Viral kinetic modeling and clinical trial simulation predicts disruption of respiratory disease trials by non-pharmaceutical COVID-19 interventions

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INTRODUCTION

Clinical research in infectious respiratory diseases has been profoundly affected by non-pharmaceutical interventions (NPIs) against COVID-19. On top of trial delays or even discontinuation which have been observed in all disease areas, NPIs altered transmission patterns of many seasonal respiratory viruses which followed regular patterns for decades before the pandemic. Clinical trial design based on pre-pandemic historical data therefore needs to be put in question.

OBJECTIVE

Assess the feasibility of clinical trials in infectious respiratory diseases during COVID-19 pandemic using mechanistic mathematical modelling by simulating in silico clinical trials under reduced viral transmission.

METHODS

We set up an epidemiological model of respiratory tract infection (RTI) sensitive to a time dependent between-host transmission rate and coupled this model to a mechanistic description of viral RTI episodes in an individual patient (within-host model, Figure 1).

The between-host epidemiological model is based on a compartmental approach describing susceptible, infected, recovered and again susceptible (SIRS) individuals and explicitly describes transmission, recovery, and immunity loss rates. The within-host model implements lytic versus nonlytic immune mechanisms during viral infection to simulate the within-host dynamics in response to respiratory virus exposure.

By reducing the transmission rate when the lockdown was introduced in the United Kingdom in March 2020, we were able to reproduce the perturbed 2020 RTI disease burden data (Figure 2).

Using this setup, we simulated several NPIs scenarios of various strength (none, mild, medium, strong) and conducted placebo-controlled in silico clinical trials in pediatric patients with recurrent RTIs (RRTI) quantifying annual RTI rate distributions. In interventional arms, virtual patients aged 1-5 years received the bacterial lysate OM-85 (approved in several countries for the prevention of pediatric RRTIs) through a pro-type I immunomodulation mechanism of action described by a physiologically based pharmacokinetics and pharmacodynamics approach (PBPK/PD).

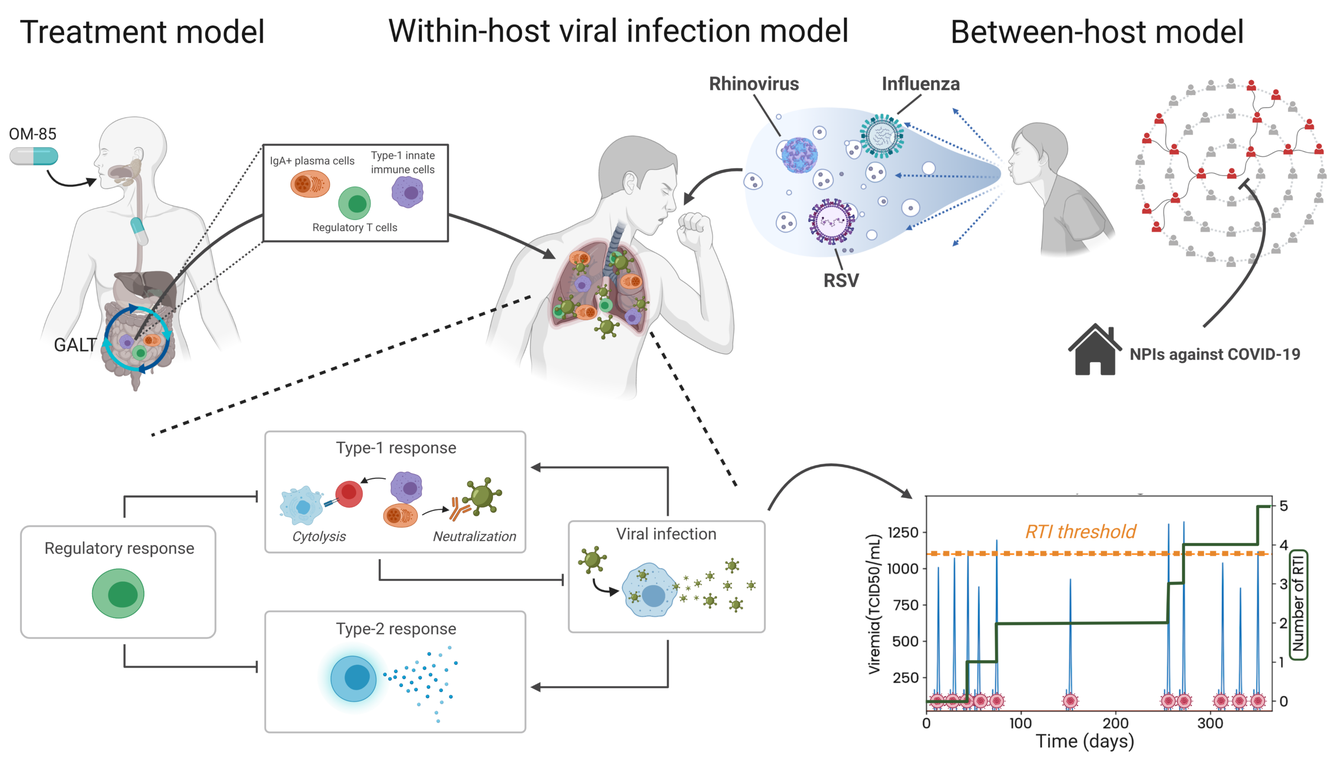

Figure 1: Multi-scale in silico approach to incorporate within-host and between-host respiratory tract infection (RTI) model as well as a treatment model with bacterial lysate OM-85. The model is used to assess feasibility of clinical trials in prophylaxis of RTIs during COVID-19 pandemic.

RESULTS

We first compared the rate of RTIs in the treated group (Rt) and in the control group (Rc) using various metrics. While the absolute benefit (AB = Rc - Rt) of OM-85 decreases in parallel to the reduction of the transmission rate, the event rate ratio (ERR = Rt / Rc) however does not vary considerably in all but the strongest NPI scenario (data not shown).

The sample size estimations commonly used in RTI prophylaxis trial designs are based on ERR and consequently, they closely follow the trend of the ERR itself (Figure 3, left). To gauge recruitment issues, we estimated the time required to recruit the estimated sample sizes if NPIs were started at the beginning of year 1 and by assuming a constant hypothetical screening rate of 1000 patients per year (Figure 3, right).

Year 1 is the selection year during which patients are screened and possibly included in an in silico trial. NPIs introduced during this period could perturb the selection process. A slight reduction of the transmission rate -- as small as 5% -- already increases the time to recruit by about 50%. The medium and strongest NPI scenarios (15% and 25% transmission rate reduction, respectively) lead to infeasible recruitment times (3 years and 288 years respectively).

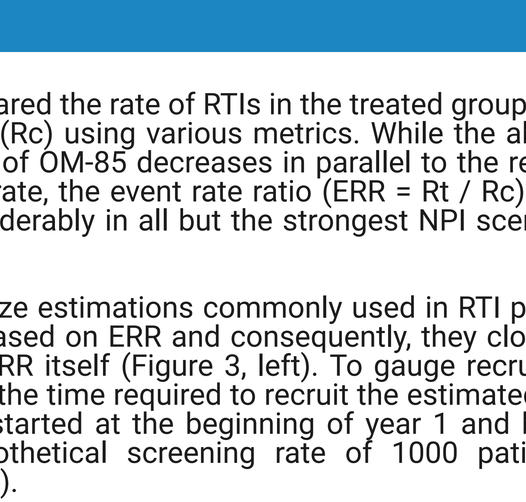

Figure 4: Effect Model plot for the four NPI scenarios. Each in silico clinical trial is plotted (symbols) with the number of RTIs in the control group as x coordinate and the number of RTIs in the treated group as y coordinate. The region of clinically relevant efficacy is indicated in orange.

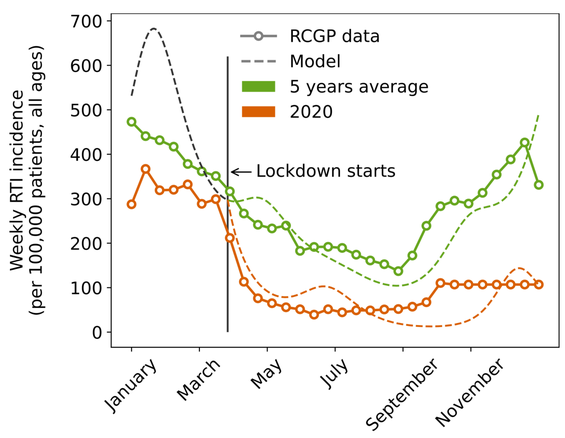

Figure 2: Comparison of model predictions (dashed lines) and data (solid lines) from RCGP for RTI weekly incidence (per 100,000 all ages) for the 5 years average (green) and 2020 (orange) with lockdown started on March 23rd.

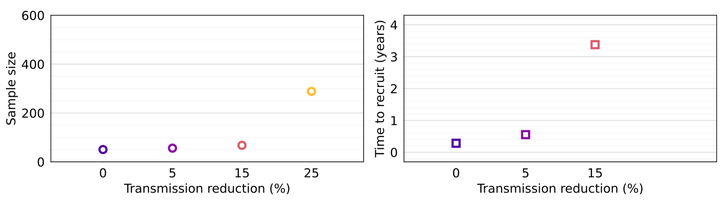

Figure 3: Left, sample sizes per arm required to show efficacy of OM-85 treatment in reducing number of RTIs for the four NPI scenarios. Right, estimated patient screening times under the four NPI scenarios.

Finally, we compared Rt and Rc directly in a two-dimensional analysis (Effect Model, Figure 4). Because Rc is often used to define the risk for RTI, this analysis characterizes the efficacy as a function of the risk. We indicate a region of clinical relevance matching three conditions (orange area in Figure 4) and found that according to this set of criteria, the trials which can be considered as feasible are those conducted when viral transmission rates are reduced by 5% but not more than 15%, even though trials with higher reduction may still meet their endpoints (given that patient selection is not impaired such as in our simulation scenario).

CONCLUSION

Model's predictions showed that sample size estimates based on the ratio of RTI rates (ERR) are not majorly impacted under NPIs which are less severe than a strict lockdown. However, milder NPIs show a stronger impact on metrics more relevant for assessing the clinical relevance of the effect such as absolute benefit.

This dichotomy shows the risk that successful trials (even with their primary endpoints being met) still get challenged in risk benefit assessment during the review of market authorization. Furthermore, we found that a mild NPI scenario already affected the time to recruit significantly when sticking to eligibility criteria complying with historical data.

In summary, our model predictions can help rationalize and forecast post-COVID-19 trial feasibility. They advocate for gauging absolute and relative benefit metrics as well as clinical relevance for assessing efficacy hypotheses in trial design and they question eligibility criteria misaligned with the actual disease burden.

REFERENCES

Arsène, S., Couty, C., Faddeenkov, I. et al. Modeling the disruption of respiratory disease clinical trials by non-pharmaceutical COVID-19 interventions. Nat Commun 13, 1980 (2022). https://doi.org/10.1038/s41467-022-29534-8