cessation (figure 1). Moreover, ENDS manufacturers are sponsoring high profile professional sports. The St Helen's Rugby League club play in the Totally Wicked stadium (figure 2), and the same logo is carried on the shirts of Championship football team Blackburn Rovers. In addition, teams have accepted sponsorship, with the ENDS industry claiming that ENDS shops are promoting health, and the ENDS industry is actively looking for sports teams to sponsor. The marketing of ENDS to younger people has been normalised and is associated with an increased use by teenagers.[12] The US Food and Drug Administration have recognised this association, and they have repeatedly warned ENDS manufacturers about their advertising tactics. The ENDS manufacturer Juul (part-owned by Altria, previously known as Philip Morris Companies) settled a lawsuit by paying US$40 million to NC, USA, who accused them of marketing its products to minors.[13] Advertisements increase interest in trying ENDS;[12] therefore, the industry makes a substantial return on their investment.

For more on **Totally Wicked sponsoring** see https://www.lancashiretelegraph.co.uk/sport/19963180.latest-blackburn-rovers-shirt-sponsor-player-contracts/

For more on **Vaping sponsorship** see https://www.vampirevape.co.uk/sponsorship

In the UK, the regulatory authorities, the Royal Colleges, and learned societies (with the exception of the Royal College of Paediatrics and Child Health),[14] are immobilised. They are ignoring the tactics of a resurgent industry that seems to be targeting children and younger people, increasing their exposure to nicotine (nicotine alone has significant toxicity, including to the fetus) and several other inhalants of unknown toxicity.[15] The tobacco industry has a record of duplicitous suppression of data; yet, with their promotion of ENDS they are regaining ground they previously lost with tobacco cigarettes. At the least, ENDS should be subject to the same legislation as tobacco, and those who supply them to under-age children should be subject to stringent penalties.

For more on **tobacco industry research** see https://tobaccotactics.org/

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*Stephen Fowler, Jayesh Bhatt, Sarah Brown, Louise Fleming, Sarah Mayell, Ian Sinha, Andrew Bush
a.bush@imperial.ac.uk

Division of Infection, Immunity and Respiratory Medicine, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK (SF); UK and NIHR Manchester Biomedical Research Centre, Manchester University Hospitals NHS Foundation Trust, Manchester, UK (SF); Nottingham Childrens Hospital, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK (JB); Department of Paediatric Respiratory Medicine, Royal London Children's Hospital, Barts Health NHS Trust, London, UK (SB); Department of Paediatric Respiratory Medicine and the Imperial Centre for Paediatrics and Child Health, Imperial College and Royal Brompton Hospital, London, UK (LF, AB); Department of Paediatric Respiratory Medicine, Alder Hey Children's Hospital, Liverpool, UK (SM, IS)

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How repeated influenza vaccination effects might apply to COVID-19 vaccines

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Many of the current questions on the public health and research aspects of the future of COVID-19 vaccines and vaccine strategies have been topics of research and debate in the influenza vaccine literature for decades. Here, we describe how the lessons learned from the study of repeated influenza vaccinations might apply to the evaluation of COVID-19 vaccines, and the prospect of future seasonal or periodic booster vaccinations.

There are many differences between COVID-19 and influenza vaccines in their design and manufacturing, immunological context, and effectiveness in preventing disease. Nonetheless, since both the SARS-CoV-2 and influenza viruses are constantly evolving and can escape vaccine-induced immunity, and since protection from both vaccines declines with time,[1] it can be expected that, similar to influenza vaccines, additional COVID-19 vaccine doses will be needed to maintain optimal levels of protection. The frequency, timing, and groups prioritised for further COVID-19 vaccine doses will depend on multiple factors, including the magnitude of vaccine effectiveness waning against the most severe COVID-19 outcomes, the differential effect of vaccine effectiveness waning on immunocompromised people and older adults, and the cost-effectiveness of different vaccine strategies.

Data on influenza vaccines suggests that repeated vaccinations in an individual might ultimately result in a blunted immune response, declines in vaccine effectiveness, and a possibly reduced duration of protection. In multiseason studies, immunogenicity after influenza vaccination and vaccine effectiveness against influenza-associated medical care were both often lower among people vaccinated in the previous and current season compared with those vaccinated in the current season only.[2] In the few studies that were able to gather vaccine records for 4–6 previous years, immunogenicity and vaccine effectiveness were highest among those with no or few previous vaccinations and lowest among those frequently vaccinated.[2]

The underlying mechanisms through which previous vaccinations can affect the effectiveness of subsequent vaccinations in an individual are unclear, but two theories are widely discussed in the influenza literature. According to the antigenic distance hypothesis, the effect of previous vaccinations is established by the antigenic distance between the vaccine antigens in the previous dose versus the subsequent booster dose and the antigenic distance between the vaccine antigen and the circulating virus. The blunting of influenza vaccine effectiveness by previous influenza vaccination has been the most pronounced when the vaccine antigen was unchanged, but an antigenically distinct virus became the predominant circulating strain.[3] Although third COVID-19 mRNA vaccine doses produce the same level of vaccine effectiveness as achieved by a second mRNA dose,[1] the antigenic distance hypothesis would suggest that COVID-19 vaccine effectiveness after a fourth or fifth vaccine dose might decline if the vaccine antigen is unchanged, and new antigenically distinct variants circulate. The introduction of updated vaccine antigens might overcome preferential antibody responses to an imprinting infection (ie, original antigenic sin) or the effects of a repeatedly administered vaccine antigen, as has been noted with influenza vaccines.[4]

The second theory focuses on changes that might occur among people who are unvaccinated compared with those who are repeatedly vaccinated. Since vaccine-induced immunity blocks or reduces the risk of infection, the theory asserts that the percentage of people who are unvaccinated with presumably stronger infection-induced immunity will increase over time (also referred to as the infection block hypothesis). Thus, estimates of COVID-19 vaccine effectiveness will probably decline as the gap in immune protection between people who are repeatedly vaccinated versus those who are unvaccinated declines.

If repeated COVID-19 vaccination leads to blunted vaccine effectiveness or a reduction in protection relative to people who are unvaccinated, findings from new studies comparing different influenza vaccine types and vaccine strategies point to at least four lessons to be learned. First, vaccine effectiveness studies might need to stratify their estimates by those with and without documented previous infection and by the differences in previous vaccination status to disentangle changes in vaccine effectiveness versus changes in population susceptibility over time. This separation has not been feasible in the evaluations of influenza vaccines, but it might be possible in the evaluations of COVID-19 vaccines given widespread virus testing and the improved documentation of infections. Second, the optimal spacing of additional COVID-19 vaccine doses over time deserves much more investigation than it has been given to date. If COVID-19 becomes an endemic virus with seasonal circulation, spacing out COVID-19 vaccine doses at 9-month intervals or 12-month intervals might provide as much protection as more frequent vaccination such as every 6 months. Third, changing the SARS-CoV-2 vaccine antigen will be especially necessary to protect people who are repeatedly vaccinated from new variants,


Dr P. Marazzi/Science Photo Library

because the focusing of antibody responses toward older strains can be an undesirable consequence of repeated vaccination.[4] Fourth, introducing alternative vaccine types might improve immunogenicity and vaccine effectiveness compared with the repeated use of the same vaccine technology. In one study, older adults who received either a high dose, adjuvanted, or recombinant protein influenza vaccine had a superior serological and cell-mediated immune response compared with older adults who repeatedly received egg-based inactivated vaccines.[5] Research is needed to assess whether systematically alternating COVID-19 vaccine schedules to introduce different vaccine types can improve the effects of the vaccine.

The future of influenza and COVID-19 vaccines are now intertwined. Long-lasting debates surrounding influenza vaccine technologies, dose spacing, and strain composition can inform parallel debates about COVID-19 vaccines. The future of influenza vaccines will be changed by the findings on COVID-19 vaccines as well. Moderately effective inactivated influenza vaccines might be less acceptable to a public who have grown accustomed to highly effective COVID-19 vaccines. New technologies for vaccines, such as mRNA, and the broader availability of second-generation influenza vaccines (eg, high-dose, adjuvanted, and non-egg-based products) could considerably improve the average annual vaccine effectiveness of influenza vaccines. The race to optimise the preventive benefit of both influenza and COVID-19 vaccines benefits everyone.

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*Mark G Thompson, Benjamin J Cowling
isq8@cdc.gov

Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA (MGT); WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China (BJC); Laboratory of Data Discovery for Health, Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China (BJC)

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