Case study

RTI: the challenge of running clinical studies during pandemic lockdowns



The challenge

OM Pharma wanted to assess the feasibility of running clinical trials of a treatment to prevent respiratory tract infections (RTIs) during the Covid-19 lockdown.

The solution

Nova built a multi-scale *in silico* model capturing how non-pharmaceutical interventions (NPI) - such as lockdown or mask-wearing - affect rates of infection with the most common respiratory viruses, and the impact of the prophylactic treatment OM-85 under different NPI scenarios in the context of an upcoming trial. The model calculated the required adjusted sample size and recruitment efficiency allowing OM Pharma to make informed clinical development decisions and take risk mitigation strategies (such as considering an adaptive design).
Results were published in Nature Communications in April 2022.[1]

Background

Even before the Covid-19 pandemic, RTIs were a leading cause of hospitalization in children, many of whom may go on to develop chronic conditions such as asthma.

Many RTIs are triggered by viruses, but bacterial infection often follows. The most common viral triggers are influenza viruses, rhinoviruses (like those behind the common cold) and respiratory syncytial virus. OM-85 combines antigens from a variety of bacterial strains involved in RTIs. Historically, scientists believed that oral administration of these antigens triggered specific immunity to the respective microbes. Since then, it has become clear that the impact of these antigens on the immune system is much more complex. It involves innate immune cell reprogramming and wider immune-system modulation that protects against both bacterial and viral infections.

There is evidence that OM-85 can help prevent RTIs both in children and adults - either as a complement to vaccination, or as an alternative in areas like RSV where no vaccine has yet been approved..

OM Pharma is planning the generation of clinical data further supporting OM-85's efficacy. Yet, running an RTI prophylaxis study had just got a lot harder. The pandemic had severely impacted clinical trial recruitment and execution across the board, while social distancing and lockdowns radically cut RTI incidence in the population.

Given rapidly-changing NPI and lockdown patterns across continents, and little visibility on when these might end, the company needed to better understand:

- how lockdowns of varying severity impact RTI incidence in the population
- how altered RTI incidence impacts the trial size required to show a preventative effect and its clinical significance
- the impact of lockdowns on the speed and ease of trial recruitment

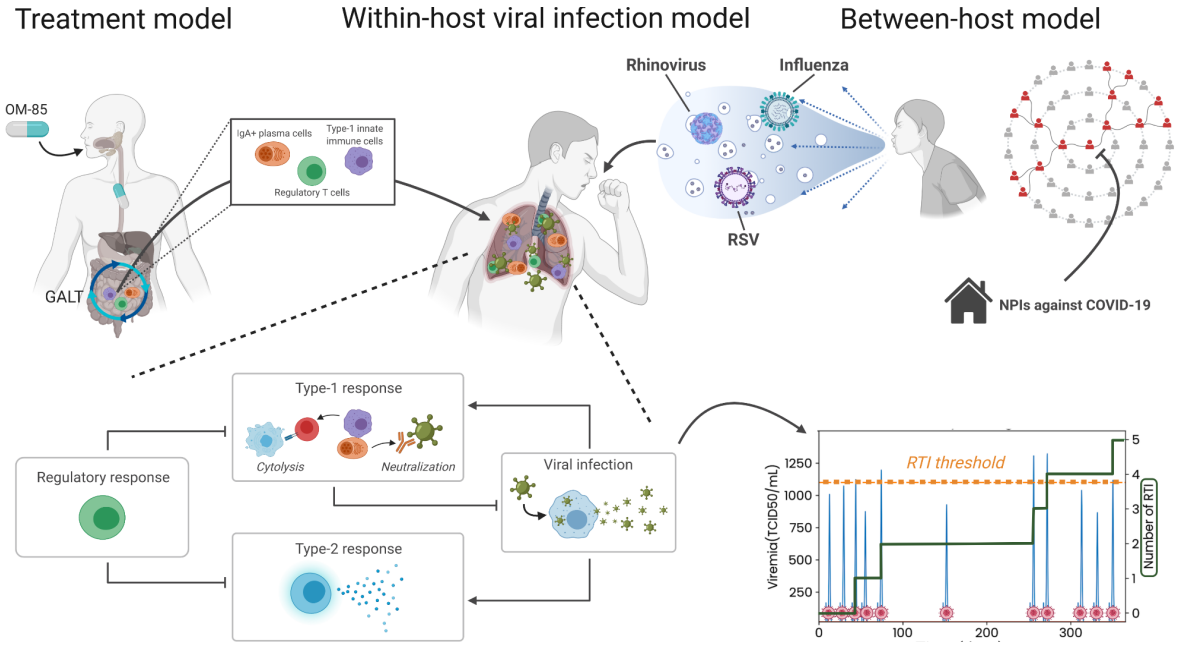
How nova approached the challenge

Nova built an in silico RTI disease model capturing the likelihood of exposure to, and infection by, relevant viruses, as a function of seasonality (winter vs summer) and lockdown status (high to low transmission rates) [1].

The model captures the impact of viral infection on immune cells and inflammatory markers, and, in turn, how these markers affect broader immune system modulation. It also simulated the effects of OM-85, including for instance the activation of gut immune cells and their circulation in the respiratory tract.

Overall, 276 biological variables and 512 parameters were included. The model was calibrated and validated using independent population and patient-level datasets. It successfully reproduced UK surveillance data from 2020 on respiratory tract disease burden under lockdown measures. The model was then used to predict RTI incidence by generating a virtual population of 4000 individuals, characterized by age and immunocompetence level.

Illustration of the RTI disease model



The multi-scale model was built using pre-clinical and clinical data plus extensive literature reviews and in-house expertise.

The outcomes

By simulating the efficacy of OM-85 on RTI risk under different NPI scenarios (no NPI, mild , medium, and strong NPI = lockdown), nova's model showed that running a sufficiently-powered trial was unfeasible during lockdown. The sample sizes required in a strong lockdown is 3-4 times higher than under normal conditions. Patient recruitment (needed to re-establish power) is already impacted during a moderate NPI, is forecasted to take more than 8 years and is already more difficult under mild NPI

While it is not surprising that lockdowns reduce the number of RTIs (thus reduce the demonstrable benefits of OM-85 in preventing disease) and also impair recruitment, it is to note that under medium NPI scenarios the chosen metrics of efficacy become important for success or failure of the trial.

By quantifying Absolute Benefit versus Event Rate Ratios versus recurrent RTI definitions, nova's model helps OM Pharma to identify the optimal analyses and reporting under current circumstances as risk mitigation strategies under which clinical trials could be conducted - for instance, with altered eligibility criteria.

Nova's model also provides an important tool similar to model-based meta-analysis [2] to re-assess the design of planned clinical trials for RTIs during episodes of pandemic containment, which may endure.

References

[1] Modeling the disruption of respiratory disease clinical trials by non-pharmaceutical COVID-19 interventions; Simon Arsène, Claire Couty, Igor Faddeenkov, Natacha Go, Solène Granjeon-Noriot, Daniel Šmít, Riad Kahoul, Ben Illigens, Jean-Pierre Boissel, Aude Chevalier, Lorenz Lehr, Christian Pasquali, Alexander Kulesza; Nature communications, 13(1), 1980 (2022). https://doi.org/10.1038/s41467-022-29534-8

[2] Mechanistic model based meta-analysis for paediatric respiratory tract infection prophylaxis trial design
Simon Arsène, Aude Chevalier, Claire Couty, Igor Faddeenkov, Natacha Go, Solene Granjeon-Noriot, Alexander Kulesza, Lorenz Lehr, Christian Pasquali; European Respiratory Journal, 58 (suppl 65) PA3152, (2021) https://doi.org/10.1183/13993003.congress-2021.PA3152