boost
infancy_vac
aP
wP