RSV VACCINES/PROPHYLACTICS: KEY LEARNINGS FROM THE RSV CHALLENGE MODEL AND EFFICACY OF VACCINES

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INTRODUCTION & OBJECTIVES

Challenge studies can be a powerful tool in the development of both therapeutic agents and vaccines. However, key decisions made in the study design process can have a profound impact on the outcome of the efficacy assessment. These include factors such as the selection criteria and screening of subjects as well as timing and frequency of the virological sampling and illness symptom data. A critical factor is selecting which efficacy endpoints to include and how precisely that is defined and calculated. While the principles of the endpoints are the same in challenge studies and field trials, subtle but vital differences in the endpoint definitions need to be made between the two clinical trial formats to account for the different context. Having access to large amounts of historical data can assist understanding of the natural variability and distribution of disease across the population, which is important for design of robust challenge studies.

METHODS

~10^4 PFU/mL of Good Manufacturing Practice Wild-Type RSV A Memphis 37b virus was administered intranasally to 339 serosuitable and eligible volunteers (10 studies, only placebo analysed here) who remained in our quarantine facility for a total of 14-16 days. 10- to 13-item symptom diary cards were completed three times daily. A subset of 7 studies with data available was used to explore the virological and disease profiles over time when grouped into uninfected and infected tertiles. Severity tertiles were data derived using the peak PCR value for each subject, as shown In Figure 1.

For the purpose of this analysis, to be positive for infection, a subject had to shed virus above the PCR limit of detection for at least 2 consecutive days (i.e. for a minimum of 1 out of 2 to 3 samples obtained daily over 2 or more days).

Main endpoints evaluated:

- Symptom score
  - Diary card self reporting
  - Physician assessment
- Vital signs
- Spirometry, ECG
- Virus titration
  - RT-qPCR,
  - Cell-based
- Mucus
  - Weight
  - Paper tissue count
- Blood markers and safety
  - Haematology, Biochemistry
  - Inflammatory pathways

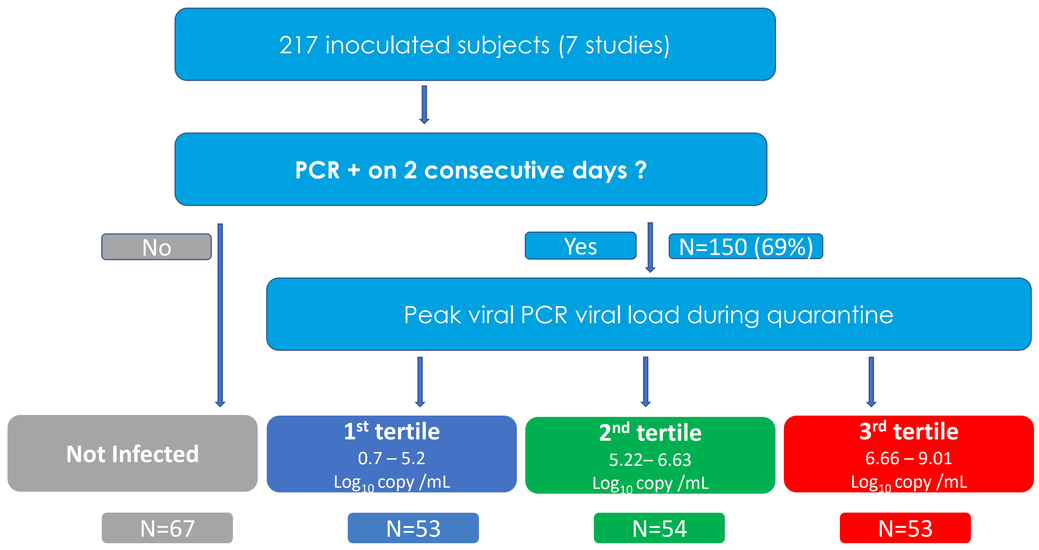

Figure 1: Method of grouping individuals based on infection status and severity of infection as derived using peak PCR.

RESULTS

HVIVO'S RSV METADATABASE

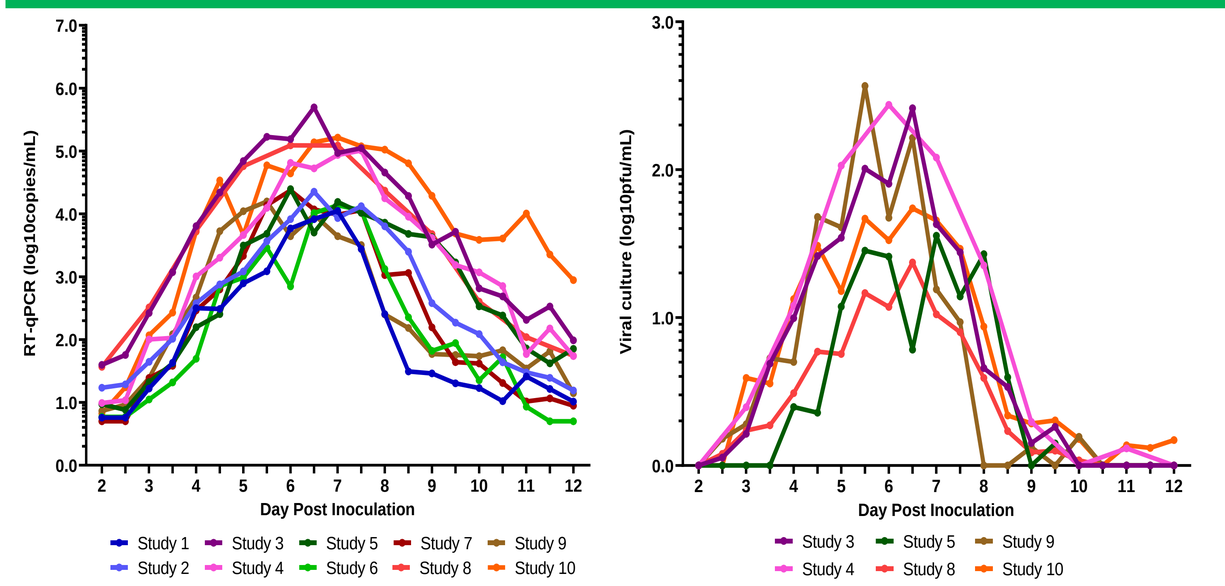

Figure 2. Time course PCR and viral culture across studies. These 2 graphs present the time-course of infected subjects, from baseline to resolution and illustrate the consistency and reproducibility of the model. On the left panel is the time course of PCR in nasal washes from 10 studies with 339 subjects inoculated and 241 infected (71%) as defined by shedding virus above the limit of detection for 2 consecutive days. On the right panel is viral culture in nasal washes from data available from 6 of those 10 studies with 256 inoculated and 189 infected (74%)

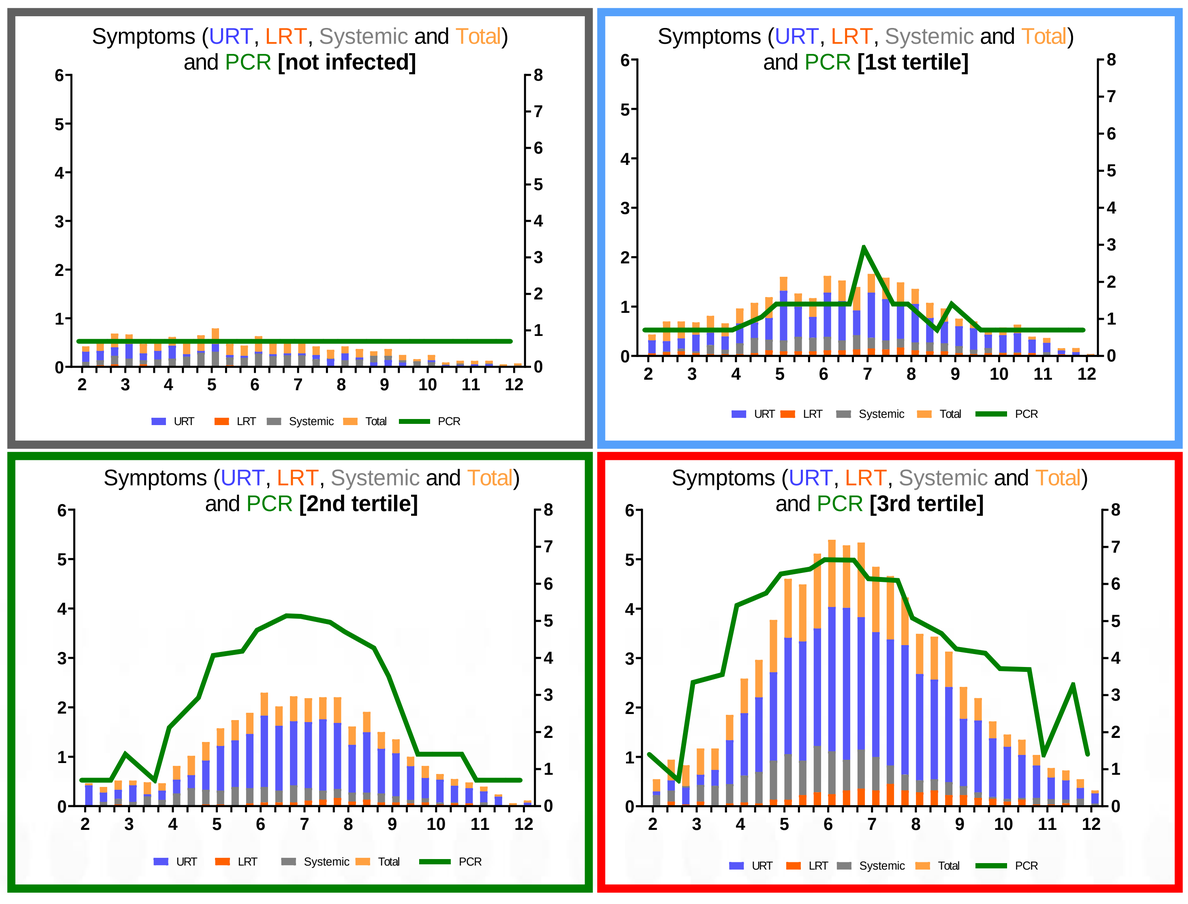

Figure 3. Time course virology and symptoms by disease severity. These four graphs present a subset of 217 subjects from 7 studies with data available and include upper respiratory tract, low respiratory tract, systemic and total symptom scores (stacked bars and left axis) and PCR results (right axis) post inoculation. Each graph shows the average results for the following subgroups: not infected, 1st tertile, 2nd tertile and 3rd tertile.

PUBLISHED RSV VACCINE CHALLENGE INSIGHTS

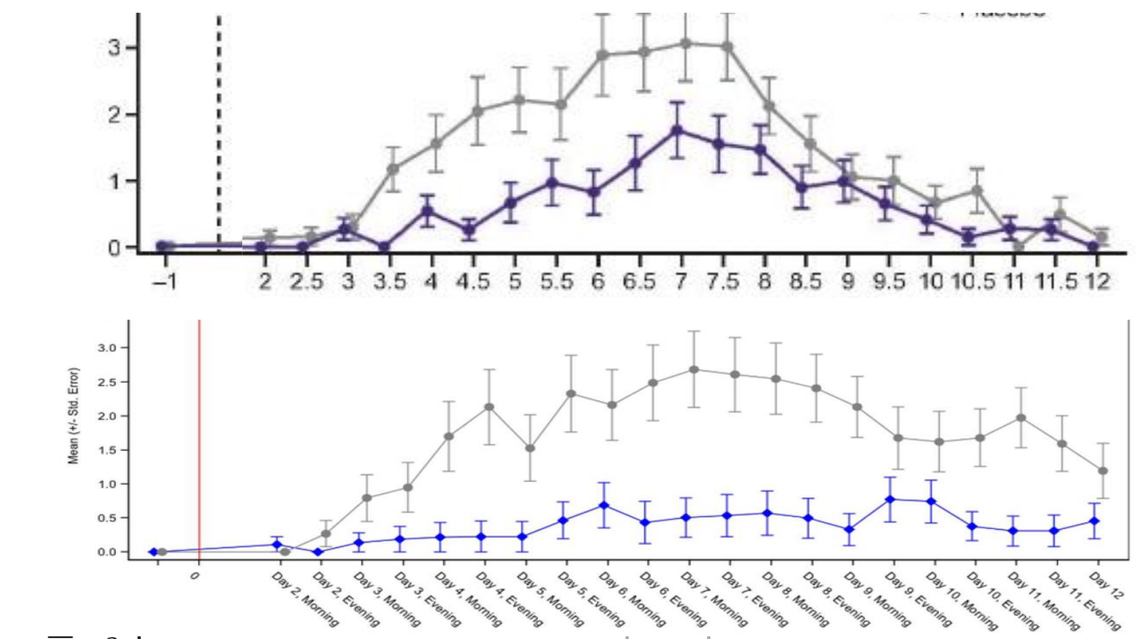

Figure 4. RSV qRT-PCR (log10copies/mL) time course mean values (SEM) for RSV vaccines vs placebo: Top panel J&J (Sadof et al, 2021), Vaccine in blue, placebo in grey; Middle panel Bavarian Nordic (corporate website Sep 2021), vaccine in orange and placebo in grey; Bottom panel; Pfizer (Schmoele et al, 2022), vaccine in blue and placebo in grey.

Incidence variable	J&J (Ad26.RSV.preF) % reduction	Bavarian (MVA-BN RSV) % reduction	Pfizer (RSVPreF) % reduction
PCR (quantifiable)-confirmed infection (any two quantifiable PCR values)	37.7 (–5.7, 69.2)	51.8 (-1.4 - 77.1)	75.0 (38.4, 90.6) *
PCR (detected)-confirmed symptomatic infection (liberal/mild to moderate severity) [1]	n/r	n/r	86.7 (53.8, 96.5)
PCR (quantifiable)-confirmed symptomatic infection (liberal/mild to moderate severity) [1]	45.8 (–1.0, 73.8)	76.2 (24.6 - 92.5)	100 (72.8, 100) #
PCR (quantifiable)-confirmed symptomatic infection (conservative/moderately severe) [2]	51.9 (–7.4, 83.2)	79.3 (13.4 - 95.1)	
Viral culture-confirmed infection	n/r	77.9 (30.7 - 92.9)	100 (72.8, 100)
Viral culture-confirmed symptomatic infection (liberal/mild to moderate severity) [1]	n/r	82.8 (29.4 - 95.8)	n/r
Viral culture-confirmed symptomatic infection (conservative/moderately severe) [2]	n/r	88.5 (14.8 - 98.5)	n/r

Table 1. RSV Vaccine challenge endpoints – how severity and efficacy go hand in hand. As endpoint definitions identify subjects that have relatively higher severity infections, the incident rate in the placebo goes down however the impact of vaccination increase.

* PCR values need to be on two consecutive days. # Symptoms required to be in different categories. Liberal: Lab-confirmed and any clinical symptom (regardless grade or class), Conservative: Lab-confirmed and clinical symptoms of 2 different categories or any grade 2. Data is % and 95% CIs.

CONCLUSIONS

- Historical data assists understanding of natural variability and distribution of disease, which is important for design of robust and appropriately powered challenge studies.
- Highly successful vaccines in the RSV challenge model, as shown above (and publicly available), tend to have a proportionally greater impact on more conservative / higher severity endpoints compared to more liberal / less severe endpoints. This is important to consider in endpoint design of vaccine challenge studies.

ACKNOWLEDGEMENTS

The volunteers, our collaborators, hVIVO clinical, laboratory and operational teams

REFERENCES

- Schmoele et al, 2022 Vaccine efficacy in Adults in a Respiratory Syncytial Virus Challenge study.
- J&J study published: Sadof et al, 2021. Prevention of Respiratory Syncytial Virus Infection in Healthy
- Bavarian Nordic Study: corporate website Sep 2021