Viral kinetic modeling and simulation of the impact of non-pharmaceutical COVID-19 interventions in different countries: model-informed respiratory disease trial design

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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 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 [1].
The objective of the work presented here is to assess the feasibility of clinical trials in respiratory tract infections (RTIs) during COVID-19 pandemic using mechanistic mathematical modelling by simulating in silico clinical trials under reduced viral transmission via NPIs in the United Kingdom (UK) and China.

METHODS

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

By reducing the transmission rate when the lockdown was introduced in UK in March 2020 and in China in January 2020, we were able to reproduce the perturbed RTI disease burden data for the two locations (Figure 2). Using this setup, we simulated several NPI scenarios of various strength (none=0%, mild=5%, medium=15%, strong=25%) 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 (PBPK/PD) approach (treatment model).

RESULTS

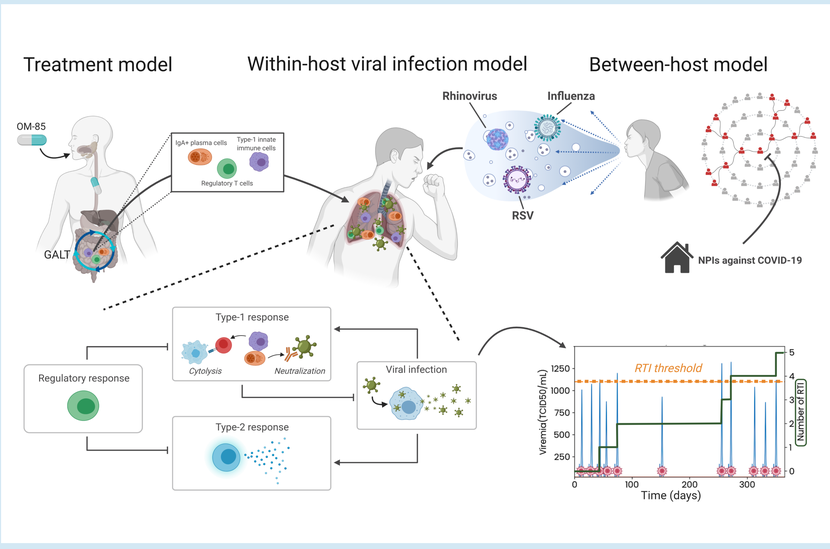

Figure 1: Multi-scale in silico approach to incorporate within-host and between-host respiratory tract infection (RTI) model as well as a treatment model with bacterial lysate OM-85. The model is used to assess feasibility of clinical trials in prophylaxis of RTIs for different non-pharmaceutical interventions (NPI) mimicking the COVID-19 pandemic in the United Kingdom (UK) and China.

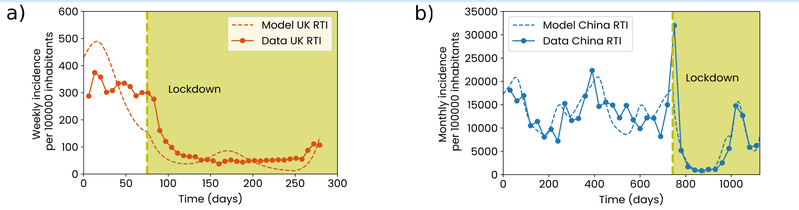

Figure 2: Comparison of model predictions (dashed lines) and data (solid lines). a) from Royal College of General Practitioners (RCGP) [2] for RTI weekly incidence in 2020 with lockdown starting on 23/03/2020; from Wang et al. [3] for RTI monthly incidence in 2018-2021 with lockdown starting on 23/01/2020.

We first compared the rate of RTIs in the treated group (Rt) and in the control group (Rc) using various metrics. While the event rate ratio (ERR = Rt / Rc) does not vary considerably in all but the strongest NPI scenario in both locations (data not shown), the absolute benefit (AB = Rc - Rt) of OM-85 in return decreases in parallel to the reduction of the transmission rate. This is highlighted in a two-dimensional analysis of Rt and Rc (Effect Model exemplarily for UK, Figure 3) . Because Rc is often used to define the risk for RTI, this analysis characterizes the efficacy as a function of the risk.
Moreover, we indicate a region of clinical relevance matching three conditions (orange area in Figure 3). We found that according to this criteria set, the trials, considered as feasible, are those that are 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).

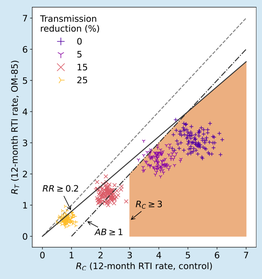

Figure 3: Effect Model plot for the four NPI scenarios in the UK. Each in silico clinical trial is plotted (symbols) with its mean number of RTIs in the control and treated group respectively as abscissa and ordinate. The region of clinically relevant efficacy is indicated in orange.

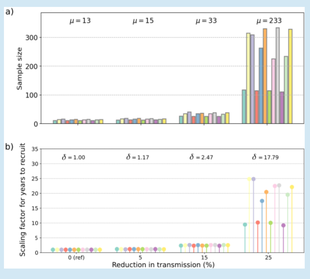

Figure 4: Clinical trial feasibility indicators for the four NPI scenarios in China. a) sample sizes per arm required to show efficacy of OM-85 treatment in reducing number of RTIs. b) estimated patient screening times, normalized by reference (no lockdown) scenario.

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. To gauge recruitment issues, we estimated the scaling factor, by which the time required to recruit the estimated sample sizes changes compared to a pre-pandemic reference scenario, if NPIs were started at the beginning of year 1 (selection year for screening and including patients in a trial). We assumed a constant hypothetical screening rate of 1000 patients per year (both analyses exemplarily for China, Figure 4).
The strongest NPI scenario yields a sample size too large to be feasible (233 patients), whereas for mild and medium NPIs it remains with a realistic range (Figure 4a).
A slight reduction of the transmission rate - as small as 5% - already increases the time to recruit by about 20%. The medium and strongest NPI scenarios (15% and 25% transmission rate reduction, respectively) lead to infeasible recruitment times (2.5 years and 17.8 years respectively) (Figure 4b). In the UK, already for a mild NPI, the time to recruit is increased by about 50% (data not shown).

CONCLUSION

The model predictions showed that sample size estimates are not majorly impacted under less than strong NPIs. However, milder NPIs show a more powerful impact on assessing clinical relevance of the effect such as absolute benefit. This dichotomy shows the risk that successful trials still get challenged in risk benefit assessment during the review of market authorization.

We found that a mild NPI scenario already affected the time to recruit significantly when sticking to eligibility criteria complying with historical data.

Our modeling approach proved insightful to encompass different regions, with their unique RTI seasonalities and NPIs.

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

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