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EDITORIAL

A comparison with historical influenza prompts better planning for Covid-19 and future pandemics, and gives grounds for optimism

Covid-19 has shaken confidence in public health. The developed democratic countries have not yet reached vaccination sufficiency, the more totalitarian ones are having difficulty sustaining it, and the low income countries have scarcely started. But with recent advances in vaccinology, encouraging trends in antiviral treatment and renewed vigilance in world surveillance for zoonotic infections, informed pandemic planning can prevent catastrophe.

Global respiratory outbreaks, very probably of influenza, have occurred for centuries, and since the pandemic of 1889 detailed clinical and public health records have been kept. Following a fortuitous transmission to a ferret at the MRC laboratory in Mill Hill, UK, in 1933 the pandemic of 1918 was belatedly shown to be due to a virus. Soon thereafter influenza virus was grown in fertile eggs and by the early 1950s it could be grown in cell culture. It then became possible to study the viral penetration of host respiratory cells, intracellular virus replication, and the liberation of the virus particles to infect more cells. Of the two proteins of the influenza virus envelope, haemagglutinin attaches to respiratory cells *in vivo*. The 'spike' protein of the Covid-19 coronavirus acts similarly in attaching SARS-2 virus to the cells of the respiratory tract.

The main twentieth century influenza pandemics, of 1918–19, 1957 and 1968–69, have all been ascribed to 'shifts' in the virus genome coding for the haemagglutinin with or without the gene for the other envelope protein, the neuraminidase. Between these pandemics there were also more subtle genomic changes referred to as 'drift', with the influenza virus chosen to grow vaccine from often having to be changed as a result.

The genomic shifts responsible for past influenza pandemics were due to interactions between human viruses and the influenza viruses of certain birds and animals (fowl plague and swine flu are typical examples of animal influenza virus infections). With the emergence of SARS-2 the coronaviruses seem to be following the same path, a SARS-like human virus having interacted with a bat coronavirus. The SARS-CoV-2 virus was first identified in late 2019 in Wuhan, China, where a laboratory had for several years been studying the coronaviruses of cave-dwelling bats. Alternatively, it has been suggested that SARS-2 originated in a live animal market in Wuhan or elsewhere. Recent accusations on social media that 'dual-use' research was responsible for it are far-fetched but impossible to dismiss.[1]

The emergence of SARS-CoV-2 'variants of concern/interest' reflects genomic drifting, and may soon necessitate vaccine modification. While the interval between the appearance of SARS and SARS-2 is comparable with that between influenza pandemics, a third SARS virus might come sooner and be just as transmissible as the SARS-2 virus.

This makes pandemic planning a matter of urgency. The spread of SARS virus between 2001 and 2004, though on two continents, was limited and relatively easily contained; but the SARS-2 virus of Covid-19 has spread worldwide even if not rampantly where vaccination is well underway. Virus genomic adaptation to obstacles put in its way such as masking and social distancing seems to have led to the emergence of the more transmissible and perhaps differently virulent SARS-2 variants, for example, 'delta', and vaccination may also have promoted that development. This genomic phenomenon may be compared with drift in human influenza viruses.

Mortality during the SARS virus outbreak was perhaps as high as 10%, but the deaths in the Covid-19 pandemic are so far largely confined to the unvaccinated elderly and the clinically vulnerable. It was also mostly older adults who died during recent pandemics of influenza though the distant past young people perished. Conscripted soldiers of the generation born after the influenza pandemic of 1889 notoriously died in great numbers in 1918 and 1919, whereas people born earlier may have retained immunity acquired in the previous, 1889, pandemic. Similarly, survivors of Covid-19, and those vaccinated against it, may enjoy long-lasting protection from severe coronavirus disease.

Post-viral clinical complications are nothing new. Encephalitis lethargica spread worldwide in step with the 1918 influenza pandemic and had a poor prognosis. As an acute disease it then disappeared in 1927.[2] Though far less common than pandemic influenza it may have been derived from it, or perhaps influenza made people susceptible to it. Other acute viral outbreaks have had lingering clinical consequences, in the case of chickenpox and measles well known to be due to virus persistence, less certainly in so-called Royal Free Disease[3] and in Long-Covid.[4]

There has been a transformation in the speed and affordability of virus genome sequencing since 2000. This has accelerated diagnostic testing and favoured the development of the new mRNA vaccines and antiviral drugs. Pandemic planners can expect these technical

advances to help meet the challenge of continuing or renewed coronavirus infections, and of further virus pandemics. Any contribution against a bacterial outbreak is less certain.[5]

Future vaccine and antiviral drug regulatory approvals will require many human volunteers[6]: they might now, on the model of organ donation cards, be recruited in advance. The efficacy of influenza vaccine was never fully established in this way which partly accounts for its disappointing uptake, notably by health workers. It is now time to improve influenza vaccines and demonstrate their value in controlled studies as has been so briskly done for Covid-19 vaccines. The prospect of a winter conjunction of Covid-19 and influenza calls for an effective combined vaccine.

Protection from severe illness and death has been shown even after a single dose of the present Covid-19 vaccines. Two doses appear to offer a tenfold diminution of risk of hospital admission in the event of Covid-19 acquisition. It may also diminish infectiousness in those who do become re-infected, as well as the cut in hospital admissions, thereby protecting health staff. Covid-19 vaccination is advanced enough for example, in Israel, UK and Western Europe to suggest that near entire population immunisation is feasible; but in culturally diverse cities like London vaccine acceptance remains lower. In the more conservative states of the USA, too, many individuals are hesitant or decline vaccination, political sentiment is contrary, and anti-vaxxers are vocal, a woeful combination. Low income countries may regard Covid-19 vaccination as desirable, but there the provision of affordable, temperature protected and hygienic vaccination will be a huge undertaking. It is one that rich nations would be wise to facilitate: otherwise importations of SARS-2 virus will be very frequent.

The stark fact is that vaccine hesitancy and refusal have to be overcome. Until there is very substantial global vaccine coverage Covid-19 is likely to remain endemic, and so its associated mortality will have to be accepted and its collateral effects accommodated. Culturally appropriate means therefore need to be devised to persuade people to accept vaccination even while individuals' autonomy, including that of the parents of children, is respected. A particular issue, the safety of vaccines and antiviral drugs in pregnancy, previously discussed in relation to influenza,[7] has yet to be addressed.

Antiviral compounds are effective against several viruses for example, herpes zoster and simplex, human immunodeficiency and hepatitis C viruses. Yet both in 2005 and 2009 '*tamiflu*', incorrectly used against influenza, failed. The experience of treating Covid-19 with a specific antiviral drug has been equally disappointing, probably because it is not being given at the first opportunity. Expensive antiviral treatment is typically being reserved for severe cases 10 or more days after onset, long after the peak of virus replication.

There is as yet no published series of Covid-19 cases promptly treated with remdesivir, the antiviral drug most active against SARS-2 virus in the laboratory and in experimental animals; but it is on record that it was given to US President Trump the day after he was diagnosed with Covid-19. He rapidly recovered. In the future those who seem to be developing a pandemic virus infection and are recognisably susceptible through advanced age and/or clinical vulnerability might receive an early home/care-home assessment with a view to immediate even if brief antiviral treatment especially if this can be given orally.

The striking development of mRNA Covid-19 vaccines implies that vaccines will be the best defence against future pandemics, whether coronavirus, influenza, or another virus. The Western democracies have experienced prolonged social disruption and economic damage due to their chosen defence against Covid-19. They must now plan to meet future pandemics with a timely vaccine response and, when possible, drug treatment. A healthy lifestyle is a further protection against pandemic mortality. Countries can scarcely afford a repetition of their recent response to Covid-19, and a fitter population might not have to resort to such prolonged and irksome safeguarding measures.

The world must become more watchful for new viruses with pandemic potential. WHO began its surveillance of influenza viruses in the 1950s, and laboratories in Australia, Hong Kong, Russia, Western Europe and USA have since contributed to it. This must now involve additional countries and be broadened to include corona- and other viruses. Surveillance was overlooked after the SARS outbreak ended, and WHO has failed to complete its investigation of the emergence of SARS-2 in 2019. Nations may be reluctant to open borders, but preparedness requires access to any site where a potentially pandemic virus strain has arisen. The continuing encroachment by expanding human populations into undisturbed habitats makes the emergence of unfamiliar zoonotic viruses ever more likely, and insect vectors may play an important part in this as, for example, in the recent Zika virus epidemic in the Americas.

Whether SARS-2 evolved naturally or is perhaps a laboratory escapee from a biosafe and biosecure[1] laboratory, testing needs to be made available to allow investigation of what are often remote outbreaks. Pandemics also require laboratory assay standardisation. The critical measurements of Covid-19 infectiousness and immunity have lacked this, and reporting of quantifying PCR signal thresholds is still not routine.

The spread of the first SARS virus was suppressed by the isolation of patients and the tracing of their contacts, but these measures never had a significant role in the containment of human influenza and they have proved difficult to apply to Covid-19. It has a short incubation period in which it quickly becomes infectious to contacts, and it remains so for several days. There is not, as there was for smallpox, a post-exposure interval of several days during which vaccine could be given, and even with the advantage of smartphones, contact tracing is often not effective. Though phone-enabled contact tracing is the mainstay of pandemic control,[8] it has encountered opposition from those who seek to guard their privacy.

In conclusion: a comparison with past influenza pandemics is instructive: analogy suggests that the world is actually much better placed to deal with threatened viral pandemics than before. Covid-19 will probably persist until vaccination can become near universal, but recent progress in vaccinology and antiviral drug discovery has made prophylaxis and hopefully early treatment possible. With more persuasive incentives to accept immunisation, sufficient scientific and

technical drive and funding, and a proper sense of urgency there are grounds for optimism.

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