A contemporary strain hMPV challenge model:

Designed for vaccine efficacy testing, exhibits high infection rates and strong correlations with baseline antibody levels and disease outcome

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INTRODUCTION & OBJECTIVES

Introduction

Human challenge models have been pivotal in accelerating vaccine development. RSV models, in particular, enabled proof-of-concept studies and expedited the advancement of preF-based RSV vaccines. Given the global burden of human metapneumovirus (hMPV), a comparable challenge model is urgently needed to support hMPV vaccine development

Objective

To establish a robust and efficient vaccine efficacy testing platform through the development of a hMPV human challenge model using a contemporary A2.2 strain of hMPV

METHODS

Virus Selection and Manufacturing process

Multiple clinical samples were collected from patients with community acquired symptomatic hMPV infection and aliquoted before use. The isolates were triaged for suitability to produce a challenge agent based on the following criteria: ability for the virus to grow in GMP Vero cell line, absence of adventitious agents, suitable genome sequence. Once the growth conditions for the isolate had been optimised in the GMP Vero cell line, an unused aliquot of the clinical sample was used to re-isolate the virus and produce the seed virus (p3) for GMP manufacture (p4). The chosen isolate was a A2.2 strain from a clinical sample collected from a patient in October 2022. The manufacturing process is described below in Fig 1.

Manufacturing Process

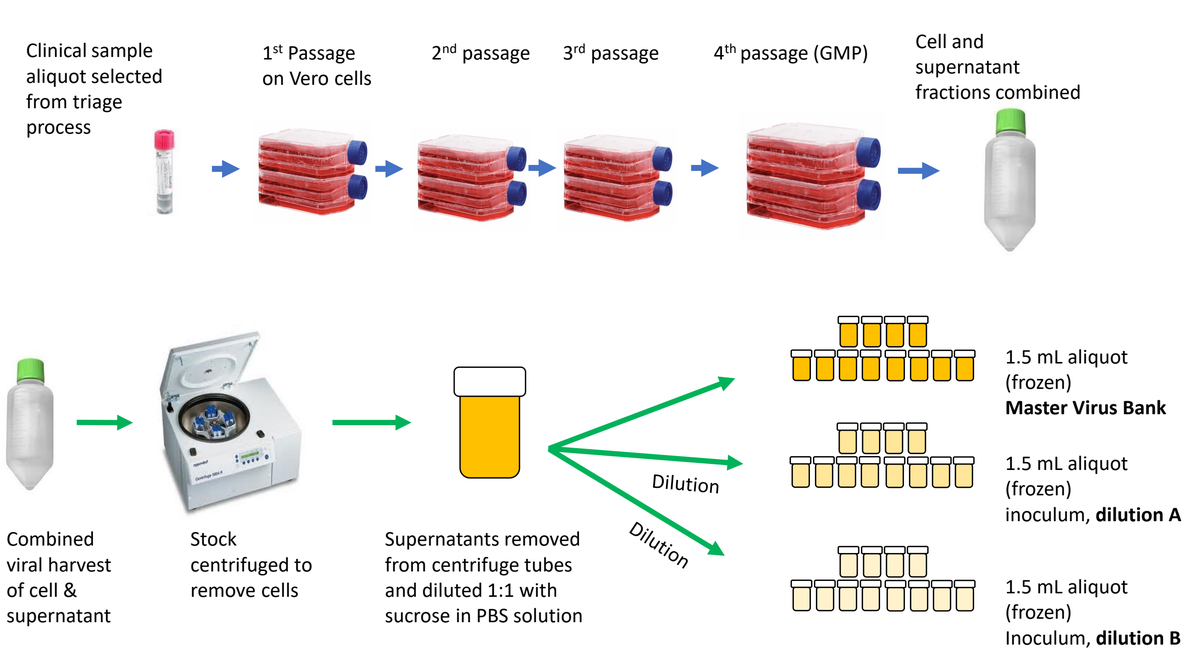


Figure 1: hMPV challenge virus manufacturing process

hMPV-A2.2 hVIVO Human Challenge Model

Volunteers were screened for suitability for participation based on their health status, excluding all volunteers with known risk factors for severe disease from participation. Volunteers' antibody levels prior to inoculation were determined by neutralisation assay but no serological antibody selection criteria applied. Fig. 2 illustrates the challenge model process, showing the screening, inpatient and outpatient phases.

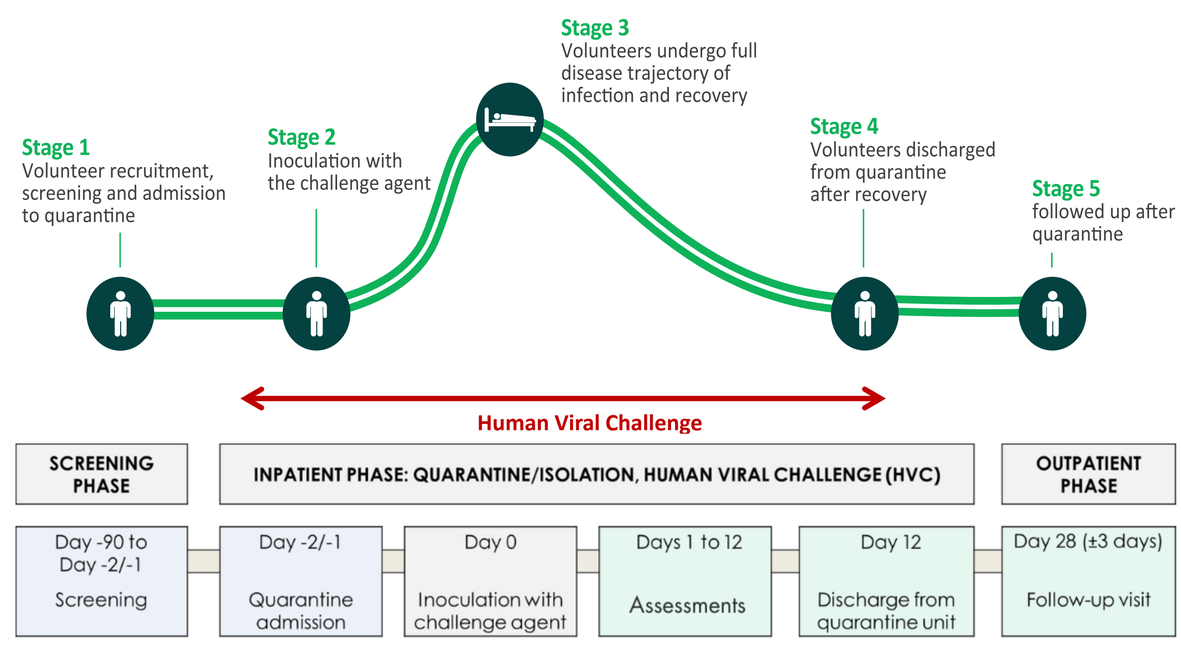
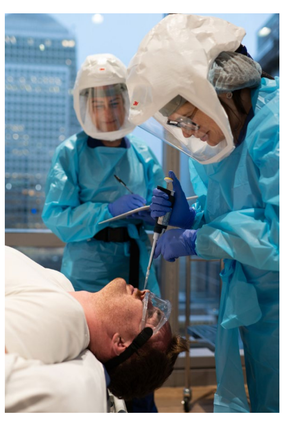


Figure 2: hMPV human challenge model process



During the quarantine phase, post intranasal inoculation with the GMP hMPV challenge virus, volunteers were monitored closely via safety assessments and examinations. Their clinical disease was monitored by completion of a symptom diary card (3x daily), vital signs (daily), nasal discharge / mucus weight (daily) and nasopharyngeal swabs (NPS) for viral load determination (2x daily). Sera was collected pre-inoculation and at follow-up to assess the relationship between infection and antibody levels.

RESULTS

Clinical Outcomes

In total, 28 participants were challenge with the newly developed GMP hMPV A2.2 virus, each receiving the same dose of approximately 4.5 PFU/ml.

- An excellent safety profile was obtained: No SAEs, all AEs mild & resolved
- High symptomatic infection rate observed
- Robust AUC (Area Under the Curve) virology determined by qRT-PCR

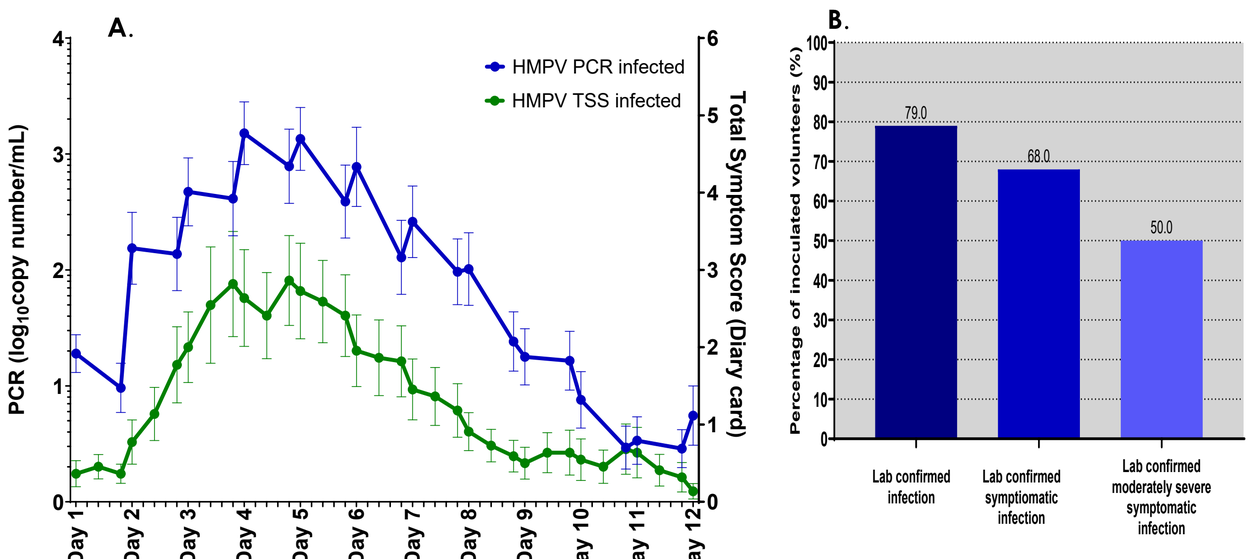


Figure 3: hMPV Disease profile of infected study participants. **A.** Group mean infected participants viral load by qPCR (blue) total symptom score (TSS) (green). **B.** Key infection status incidence endpoints.

Lab-confirmed infection (LCI): >=2 quantifiable PCR over 48 hours

Lab-confirmed symptomatic infection: LCI plus symptom score ≥ 2

Lab confirmed moderately severe symptomatic infection: LCI plus ≥ grade 2 symptoms

(diary card scored 0, 1, 2 or 3 for each symptom)

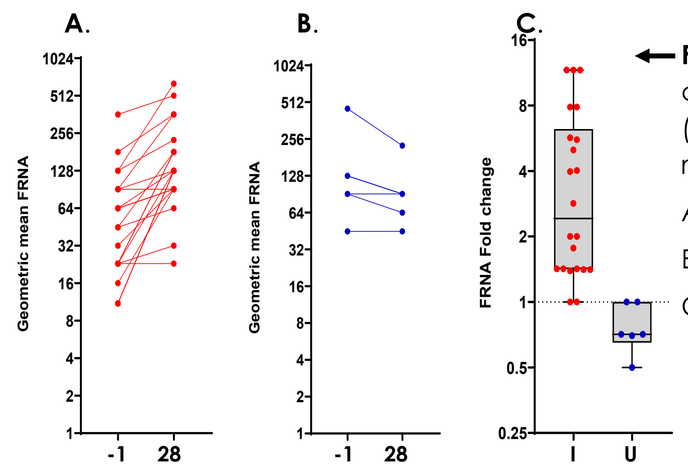


Figure 4: Serum antibody titres pre challenge (day -1) and post challenge (day 28 follow up) measured by Focus reduction neuralisation assay (FRNA)

A. Mean titre: Infected participants

B. Mean titre: uninfected participants

C. fold change: infected (I) vs uninfected (U)

- Red = Infected
- Blue = uninfected

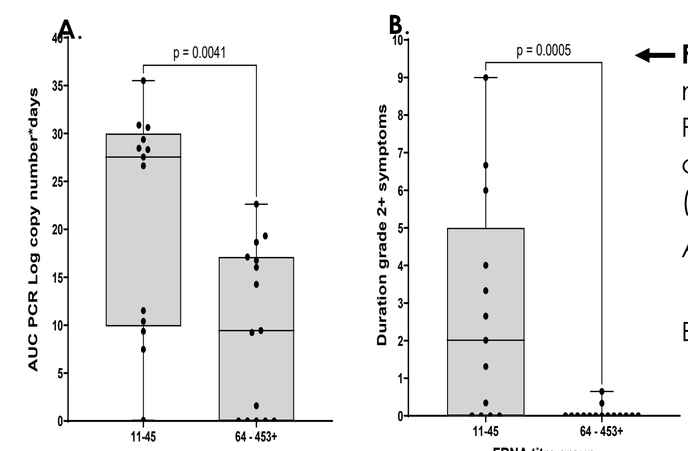


Figure 5: Impact of baseline serum neutralisation titres on disease severity. Participants with low (11-45) titres were compared to those with higher titres (64-453+).

A. Low and high FRNA titres impact on viral load AUC by qPCR

B. Low and high FRNA titres impact on duration of more severe symptoms (grade 2+).

Clear differences were observed in the change from baseline for infected and uninfected participants, with only infected participants showing increases (Fig. 4). In addition, baseline serological antibody titres were shown to have a significant Impact on both viral load AUC and symptom severity was significant (*p* values indicated in Fig. 5)

ACKNOWLEDGEMENTS

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Use QR code for further information

CONCLUSIONS

This contemporary A2.2 strain hMPV challenge model, demonstrated an excellent safety profile, **high infection rates**, reproducible symptomatic disease, and strong correlations between baseline immunity and clinical outcome. The model provides a **powerful platform for vaccine efficacy testing** without the need to exclude participants based on pre-existing antibody titres. The data indicates that infection rates and disease severity may be further enhanced through exclusion of participants with high baseline serology titres to the challenge strain. Together, these data underscore the model's utility in advancing hMPV vaccine development as well as for therapeutic efficacy testing.