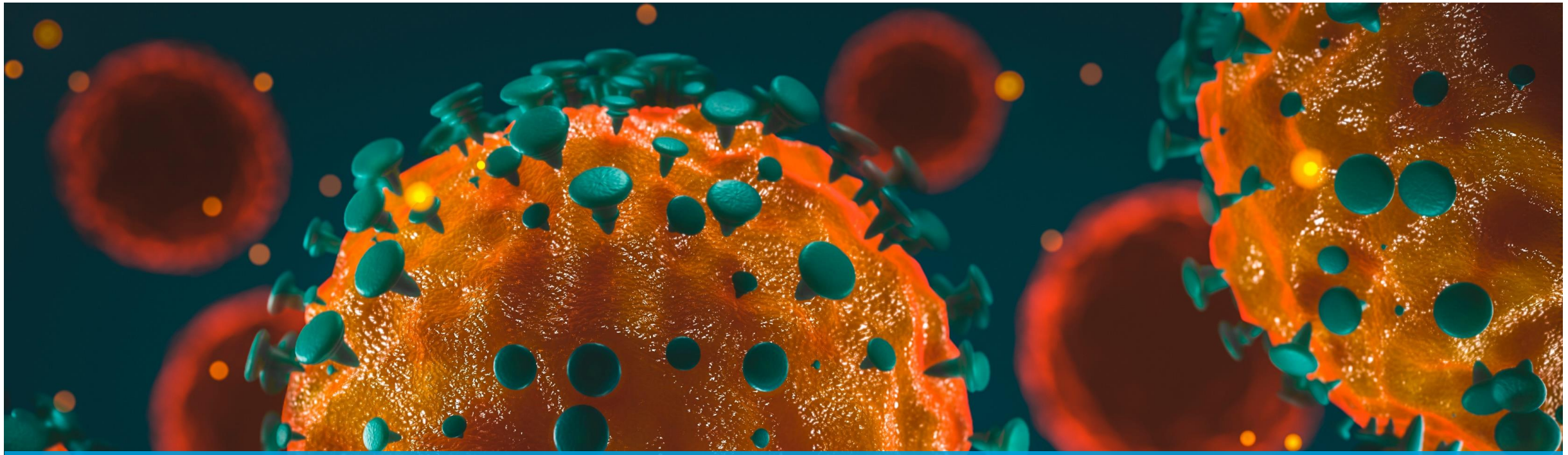


Statistical Considerations Underlying a COVID-19 Vaccine Phase 3 design

COVID-19 team

27 July 2021

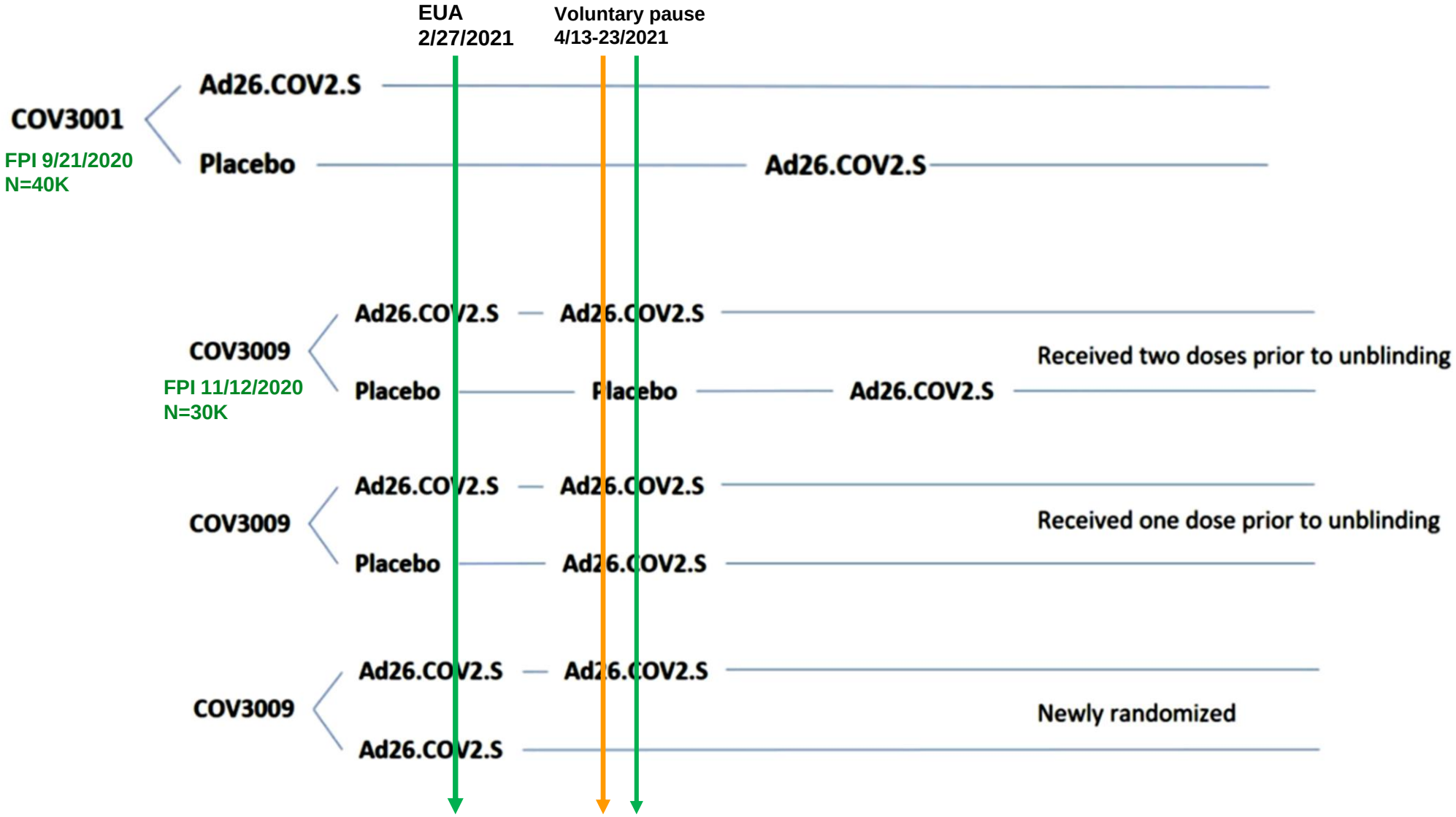
Pictured: a representation of a coronavirus

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Simulation supported decision making

- Design for study 3001 and 3009, including cross-over after end of double blind phase
- Design decisions evaluated through extensive simulation
- Monitoring of trial progress to make decisions about timing of EUA and BLA
- Lessons learned

COV3001 and COV3009 design with cross-over



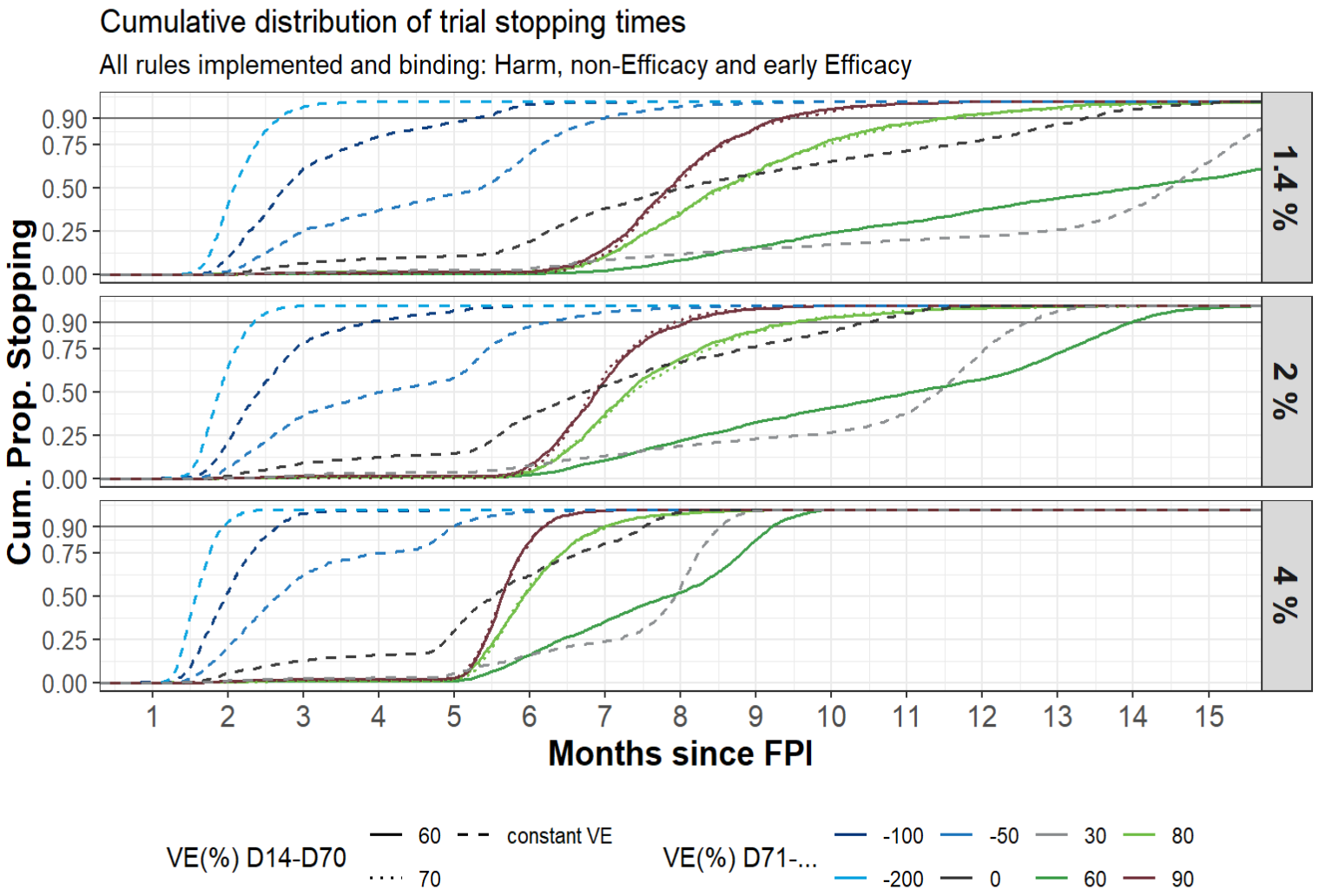
Primary questions

- Double blind phase
  - 3001: a single dose in sero-negative subjects at baseline has vaccine efficacy >= 50% compared to placebo, in molecularly confirmed COVID-19 moderate and severe cases, in both timepoints of 14 and 28 days after vaccine
  - 3009: two dose has VE >= 30% 14 days after second dose (71 days after first) in moderate and severe cases against placebo
- Open label phase
  - 3001: assess durability of vaccine efficacy of one-dose regimen
  - 3009: demonstrate two-dose regimen has vaccine efficacy >= 0% relative to one-dose regimen (FDA guidance requires noninferiority: relative VE > -10%)
- Other objectives include
  - Efficacy in more severe disease
  - Efficacy in elderly population
  - Efficacy against mild disease
  - Efficacy against asymptomatic infection, burden of disease, medical intervention
  - Viral Load

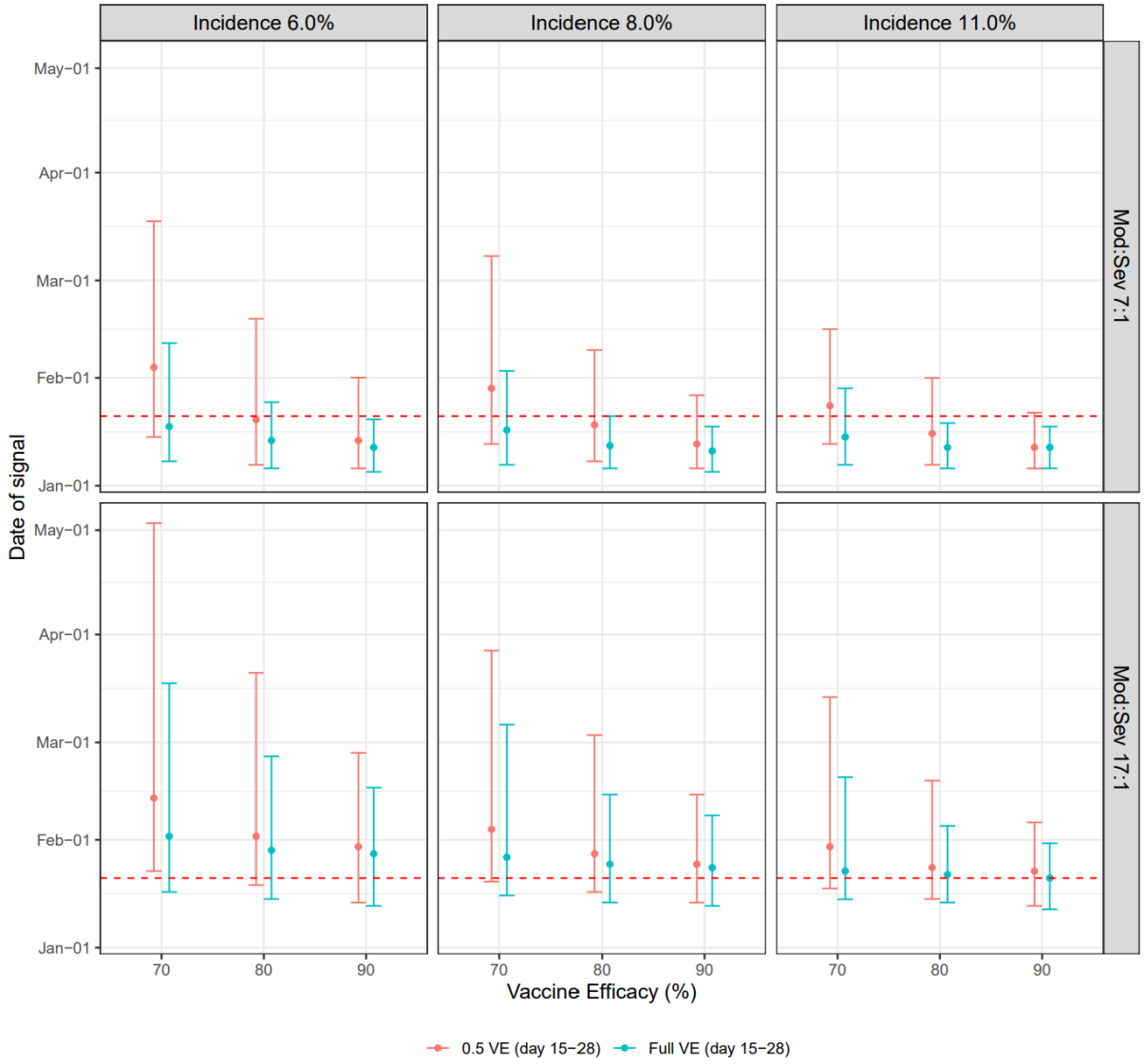
Some issues considered for design and analysis

- Background rates, changing over time, and across different countries
- Vaccine efficacy, possibly changing over time as well
- Prevalence of moderate and severe infections
- Time to signal
- Monitoring for harm, non-efficacy, efficacy
- Minimum data requirements
  - To ensure enough exposure e.g. 2 months of follow up for 50% of subjects
  - To ensure enough cases observed in the severe symptom category
  - To ensure enough cases observed in the elderly population
- Hypothesis testing for double blind phase
  - >50% for 3001, >30% for 3009
- Hypothesis testing for open label phase
  - relative VE > 0% (FDA guidance requires noninferiority: relative VE > -10%)
- Type I error control under a sequential design
- Over-run
- Testing strategy for multiplicity control
- Impact of clinical pause of April 13
- Impact of unblinding of 3009 due to EUA and availability of other Vx
- Potential confounding: High risk groups likely cross-over first
- Can 3001 and 3009 data be pooled to better assess durability of VE?

For design: How quickly can a positive VE be established under what sample size?

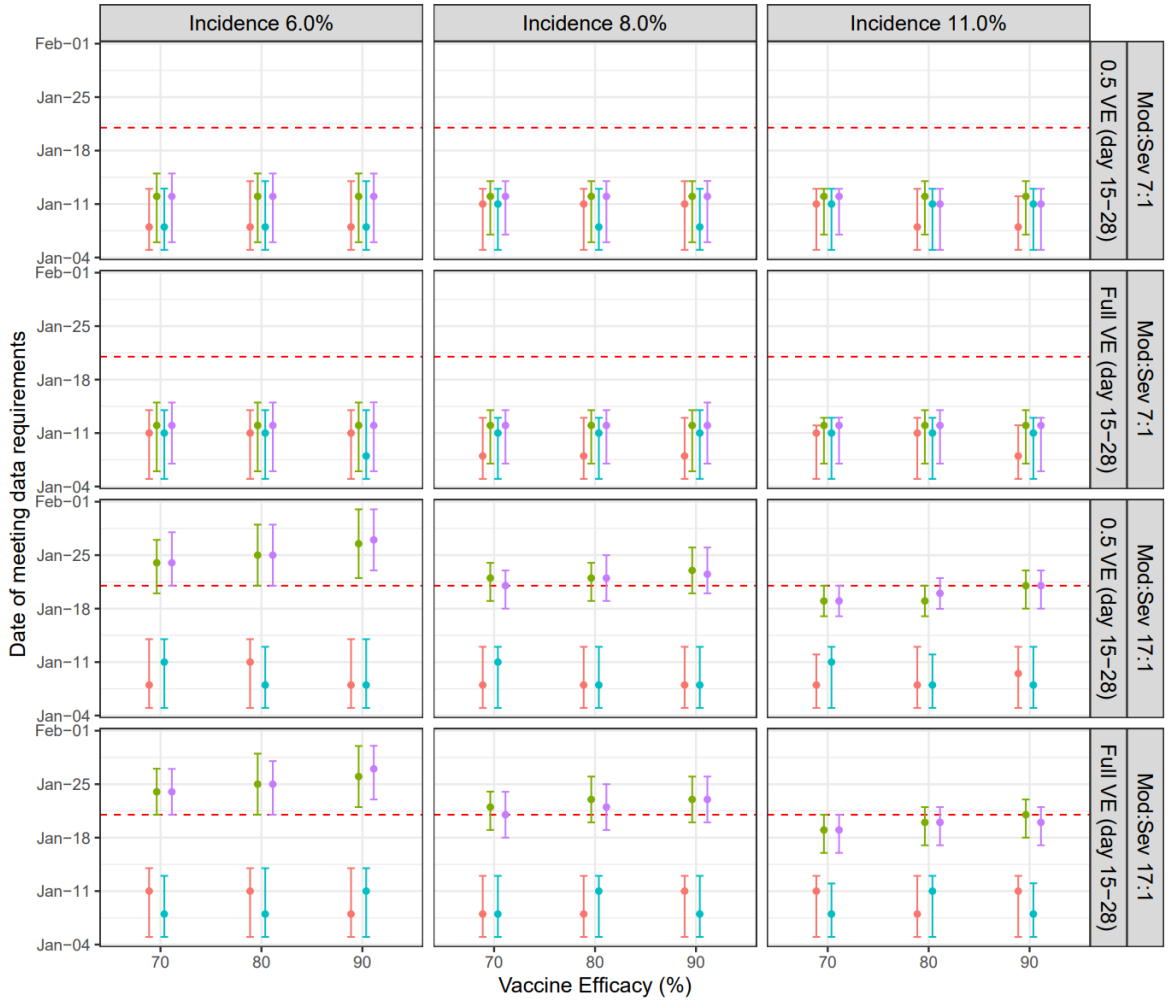


Trial monitoring: When can a positive VE established, given observed (blinded) data so far?



Dot refers to median date of signal
Interval between upper and lower bar spans period in which there is an 80% probability of reaching a signal
Dashed horizontal line marks the date when 2 month median follow up requirement is met (1/21/2020)

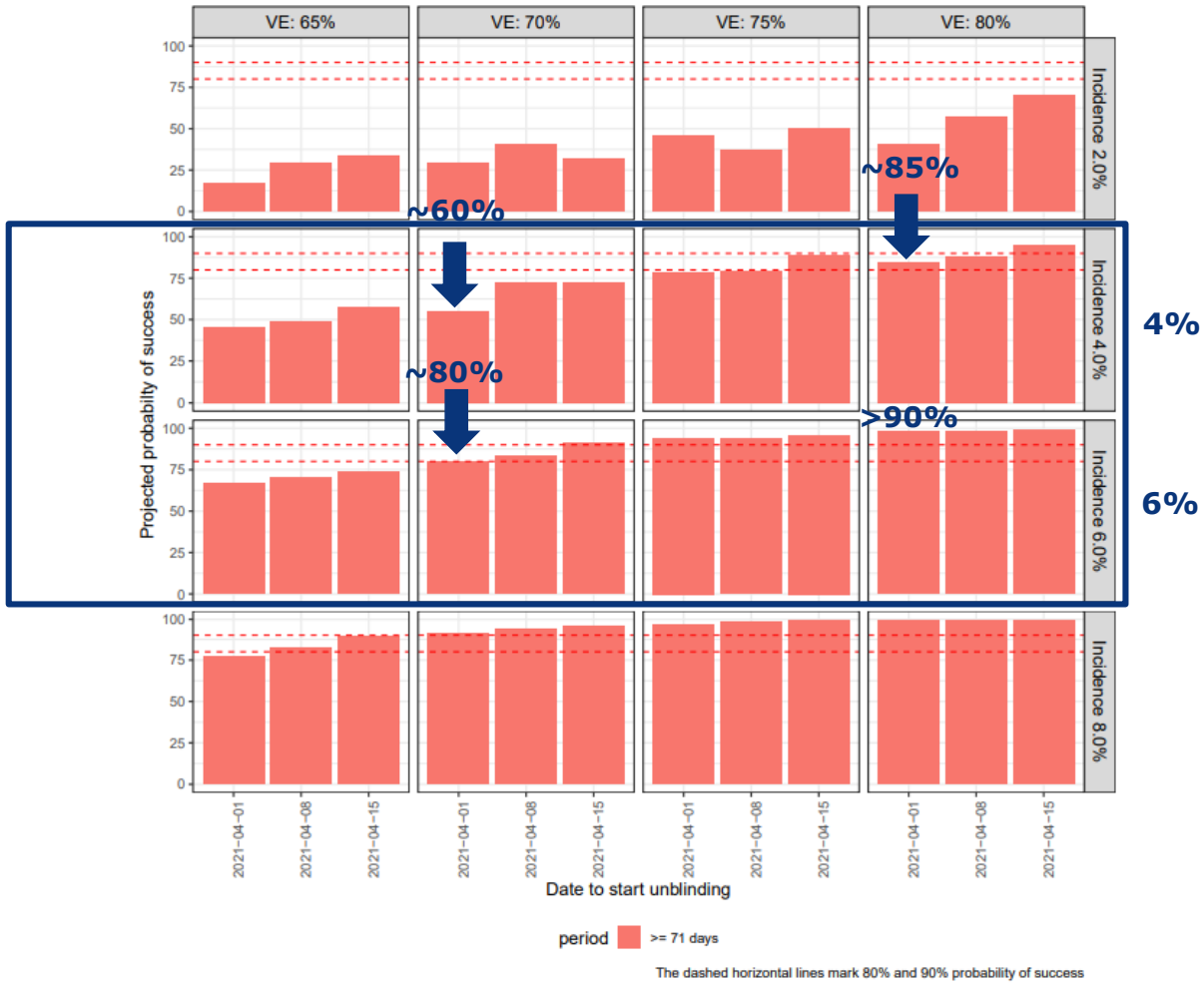
During trial: How are different data requirements impacting timeline, given observed (blinded) data so far?



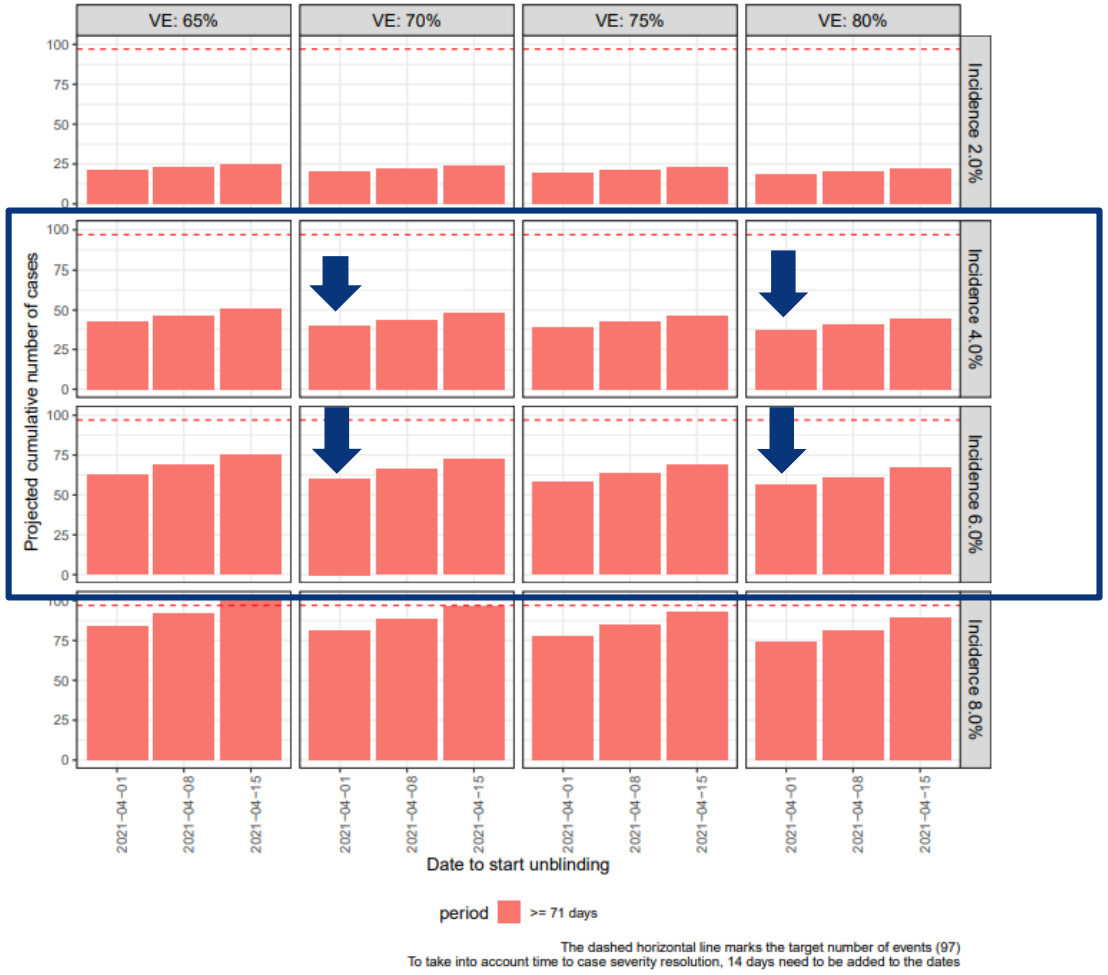
Dot refers to median date of meeting the data requirements
Interval between upper and lower bar spans period in which there is an 95% probability of meeting the data requirements
Dashed horizontal line marks the date when 2 month median follow up requirement is met (1/21/2020)

During trial : How is timing of unblinding impacting probability of success?

Projected probability of success



Projected number of infections when 90% participants unblinded



Simulation is critically important

- For every stage of clinical trial development
  - Design
  - On-going monitoring
  - Analysis
- Simulation helps better understanding of theory
  - Fully sequential, test-at-every-infection design
- But at the same time helps better adapting theory to reality
  - Centrally confirmed infections come in batches
  - Data requirements imposed by FDA and sponsor
  - Potential over-run induced by frequent looks and delayed confirmation
- Simulation helps better decision making
  - Incorporating observed (blinded) up-to-date data for more realistic projections
  - Understand impact on the big picture (PoS, time-to-signal) through one factor at a time when there are many sources of interactions
- Zoom into more likely scenarios as more external data such as infection rates become available

Backup

Incidence rates way higher than planned