

# The return of the seasonal flu and cold

Other diseases are set to rebound as Covid-19 restrictions ease

Philip Hunter\*

As restrictions and lockdowns are being relaxed in many countries, the impact of the COVID-19 pandemic on other diseases is gaining attention. While the overall picture is diverse, it is clear that the incidence of other respiratory diseases, including seasonal influenza and common colds, has declined greatly, especially in temperate climates. On the other hand, the ongoing fight against major tropical diseases has been severely impaired as a result of attention being diverted towards COVID-19 with grave concerns over a surge in TB cases and a delayed impact on HIV due to reduced testing.

## The impact on seasonal flu

Seasonal flu has received greatest attention so far, with a dramatic decline in most but not quite all of the leading economies away from the tropics, especially North America, Europe and Australia. There is ongoing debate whether this decline has been caused by social distancing, travel restrictions and wearing masks, and what will happen when these are relaxed and the viruses rebound on populations with probably reduced community resistance. Flu's vanishing act has been chronicled in numerous studies around the world over the course of the pandemic. One of the first came from Hong Kong covering an eight-week period early in 2020 during which COVID-19 transmissibility measured by  $R_t$  had remained at about 1 (Cowling *et al.*, 2020). Influenza started at a higher  $R_t$  of 1.28 but, after implementation of social distancing measures and changes in behaviour in late January 2020, declined to 0.72, resulting in a 44% reduction in transmissibility.

"The most likely explanation is that changes in population behaviours had an indirect consequence on occurrence of other

infections," commented Ben Cowling, Head of the Division of Epidemiology and Biostatistics at the University of Hong Kong, and lead author of that study. Cowling added that this impact was not limited to respiratory infections, but extended to others that involve some form of transmission within the community.

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Indeed, a Chinese study that examined 514,341 cases of 39 types of Notifiable Infectious Disease (NID) in the Guangdong region of China estimated that across all these diseases, the  $R_t$  number during the emergency response period in 2020 was 65% lower than expected (Xiao *et al.*, 2021). The largest reduction by age group was among children aged 0–14 years. Respiratory diseases only registered the second largest fall of the disease categories at 87%, after insect-borne diseases at 89%. Intestinal infectious diseases were down by 59%, and blood-borne or sexually transmitted infections by 18%. Among individual diseases, dengue and influenza were reduced the most, by respectively 99% and 95%.

There is some evidence from countries that implemented strict lockdown and quarantining measures that non-pharmaceutical interventions (NPIs) rather than greater competitiveness of SARS CoV-2 was the main factor behind this decrease. "There is a clear consensus that the reason why

colds and flu declined during the pandemic in 2020-2021 was due to human behaviour, for example, mitigation measures such as social distancing, working from home, school closures, masks, more attention to hand hygiene and staying home if sick," explained Ellen Foxman at the Yale School of Medicine who studies antiviral defence in the human respiratory tract. "This is clear because the population-wide prevalence of SARS-CoV-2 was much too low in 2020 to explain the dramatic drop in other infections as resulting from competition or interference from SARS-CoV-2. For example, during the flu season in Australia in July and August 2020, very few Australians had been exposed to COVID at that point, but the flu virtually disappeared. This shows how effective such mitigation measures can be in stopping the spread of respiratory viruses." Foxman added that competitive factors may have kicked in later. "Now that COVID is incredibly prevalent in 2022 and fewer people are isolating, the situation may change and we may in fact observe interference between COVID and other viruses, but it is too early to know that," she said.

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## An unprepared immune system?

Whatever the balance between mitigation measures and competition, these other

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infections have been in abeyance, and the question is what impact they will have when they return. “There is speculation that the disappearance of other viruses for 1.5 plus years may have a rebound effect, making people more susceptible due to lack of adaptive immunity re-stimulation during that period,” Foxman said. She noted particular concern not just about flu, but also Respiratory Syncytial Virus (RSV), which can cause severe infections often described as common colds, especially among children. “Babies who were born during that time had no exposure to RSV, a common early childhood virus, creating a larger than normal population of susceptible infants and in fact when things reopened in summer of 2021, we saw an out-of-season RSV epidemic in that age group in our healthcare system,” Foxman commented.

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She has been involved in several studies on the relationship between background infection from relatively mild viruses and maintenance of ongoing resistance to more dangerous pathogens, and she thinks that such protection may have waned during the pandemic. “Current work from our group and others suggests that a low level of stimulation of the innate immune system, not the virus-specific immune system, but general defences that work against all viruses, provides cross-protection among even unrelated viruses, and that this could be a mitigating factor putting an upper limit on how much respiratory virus circulation can happen at any given time,” she explained. “Our work also implies that relatively innocuous viruses like rhinovirus, the most frequent common cold virus, can protect against more dangerous pathogens such as SARS-CoV-2 or influenza” (Wu *et al*, 2020).

For such reasons, John McCauley from the WHO Collaborating Centre for Reference and Research on Influenza at the Francis Crick Institute in London, UK, is concerned that flu could make a serious comeback. “If flu comes back, we will need to watch out

for a big season,” he said. “The vaccines are still being updated to be able to cover the most likely viruses of those being seen currently to cause the next epidemic. However, if that virus has yet to emerge, we cannot be sure of having the best vaccine for it.” McCauley added that vaccine protection for flu cannot be relied on to stem a major seasonal outbreak at present. “Although vaccines will stimulate immunity in those vaccinated, overall the proportion of the world’s population that is vaccinated for flu is small, and the vaccine protection is far from perfect.” he explained. “When we have a flu epidemic lots of people get it but lots do not. We assume they have residual immunity. It may also be that many have sub-clinical infections, and this might stimulate immunity. With no flu, there will also be none of these sub-clinical infections to boost population immunity.” Such considerations lead McCauley to conclude that strategies to exclude respiratory viruses from given countries or populations are counter-productive or even dangerous. “I do not think a zero-virus strategy is really feasible. I suppose we had better look at New Zealand,” he said.

### The effect on tropical diseases

The impact of COVID-19 has extended far beyond influenza and respiratory diseases, with a profound effect on the major diseases of developing countries in the tropics, notably TB, malaria and HIV. “We’ve been working in HIV, TB and malaria for 20 years and COVID-19 has really had an impact on the progress in these areas,” said Christy Feig, Head of Communications for the Global Fund, a multistakeholder international fund in Geneva that invests US\$4 billion a year to combat those three diseases; he further referred to a comment by Peter Sands, the Global Fund’s Executive Director, that underlines the impact of COVID-19 on those three diseases which had been most devastating in the case of TB. “In 2020, the number of people treated for drug-resistant TB in the countries where the Global Fund invests dropped by 19%, with those on treatment for extensively drug-resistant TB falling by 37%,” he wrote. “This means around one million fewer people with TB were treated in 2020 compared with 2019” (<https://www.theglobalfund.org/en/blog/2021-09-17-covid-19-hit-hiv-tb-and-malaria-programs-hard-we-re-fighting-back/>).

The impact on HIV has also been significant. “While it is encouraging that the number of HIV-positive people receiving antiretroviral treatment has continued to grow, the declines in prevention services and testing in 2020 were alarming,” Sands wrote. “People reached with HIV prevention programs and services declined by 11%, while HIV tests taken declined by 22% compared with 2019. Because of the disruptions resulting from COVID-19, the people at greatest risk of infection have had less access to the information and tools they need to protect themselves.”

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It is too early to tell what the longer-term impact on HIV burden will be. But most in the field believe there will be a significant toll. “As an infectologist working in Brazil, I believe the COVID-19 impact on HIV will be more important than we can measure by now,” said Fernanda Rick, who was assistant director of global medicine at the Aids Healthcare Foundation in Sao Paulo. “We already know that there was a huge drop on ART (Anti-Viral Therapy) initiation and diagnosis in this country in the past 2 years” (<http://www.aids.gov.br/pt-br/gestores/painel-de-indicadores-epidemiologicos>).

The story for malaria is less pessimistic, partly because measures such as use of insecticide protected mosquito nets are already well established. “Thus far, interventions to combat malaria appear to have been less disrupted by COVID-19 than the other two diseases,” Sands wrote. “Other than suspected cases of malaria tested – which fell by 4% compared with 2019 – rapid adaptation of malaria services seems to have limited the reverses. However, progress stalled: we did not see the year-on-year growth in provision of malaria services that we need to beat the disease.”

### Lack of funding

The economic impact of COVID-19 will further jeopardize efforts to resume the pre-pandemic fight against tropical diseases.

This has been detailed in a recent paper involving Peter Hotez, Dean of the National School of Tropical Medicine at Baylor College in the USA (Hotez *et al*, 2021). The study estimated that more than 100 million people faced a return to extreme poverty because of COVID-19, suggesting that India, Nigeria and the Democratic Republic of the Congo would suffer the greatest economic contractions, at least in numerical terms given their size. Hotez also highlighted the indirect impact of COVID-19 by diverting away attention and funding among leading economies on their internal responses to the pandemic. He pointed to the UK that ended funding its flagship Neglected Tropical Disease (NTDs) programmes in 2021 as part of a £4 billion (€4.7 billion) cut in foreign aid. This was clearly in response to the huge financial outlay of NPIs related to COVID-19, including lockdowns and it came at the worst possible time for the ongoing fight against NTDs.

Hotez also stressed the need for accurate metrics to assess the impact of these actions and events on NTDs. Such assessments will be needed to effectively restore momentum towards previously set targets by the World

Health Assembly, especially the 90% reduction in the number of people who require treatment for NTDs by 2030. In addition, that roadmap calls for eradication of two diseases: dracunculiasis, commonly known as Guinea-worm disease, and yaws, a chronic skin disease. Inevitably, these efforts have been derailed by COVID-19.

The loss of funding has therefore come at a critical time, as Hotez explained. “Currently the global support for mass drug administration for the world’s neglected tropical diseases relies on modest support from very few countries,” he said. “Therefore, losing UK Govt support is a devastating blow to our NTD ecosystem. Unless the European countries are prepared to make up for the loss – and so far they haven’t shown an interest in doing so – I’m very worried about the future of global NTD control and even reversing hard fought gains. Even though in the big picture of things the UK Govt support was modest, it was nonetheless game changing.”

Health agencies and governments then face two great challenges as the world emerges from the pandemic: to manage the resurgence of circulating infectious patho-

gens, especially respiratory viruses, and to get back on track with their programmes against major and neglected tropical diseases. This is not made easier by the economic havoc that COVID-19 has left in its wake.

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