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Cycles of susceptibility: Immunity debt explains altered infectious disease dynamics post-pandemic

Dr Alasdair P S Munro, PhD^{1,2,*}

Professor Thomas House, DPhil³.

¹ NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

² Clinical and Experimental Sciences, University of Southampton, Southampton, UK

³ Department of Mathematics, University of Manchester, Manchester, UK

* Corresponding author: a.munro@soton.ac.uk

Non-pharmaceutical interventions (NPIs) implemented during the COVID-19 pandemic suppressed not only transmission of SARS-CoV-2, but also many other endemic pathogens worldwide. Many of these pathogens would typically follow a seasonal circulation pattern, with annual resurgent epidemic waves largely influenced by levels of population immunity. This immunity wanes over time due to factors such as diminishing levels of specific antibodies, the birth of immunologically naive infants, and genetic mutations in the pathogen which diminish the efficacy of existing immunity. This slow reduction in population immunity leads to periodic increases in disease incidence until enough immunity is reestablished to suppress further transmission.

It was hypothesised early in the pandemic that the suppression of transmission of these "off-target" pathogens might alter their epidemiological patterns due to a reduction in pathogen-specific population immunity (1), a phenomenon often termed as "immunity debt" or "immunity gap" (2, 3). This concept should not be conflated with an overall decrease in immune system competence, which some commentators have inaccurately suggested (4).

Since the easing of pandemic restrictions, several regions have observed significant disruptions in the transmission of various diseases, with some of the most notable relating to Respiratory Syncytial Virus (RSV). The population most impacted were children under the age of 2 years, which is unsurprising

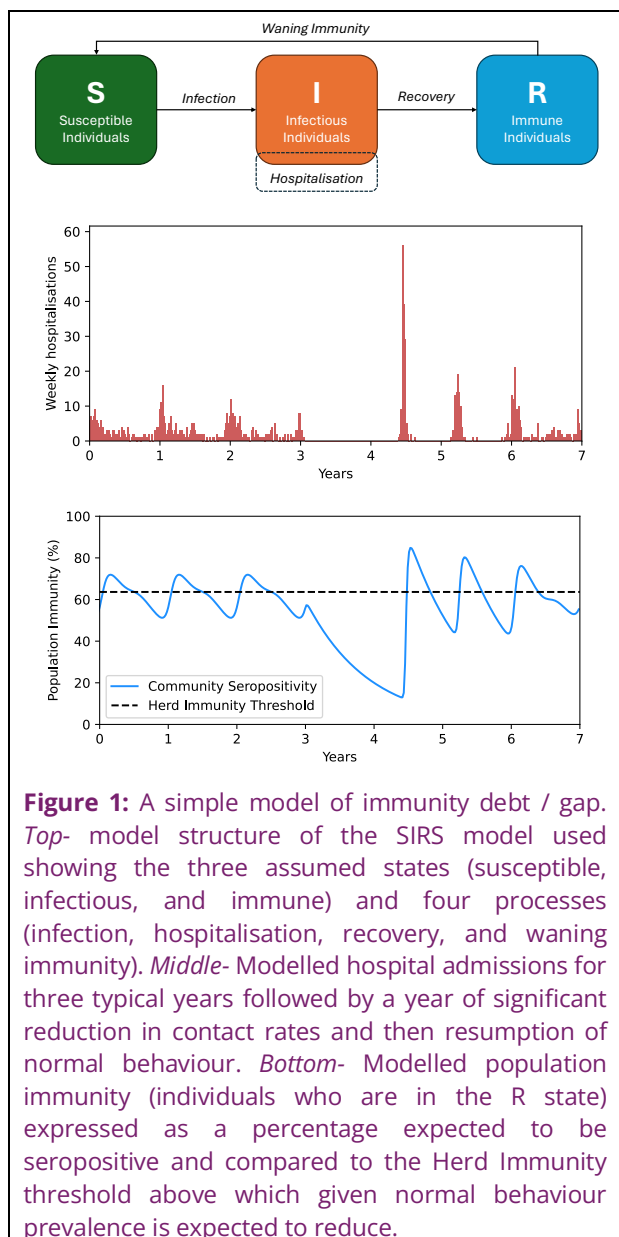
given this is the group known to be highest risk of severe illness from RSV and given that 90% of children will have been exposed at least once to RSV infection by this age (5). Notably, this disruption was observed in countries which were initially successful in suppressing COVID-19 such as Japan, and South Korea (6, 7), and additionally in countries such as Australia and New Zealand where large, unseasonal summer waves of RSV occurred in 2020 prior to any significant COVID-19 transmission (8, 9). Occurrence of these disturbances in such countries prior to any significant COVID-19 exposure demonstrates that postulation of any impacts of COVID-19 itself on susceptibility to other respiratory pathogens is unnecessary to explain these phenomena. Similar summer waves of RSV were observed in the UK and across Europe in 2021 (2, 10). North America experienced an unusually large and prolonged winter wave of RSV in 2021 beginning in May rather than October, followed by an earlier and larger wave than usual in 2022 (11), although increased testing appears to account for a significant amount of the observed excess (12). The study by Petros et al. also makes note of a reduced severity in RSV disease, although this is also likely a reflection of increased testing of children with less severe disease, and increased rates of illness in older children who will experience a milder course (12). Denmark also experienced an unusually large winter RSV wave in 2021, however increased testing was only able to explain 70% of the difference to the pre-pandemic period (13). Difficulties in adjusting for differing testing regimes shows

the importance of surveillance studies which are agnostic to clinical testing strategies or test seeking behaviour, such as the UK surveillance program conducted by the Office for National Statistics (14), and it is notable that such studies typically show that testing behaviour alone is seldom enough to explain large waves of detected cases. Indeed, increased testing alone would fail to explain many features of RSV waves during their resurgence, primarily their unusual timings since they often occurred during summer months.

In addition, several other pathogens have also experienced unusually large, or out of season surges. Gastrointestinal Adenovirus infections surged in the UK prior to the well documented spike in cases of paediatric hepatitis across Europe (later attributed to Adenovirus Associated Virus 2 and associated genetic link) (15). December 2022 saw an unprecedented surge in Group A Streptococcal (GAS) infections in the UK, including many cases of invasive GAS disease and empyema (16). Rates of invasive infection such as iGAS are not sensitive to altered testing regimes, as testing for these pathogens is always routinely performed in critically ill children. More recently, *Mycoplasma pneumoniae* has experienced an apparently global increase in circulation, despite its usual pattern being to recur every 3-5 years in different regions (17). These examples illustrate the complex interplay between reduced pathogen exposure due to NPIs and subsequent increases in disease due to a lack of immunity.

An interesting exception to this phenomenon is Influenza, for which there was particular concern regarding a large resurgence upon lifting of NPIs for COVID-19 (18). Whilst recrudescence epidemic peaks of influenza were often not typical in shape (such as the taller and shorter initial wave in the UK), the lack of an unusually large volume of transmission speaks to the slight difference in aetiology of the seasonality of flu transmission. The decrease in population immunity to 'flu is driven largely by antigenic drift in the virus itself (19), unlike RSV which does not undergo such shifts and simple waning of population

immunity itself is responsible (20). Suppression of transmission during the pandemic will have reduced the volume of viral replication, therefore leading to an evolutionary bottleneck with reduced volume of mutation and subsequent antigenic drift (21). As such, one might expect the degree of population immunity to influenza to be impacted to a lesser extent than a pathogen such as RSV. In addition, the availability of influenza vaccination to buffer immunity in the most vulnerable populations may have blunted any excess in resurgence.



Where a pathogen's circulation is predominantly controlled by population

immunity and immunity receives an appreciable contribution from infection, then a prolonged absence of infections will inevitably result in a lower level of population immunity: so-called immunity debt, or immunity gap. While the exact impact of this decreased immunity on disease patterns post-pandemic is still debated, the principle of immunity debt is based on well-established epidemiological models (3) and was anticipated by the scientific community. To illustrate this, we have created a simple model of this phenomenon with code publicly available at <https://github.com/thomasallanhouse/covid-19-incidence/blob/main/debt.ipynb> and results shown in Figure 1. We consider a scenario in which there is annual oscillation in infectious contacts, which we would expect to arise from factors like school holidays, weather and variability in time spent indoors and outdoors interrupted by one year of significantly reduced transmission. This shows that even a very simple model only representing the processes of infection, hospitalisation, recovery, and time-limited immunity, can generate annual waves of hospitalisation followed by a complete absence of disease in secondary care, after which there is an exceptionally large wave of infections and associated admissions that is followed by setting to behaviour like that seen before the perturbation in transmission. While not explicitly calibrated to any specific pathogen data, this model is intended to represent dynamics of viruses such as RSV in a stylised manner.

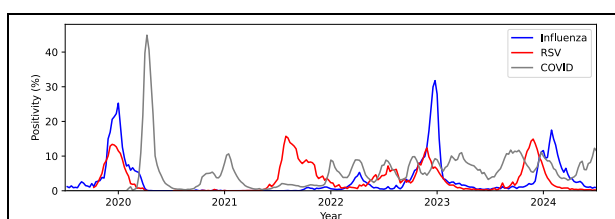


Figure 2: Public hospital surveillance data on three respiratory viruses from <https://www.gov.uk/government/collections/weekly-national-flu-reports>. Percentage positivity in secondary care is shown, which is more indicative of relative than absolute burden

In practice, the situation with RSV has been complicated and different behaviour has been seen in different parts of the world depending on local details. For example, Waikato in New Zealand experienced complete absence of RSV in 2020 with a large resurgence in 2021 peaking at around the pre-pandemic time of year (9). Tokyo, Japan, experienced a similar phenomenon with no RSV in 2020 but a very large and slightly early 2021 peak (6). Belgium in contrast did not entirely miss an RSV season, but rather its 2020-21 season was delayed, longer and involved a lower peak than previous (22). In Figure 2, we show publicly available secondary care data from the UK showing a mixture of these. The important observation, however, is that explanation of all such disease behaviour requires postulation of no extra phenomena, and careful accounting for timing of NPIs and associated growth in the susceptible population is all that is required. In conclusion, while NPIs have been effective in controlling COVID-19, their broader epidemiological impacts, particularly the concept of immunity debt, deserve further attention. These effects cannot be dismissed as secondary only to increased testing, as this fails to account for the total excess in infections, alterations in seasonality, and impact on other pathogens and invasive disease which are not sensitive to altered clinical testing. Disease surveillance strategies such as the ONS infection survey which are immune to longitudinal testing strategies will be vital to unbiased assessments of these impacts. This underscores the need for comprehensive public health strategies that consider long-term outcomes of widespread NPI usage and ways to mitigate them.

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