Whole-system pandemic modelling including pathogen evolution

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Abstract. During the global SARS-CoV-2 pandemic models played a prominent role in predicting the near- and mid-term course of the pandemic as well as in helping governments to evaluate the effect of interventions or the lack thereof. While usually a number of different models and modelling approaches were used, in most cases the various aspects that affect the system dynamics, such as disease and transmission properties, immunity due to infection and vaccination, behaviour changes in the population due to the spread of official and unofficial information as well as government interventions and the evolution of the pathogen itself were only modelled in subsets. Here we show that interactions between interventions, behaviour and evolution can lead to substantially different dynamics than any subset of these factors. We use a prototype co-evolutionary simulation in which a simulated virus continually evolves as the agent population alters its behaviour in response to the perceived threat posed by the virus as well as to government interventions. Both intra-host and inter-host evolution are simulated. The model shows that evolution can dramatically alter the effect of individual behaviour and policies on the spread of a pandemic. In particular only a small proportion of non-compliance with policies is sufficient to render countermeasures ineffective and lead to the spread of highly infectious variants.

Keywords: Pandemic modelling · Viral evolution · Policy modelling.

1 Introduction

The global SARS-CoV-2 pandemic has demonstrated the utility of statistical and compartmental simulation approaches to predicting the near- to mid-term behaviour of the pandemic [1,10], and agent-based modelling provided useful platforms for evaluating the efficacy of numerous potential and actual policy interventions [3,5]. However, generally these models included some subset of the epidemiological properties of the virus, potential behavioural responses in the population, the possible effects of public health interventions, and viral evolution, but at the time of writing, no current models include all these elements simultaneously.

The rapid and continual emergence of new SARS-CoV-2 variants has highlighted the need for greater understanding of the dynamics of viral evolution. While many theories exist as to how these variants emerge, the precise origins of the most successful variants are still uncertain [11,2]. After the emergence of the Omicron lineage, and the recombinant XBB strains, transmissibility of the virus has seemed to reach a peak; as a result, the latest variants are demonstrating increased antigenic drift [13]. Given that SARS-CoV-2 spreads highly effectively during the incubation period and via asymptomatic infections, new variants with highly increased virulence could emerge without negatively affecting the fitness of the virus; the appearance of such variants could present a very serious threat to global public health [8].

Despite the importance of furthering our understanding of the evolutionary behaviour of SARS-CoV-2, very few models have included evolutionary components to simulate the emergence of new variants. In addition, while SARS-CoV-2 has shown significant diversity within individual hosts [12,7], the impact of within-host evolution has been largely ignored. Zhang et al. [14] produced an abstract model of intra- and inter-host evolution, but the model did not simulate individual behaviours or their impact on evolution; Mellacher's [9] evolutionary model is significantly more detailed, but once again individual behavioural responses are not modelled.

In this paper we present an early-stage agent-based model that models human behavioural change in response to the pandemic and related policy interventions, and the subsequent impact of these changes, both voluntary and policy-mandated, on viral evolution. The model includes both intra-host and inter-host evolution; viral mutations can generate changes in both antigenicity and infectivity. Model results show that the inclusion of viral evolution can dramatically alter the impact of policy interventions, suggesting that modelling of future SARS-CoV-2 variants and other possible pandemics must include all these elements to present a more realistic picture of the potential outcomes of policy interventions.

2 Methods

We implemented an agent-based simulation of the spread of an infectious disease in an urban area. The model and the data analysis are implemented in Julia. The source code for the simulation as well as detailed documentation is available at `https://doi.org/10.5281/zenodo.8147244`.

2.1 Environment

The simulated environment consists of a simplified town consisting of a grid of 100x100 buildings of different types. Agents live in residential buildings, they work or study in commercial buildings and schools, depending on whether they are adults or children respectively, and they spend free time in leisure buildings. Randomly generated public transport links connect areas of the map, allowing

agents to move around the map. Agents are always present at either a building or on public transport.

2.2 Population and agent properties

Buildings are generated to fill the available area according to fixed ratios between building types (113 schools, 1589 commercial buildings, 50 leisure buildings). Population size is calculated from the number of available residential buildings according to a given density, which in our simulations results in a population of roughly 19,000 agents.

A proportion of 17% of the population are designated as children. Each agent has a randomly assigned home and school or place of work, and 5 randomly-selected preferred places of leisure. All agents living in the same house are considered members of the same family. Friendship connections are generated as a random network with degree $k = 15$.

2.3 Agent behaviour

Each agent follows a daily schedule with some stochastic variation in timings. During weekdays agents leave their home in the morning, travel to their place of work or school by public transport, if closer than 4 houses, or independently, and return home in the afternoon. On weekends, agents have a given probability of travelling to one of their preferred leisure centres, again using public transport if available.

An agent's response to the simulated epidemic varies according to their individual level of virus awareness. The change in awareness in each time step is calculated as

$$\Delta a = -0.05a + \sum (1 - a)\omega_i s_i$$

Where for each group out of self, family and friends, s is the proportion of symptomatic individuals and ω is the weight of the corresponding group. An individual's probability to abstain from a specific activity p_A (work/school, leisure or public transport) is determined by the individual's awareness a and the general activity-specific level of caution c_A:

$$p_A = a^{1/c_A}$$

If government policies are in effect, agents decide whether to follow the official guidance based on their individual level of compliance. The level of compliance varies according to the scenario being tested.

2.4 Virus evolution

Virus evolution is modelled in two parts. For the evolution of inter-host fitness we implemented a slightly more mechanistic version of a recent model on the evolution of inter- and intra-host fitness [14,4]. Briefly, we assume that effects of

mutations on inter- and intra-host fitness are not correlated and that therefore the evolution of inter-host fitness between transmission events can be described as a random walk. On transmission a value for inter-host fitness is picked from the resulting random distribution and is used as the starting value for the newly infected host's population.

To model immunity and immune-escape we implemented a very simple antigen-antibody system. The virus antigens are represented as 5 numbers out of (1, 100). As long as a host is infected antigens mutate with a constant rate. When a new host is infected the antigens are copied over identically.

At the beginning of each simulation run, 100 randomly-selected agents are infected with the same (genetically identical) random virus.

2.5 Transmission and immune response

If more than one agent is present in a building or compartment of public transport, encounters can take place. An encounter between an infected and an uninfected agent can lead to infection. The probability that a given host infects an uninfected person during an encounter is calculated from the mean inter-host fitness of its virus population f as:

$$p_I = 1 - (1 - p_{I,0})^{r+f\cdot(1-m)}$$

where r is the individual's risk level (e.g., due to immune issues) and m is a possible mitigation effect (0.5 if a mask is worn, 0 otherwise).

On infection inter-host fitness and antigenic properties of the infecting host's virus population are copied over to the infected individual. The host's immune system then starts generating antibodies by generating an approximate copy of a sub-sequence of two of the virus' antigens.

The strength of the immune reaction, i.e. the number of antibodies of a specific type produced, changes over time. In each time step all of the antibodies a host "knows" are matched against the virus antigens. If the match is above a specific threshold, the strength of that particular immune reaction grows, otherwise it decreases. If the reaction strength decreases below a given threshold that antibody is removed entirely. New types of antibodies are generated if no existing antibody matches well enough.

The strength of the overall immune response is calculated from the match m and strength of reaction s of a host's antibodies as:

$$I = 1 - \prod 1 - m_i s_i$$

Agents recover with a constant probability per time step discounted by their risk, as well as when immune response (again discounted by risk) is higher than a given threshold.

Infected agents start developing symptoms with a constant probability per time step.

2.6 Health behaviours and policies

We simulate a simple form of government in the form of a general level of alertness and different policies that can be triggered if alertness crosses certain thresholds. The alert level increases by a set amount if the proportion of symptomatic individuals in the population exceeds a specific threshold; decrease similarly is determined by its own threshold and amount of change. Three policies are implemented in the current version: self-isolation for sick agents; mask mandates; and a general lockdown (all agents stay home at all times). Agents follow these rules according to their individual disposition (see above).

2.7 Optimal policies

For a given scenario we determined the best policy by optimising the seven parameters that determine a policy (thresholds and amount of change for increase and decrease of alert level; alert level thresholds for the introduction of self-isolation, mask wearing and full lockdown) using an evolutionary algorithm. In the standard scenario we assumed that the quality of a policy is simply determined by the number of infected agents N_{inf} after one year:

$$q = \frac{N}{N_{\text{inf}} + 100}$$

In the policy costs scenario we also simulated the political costs incurred by interventions (such as effects on the economy, population mental health or policy acceptance). We did this by decreasing a policy's quality with the number of days that each of the three interventions was active (t_*), with lockdowns having the strongest effects and mask mandates the weakest.

$$qc = q \cdot (1 - \frac{20t_{\text{lockdown}} + 5t_{\text{masks}} + t_{\text{isolation}}}{26})$$

3 Results

We find that, as expected, overall the proportion of infected individuals decreases with stricter policies, higher caution and and better compliance with the rules, and that an evolving pathogen leads to worse outcomes in term of number of infected individuals (see Figure 1).

Within that general pattern, however, interactions between factors dominate the behaviour of the system. Without evolution, policy is the factor that has the strongest effect on the outcome - neither changes in cautiousness nor compliance lead to substantial changes in the proportion of infected individuals. If evolution is included, infection rates are generally higher and - in contrast to the non-evolution scenario - do not appear to reach equilibrium (see Figure 1, right hand side). This effect is amplified dramatically when compliance is not perfect (Figure 1, bottom panels). Similarly, cautious behaviour has a much stronger effect if the pathogen evolves and at the same time compliance is not optimal.

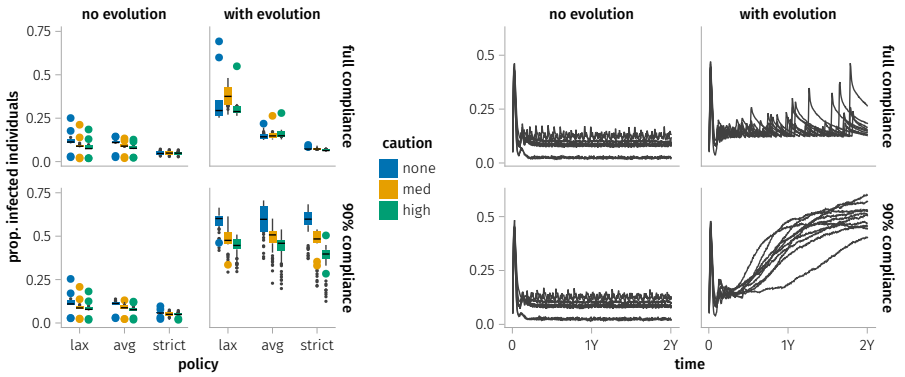

Fig. 1. Left: proportion of infected individuals dependent on policy, behaviour and evolution. Final (box plots) and average (dots) proportion of infected individuals shown (10 replicates per scenario). Right: Proportion of infected individuals over time dependent on evolution and compliance for medium cautiousness and average policy strictness (10 replicates).

Policy, on the other hand, can make an even bigger difference in evolution scenarios than in those without evolution if at the same time compliance is perfect, while it becomes nearly entirely ineffective if evolution is combined with limited compliance.

A similar picture emerges when we look at the best policies for a given scenario (Figure 2). Under perfect conditions, that is when interventions bear no costs, similar strict policies clearly win out in all scenarios (see Figure 2, left). As soon as interventions are not free, however, the best government strategy depends on the specifics of the scenario (see Figure 2, right).

4 Discussion

Our simulations show that in isolation, the effects of individual behaviour, government policy and pathogen evolution play out very much as expected. When seen in combination, however, a more complicated picture emerges and interactions between different factors become important.

Most notably, the inclusion of viral evolution significantly alters the potential efficacy of public health interventions to control transmission. With even small reductions in compliance, infection rates increase dramatically, and the interventions fail to contain the evolving pathogen.

Our results show that as soon as political decisions are not free there is no single policy that is optimal for all possible scenarios. The best decision can therefore only be made if a combination of epidemiological, evolutionary, social and political aspects is taken into account.

At this point our model is not calibrated to any real system and can therefore not support quantitative statements. What we expect, however, is that the

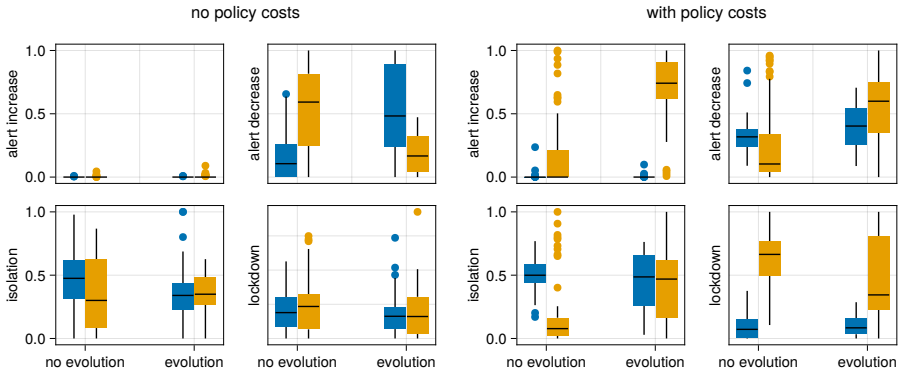

Fig. 2. Optimal policies if interventions are free (left) and if they are costly (right). Top panels show optimal threshold values for infection rates at which to start changing alertness; bottom panels show optimal threshold values for alert levels at which to implement interventions (blue: full compliance, yellow: 90% compliance).

overall dynamics that we observe are in principle applicable to real-world systems. We can therefore make no recommendations concerning best strategies for a given situation, based on our results. We can, however, *qualitatively* state that any policy decision in a pandemic situation that relies only on purely epidemiological modelling or even on separate modelling of epidemiological, behavioural and political aspects is likely to be sub-optimal.

In future work, however, we do intend to calibrate the model to reflect the real-world properties of SARS-CoV-2 in terms of its antigenicity, transmissibility, and the historic emergence of prior variants. This will allow for systematic testing of realistic policy scenarios in real-world situations [6].

We propose that future models of SARS-CoV-2 variants or future pandemics should adopt a whole-systems approach. Our models demonstrate that without including the effect of human behavioural change on the pathogen itself, policy-makers may make key decisions regarding containment policies that could fail dramatically in the longer term. In that sense, the present situation with SARS-CoV-2 is illustrative: the emergence of Omicron during a period of lesser public-health restrictions led to an enormous increase in infections worldwide, resulting in a state in which infection rates remain high in much of the world, and the potential for new variants with higher virulence remains a potential threat.

As we review the global response to the SARS-CoV-2 pandemic, the role of modelling was and will continue to be critical in shaping our response to future challenges, either from SARS-CoV-2 itself or other pathogens. We suggest that future modelling of containment strategies must account for not only near-term viral transmission and behaviour change, but also longer-term interactions between viral evolution, behavioural change and intervention compliance.

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