THE HUMAN VIRAL CHALLENGE MODEL WITH A/PERTH/16/2009 H3N2
A SYSTEMATIC ANALYSIS FROM FIVE CLINICAL STUDIES

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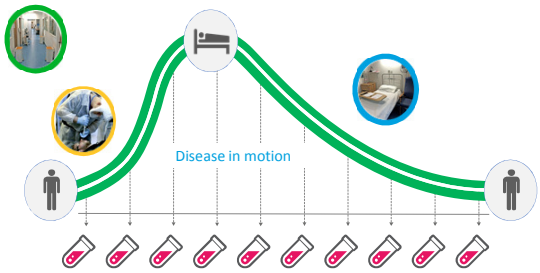
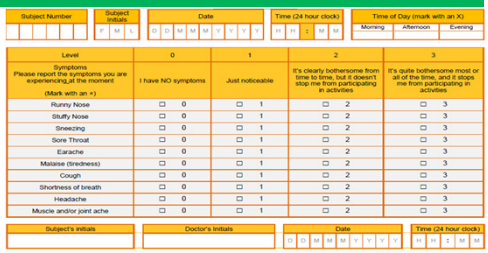
INTRODUCTION & OBJECTIVES

The human viral challenge model is well established, safe and ideal to study influenza. It allows researchers to illuminate each step of the infection: baseline, peak and return to healthy. It is possible to stipulate each experimental parameter such as virus strain, environment, sampling methods, schedule of intervention and subjects' demography (young, older, HLA type, pre-challenge immune response).

The objective of this analysis is to illustrate the complexity of the data at the subject-, study- and cohort levels.

HUMAN VIRAL CHALLENGE MODEL





- Standardised Symptom Diary Card (self-assessment)
- Facilitating powering assumptions

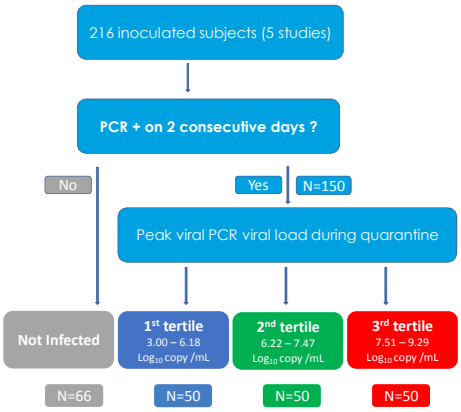
METHODS

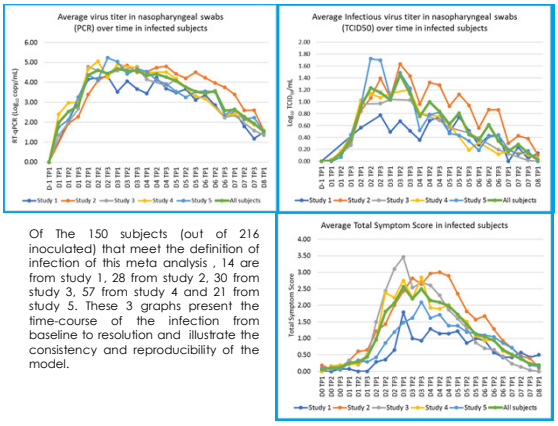
3.6 x 10^5 $TCID_{50}$ of Good Manufacturing Practice Wild-Type A/Perth/16/2009 H3N2 influenza virus was administered intranasally to 216 serosuitable and eligible volunteers (5 studies, only placebo analysed here) who remained in our quarantine facility for a total of 10-11 days. 10- to 13-item symptom diary cards were completed three times daily.

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:

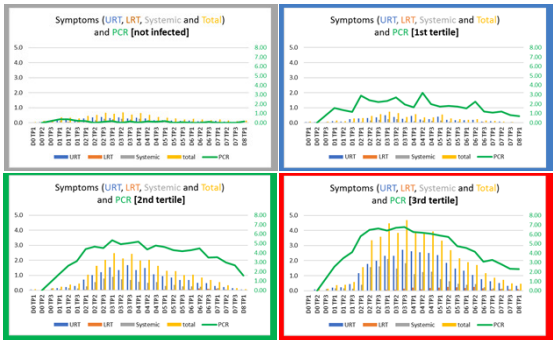
- Symptom score
  - Diary card self reporting
  - Physician assessment
- Vital signs
- Spirometry, ECG
- Blood markers and safety
  - Haematology, Biochemistry
  - Inflammatory pathways
- Virus titration
  - RT-qPCR,
  - Cell-based
- Mucus
  - Weight
  - Paper tissue count



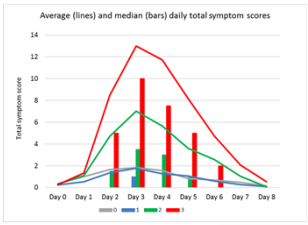


Of The 150 subjects (out of 216 inoculated) that meet the definition of infection of this meta analysis , 14 are from study 1, 28 from study 2, 30 from study 3, 57 from study 4 and 21 from study 5. These 3 graphs present the time-course of the infection from baseline to resolution and illustrate the consistency and reproducibility of the model.

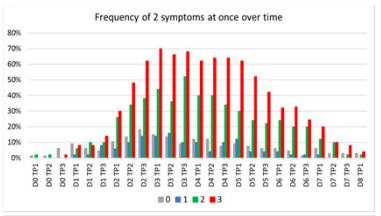
RESULTS

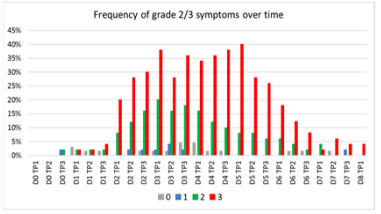


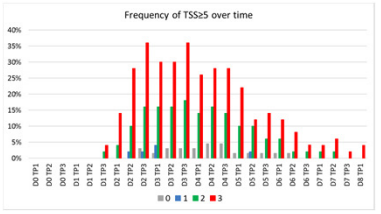
These four graphs present upper respiratory tract, low respiratory tract, systemic and total symptom scores (bars and left axis) and PCR results (right axis) post inoculation. Each graph shows the average results for the following subgroups: not infected, 1st tertile, 2nd tertile and 3rd tertile.



The left graph shows daily total symptom scores (average and median) per subgroup (not infected, 1st tertile, 2nd tertile and 3rd tertile). The score is obtained by combining the total symptom scores from morning, midday and evening symptom diary cards. Day 3 is the peak time point for all subgroups.

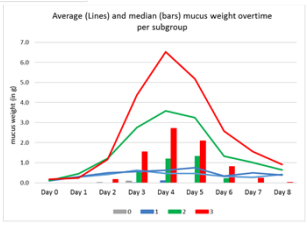




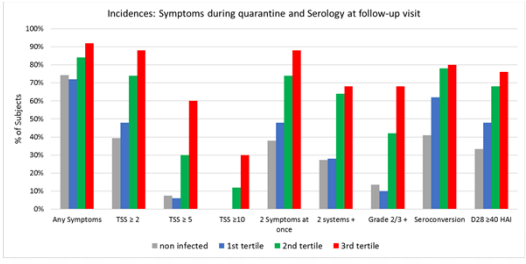


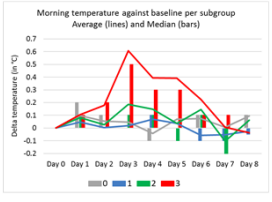
This figure shows the frequency of 2 symptoms at once (top graph), grades 2 and 3 symptoms (middle graph) and total symptom score greater or equal to 5 (bottom graph) per time point during the quarantine period.

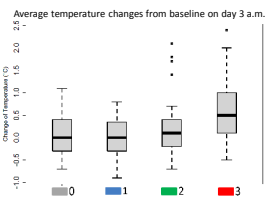
The right graph shows daily mucus weight (average and median) per subgroup (not infected, 1st tertile, 2nd tertile and 3rd tertile).



The below figure shows incidences of single and composite endpoints per subgroup (not infected, 1st tertile, 2nd tertile and 3rd tertile). We focus here on symptoms and serology. "2 systems" refers to 2 of the following: upper respiratory, lower respiratory and systemic symptoms.







Subjects' aural temperature were measured 3 times daily from admission to discharge. Each subject serves as their own baseline (defined as day 0 morning). The left graph presents the average and median of delta temperature for each morning reading for the 4 subgroups. The right graph focusses on day 3 a.m. time point and highlights the fact that temperature increases are not always observed during influenza infection.

CONCLUSIONS

These results demonstrate the broad variety of phenotypes of influenza infection and are key to discovering correlates of protection and predictors of outcome of infection. Thus, this novel analysis allows for improved design and powering of human challenge and field studies. Additionally, deep mining of data and samples is pivotal to the discovery of, and the decision-making process for, new therapies.

The human viral challenge model of infection with influenza provides a unique opportunity to fully understand the course of the disease. Although this model of viral infection is well understood and widely accepted on a study per study basis, the systematic analysis of a placebo dataset across multiple studies run by one group at a single centre can assist to optimise the design of human viral challenge studies.

PERSPECTIVES

As most parameters can be standardised, combining data and analysis at subject-, study- and cohort levels will be key to future research. In addition to the most obvious ones, novel and more refined endpoints can be selected and virus-host interaction responses targeted more precisely.

Study design: Typically randomised double-blind placebo-controlled studies that evaluate IMP antiviral activity, safety and efficacy
Study population: 18 to 64 year old healthy subjects with low serum Ab response
Study size: 40 to 140

ACKNOWLEDGEMENTS

The volunteers, our collaborators, hVIVO clinical and laboratory teams

REFERENCES

- The manufacturing of human viral challenge agents for use in clinical studies to accelerate the drug development process. *Andrew Catchpole et al. BMC 2018*
- The human viral challenge model: accelerating the evaluation of respiratory antivirals, vaccines and novel diagnostics. *Rob Lambkin-Williams et al. Respiratory Research 2018*