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COMMENTARY

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Lessons learned from 2 years of influenza vaccinations in the UK and USA during the COVID-19 pandemic as respiratory viruses return

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ABSTRACT

During the COVID-19 pandemic, immunization programs for other respiratory infections, notably influenza continued worldwide but attracted less public or political attention than COVID-19 vaccinations. Due to non-pharmaceutical intervention measures the global influenza burden decreased substantially; but with lifting of restrictions a rebound in other respiratory virus pathogens is both plausible and likely. This article discusses lessons identified from the UK and USA, and provides recommendations for future influenza vaccination programs in light of emerging data from the southern hemisphere and the need for harmonization with COVID-19 vaccination, focusing on operational delivery and messaging to practitioners and the public.

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Introduction/background

Beginning in 2020, and continuing into 2022, the world experienced a global pandemic, caused by the SARS-CoV-2 coronavirus, the size of which has been unparalleled since the 1918–1919 influenza pandemic. During these two years of the COVID-19 pandemic, influenza vaccination programs have continued worldwide but have figured less prominently in the public's consciousness than COVID-19 vaccination, the latter rightly viewed as an emergency public health measure. Influenza vaccination rates during the first two years of the COVID-19 pandemic remained largely stable or increased slightly. Vaccination coverage for the US in adults for the 2019/20 season was 48.4% vs 45.4% in the 2021/22 season.[1] In children coverage was 63.7% for 2019/20 vs 58.4% in 2021/22.[1] Conversely, the data for the UK showed an increase of 9.9% in vaccination uptake from 72.4% (2019/20) to 82.3% (2021/22) of the eligible population ≥65 years. In other reported populations (6 months – 64 years 'at risk,' pregnant women and health-care workers) the changes from 2019/20 to 2021/22 were +8.1%, −5.8%, and −13.8% respectively.[2,3] However, due to the non-pharmaceutical interventions (NPI) implemented to mitigate the pandemic, there has been minimal influenza activity since 2019.[4] As a result of this absence of disease, public and policymakers may underestimate the potential risks of influenza and urgency of vaccination for the upcoming 2022–23 northern hemisphere season, particularly against the backdrop of general vaccination fatigue, further COVID-19 boosters, continued operational challenges in the healthcare delivery system, and reduced NPIs. As more jurisdictions have relaxed NPIs, increased reports of respiratory illnesses are occurring, including anticipation of increased influenza cases as witnessed in parts of the southern hemisphere.

Influenza epidemiology during the COVID-19 pandemic

In many jurisdictions, the accuracy of estimation of influenza activity is proportional to the extent of epidemiological and virological surveillance. Nevertheless, the magnitude of differences observed from pre-pandemic levels to the 2021/22 season are profound.[5,6] According to CDC estimates, approximately 35 million people in the US were diagnosed with symptomatic influenza and more than 20,000 of them died during the 2019/20 season (the influenza season just prior to the onset of the pandemic) across all age groups.[6] In contrast, the methodology applied by the CDC to formally estimate the overall flu burden for 2020/21 could not be applied due to extremely low numbers of influenza cases.[5] Additionally, there were 19,302 laboratory confirmed influenza-related hospitalizations in 2019/20 compared to 230 recorded in 2020/21.[5,6] This trend in reduction of influenza was also seen across other outcomes, resulting in an informal estimate of an overall flu burden for 2020/21 of approximately 1% of the preceding year.[5,6] The numbers for the UK were similar (122 hospital admissions 2020/21 vs. 30,600 2019/20 refs) and this was mirrored in most parts of the world.[7–10] This is unsurprising since the NPIs in place episodically in 2020 and 2021 are blunt, nonspecific, instruments whose transmission-suppressing effect will be far greater for pathogens with relatively low R0 values (influenza: 1.2–1.5)

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compared to those with higher R0 (SARS-CoV-2: 5–6) {ref}.[11,12] Metrics for the 2021/22 season are not yet finalized but seem to indicate 8–13 million symptomatic influenza infections in the USA; this is well below pre-pandemic baselines but is a substantial ‘rebound’ compared with 2020/21.[13]

The possible explanations for this stark difference could theoretically include an immunological phenomenon of viral suppression; however, expert consensus is that a far more likely explanation is the effect of NPIs.[4,9,14] This fits with the emerging data suggesting a degree of rebound in 2021/22 correlating to fewer NPIs used after COVID-19 vaccines were deployed. Given the lifting of most NPIs in most northern hemisphere countries in the first half of 2022, and the low likelihood of public or political support for meaningful re-imposition of these NPIs in the autumn and winter of 2022/23, it is highly likely that influenza and other respiratory pathogens will reemerge alongside the continued circulation of SARS-CoV-2, in populations that have hardly encountered influenza viruses in the last two years. In order to illustrate the potential impact, it may be worthwhile looking toward the SH where emerging data from the current influenza season in Australia indicate that from mid-April 2022 the number of notifications of laboratory confirmed influenza infections exceeds the 5 year average. Specifically, comparing numbers from start of the reporting period (April 1st) to the second week of July (time of writing of the manuscript) shows the following picture: number of notifications for 2022, 2021, and 2019: 204,911; 419; 153,272 respectively, thus 2022 showing an approximately 25% increase over 2019.[15–17] The distribution amongst age groups differs between 2019 and 2022 in that in 2019 the notification rates were highest in children aged 5–9, followed by adults aged >85 years.[15,16] In 2022, the highest notification rates were observed in children and adolescents/young adults only.[17] A potential explanation for this difference could be the extended application of NPI measures in residential aged care facilities and persistence of reduced social mixing in older cohorts versus more relaxed adherence to NPIs among children, adolescents, and young adults.[18–20] This difference in age groups might also explain why at this stage the trend toward a higher overall case burden does not appear to translate to an increased hospitalization rate, currently at 1489 versus 1832 in the same reporting period in 2019. Admittance to ICU (6.2% 2019 vs. 6.7% 2022, reporting period from 1st April to second week of July) appears comparable.[15,17]

Recognizing that every influenza season is unique, it is possible that the epidemiological patterns seen in the SH’s current influenza season might predict a rebound of influenza in the NH with earlier than usual onset and accompanied by COVID-19 and other respiratory pathogens.[21] Therefore to minimize the potential for illness and healthcare surges it seems prudent to make substantial efforts toward overcoming potential vaccination fatigue and operational barriers to facilitate influenza vaccination uptake alongside potentially autumn booster doses of COVID-19 vaccine. It is important to consider the potential additional impact of influenza and SARS-CoV-2 co-infections. A retrospective UK study investigating clinical outcomes in 212,466 hospitalized adults with SARS-CoV-2 infection performed tests for viral co-infections in 6965 patients. [22] Viral co-infection was detected in 583 (8.4%) of patients with 227 showing influenza, 220 RSV, and 136 adenoviruses. As tests for co-infections were not routinely performed in all patients, bias is likely. Therefore, the study used a weighted multivariable regression methodology to extrapolate the risk to a more representative hospitalized population. The weighted odds ratio (OR) for requirement for mechanical ventilation is 4.14 in patients with SARS-CoV-2 and influenza co-infection with a corresponding OR of 2.35 for death during hospitalization.[22]

It is also relevant to consider the impact of pneumococcal co- or super-infection in patients with respiratory viral infections. Whilst the interactions and poor outcomes of influenza and pneumococcal co-infections are well described, data on possible interactions and outcomes of COVID-19 and pneumococcal co-infections remain sparse at this stage. Current data suggests that such co-infections are rare but may lead to an increased risk of death.[23,24]

Operational barriers: non-alignment of COVID-19 and influenza vaccine schedules and logistics

Broadly speaking, a key challenge for the effective and efficient coordination of influenza and SARS-CoV-2 vaccinations is that to date the schedules have often been desynchronized. This is unsurprising considering the urgency of addressing the COVID-19 pandemic. In addition, the scheduling and recommendations regarding primary and booster vaccinations were changing as we learned more regarding the disease and vaccine use. Many of the recommendations regarding who should be vaccinated were determined by risk category and emerging safety data in relevant age groups, so that any attempt at coordination of the different vaccination programs was almost futile in the initial phases of COVID-19 vaccination programs. Later models to facilitate co-administration were developed but still faced some challenges in uptake at the prescriber level. It remains to be seen if SARS-CoV-2 will settle into a longer term seasonal epidemiological pattern as seen with influenza but this is certainly plausible. The autumn 2022 season may now present an opportunity to improve coordination on a programmatic level as, in the absence of new waves of vaccine-resistant SARS-CoV-2 variants which could trigger a potential change in strategy before autumn in the NH seems lessened. The timing of COVID-19 booster and seasonal flu vaccinations are expected to further coalesce consistent with the known timing of onset of the NH flu season.

Such a coordinated approach could be strongly facilitated by more widespread adoption of co-administration of COVID-19 and influenza vaccines.[25] After initial hesitancy to recommend this approach, mostly driven by the need to obtain real-world undiluted safety data of the COVID-19 vaccines, there is now definitive controlled, randomized, and double-blind data demonstrating the safety and immunogenicity of this strategy for various combinations of COVID-19 and flu vaccines. Thus, co-administration is now fully permitted and encouraged for operational simplicity by the CDC in the US and JCVI in the UK.[26,27]

However, co-administration depends on smooth logistics and influenza and COVID-19 vaccinations in the UK currently have highly disparate purchasing and reimbursement mechanisms, incomplete geographical alignment of vaccinations services, and eligibility criteria which differ at the margins. These differences add significant complexity. Additional logistical barriers to co-administration of both vaccines lie in the manufacturing of COVID-19 vaccines in multi-dose vials.[28,29] Whilst this was a vital approach to increase the speed of manufacturing of large amounts of vaccine due to worldwide shortages and fill and finish capacity, the utility of multi-dose vials becomes problematic in the context of routine/seasonal COVID-19 boosters in GP or pharmacy settings where the counterfactual is influenza vaccines supplied for decades as pre-filled single-use syringes; this makes opportunistic vaccinations as part of routine consultations, and co-administration of influenza and COVID-19 vaccines more challenging.

A distributed purchase and delivery model (GP, dedicated vaccination clinics and pharmacies) has been in place for some time in both the US and some parts of the UK for influenza vaccinations, the urgency of rapid COVID-19 immunization, and scarcity of supply led to central government purchasing models and the creation of large-scale vaccination hubs.[27,30,31] These two systems are not readily compatible. Though central community vaccination sites have existed in the US prior to the COVID-19 pandemic, mainly focused on influenza vaccinations, in many jurisdictions specific vaccination hubs were created with the sole purpose of rapid immunization against COVID-19.[30,31] Besides limitations in manpower, they were usually not equipped to follow up on other vaccination schedules as they may not have been linked to relevant existing IT systems and important patient information, on risk conditions and concomitant medication, could not be obtained from electronic health records held by individual health-care providers. In the UK, the majority of COVID-19 vaccinations were delivered by local vaccination services (57–97%, depending on risk group vaccinated), whereas in the US pharmacies performed the majority of COVID-19 vaccination activity with >50% of COVID-19 vaccinations delivered by pharmacist-led teams.[32–34]

Whilst the distributed administration model has proven quite effective in facilitating access to vaccinations, particularly in disadvantaged and marginalized groups and in working individuals. The introduction of pharmacies as vaccination sites in the UK may have further increased what was already very high uptake of influenza vaccine, compared to most other countries: however it remains debatable whether this truly represents an increase in coverage versus at least a partial redistribution of activity from the GP to the pharmacy, with increased user convenience but more modest impact on overall coverage.[35] This has become more significant as GP and other provider access during COVID-19 activity has become a concern. This has been seen in the United States where the vaccination coverage rates have not increased dramatically over the course of the past 5 years, but there has been an increase in vaccinations given at pharmacies and at places of employment accompanied by a decline in vaccinations given at the primary care physician office.[36,37] Another downside of a broadly distributed delivery model is the commercial risk which has to be taken by the sites to have vaccines readily available. Typically, reimbursement by the NHS in the UK or the various health plans in the US occurs by dose delivered which can lead to high up-front expenses in acquisition costs which may not always be recoverable and given that a patient has the choice of attending their GP or a local pharmacy may drive over-procurement and concomitant wastage. The uncertainty in forecasting site-specific demand increases with the number of access routes available to individual patients. This challenge can be addressed with early communication and surveying of patients and communities, the establishment of appointment-based care delivery and coordination among members of the immunization neighborhood.

Keeping in mind the rapidly evolving nature of both, the COVID-19 pandemic as well as the seasonal flu activity in both hemispheres, key recommendations are summarized in Table 1 below.

Table 1. Key recommendations.

Key recommendations	
Strong and coordinated messaging to practitioners and the general public is required to counteract potential vaccination fatigue.	The reduction of influenza infections during the COVID-19 pandemic were a consequence of NPIs and resurgence is highly likely
	Respiratory virus co-infection is associated with increased morbidity and mortality
	Co-administration of COVID-19 booster and flu shots is safe and efficacious
	Very low levels of flu circulation during the last two flu season may have reduced the levels of population immunity against flu viruses with likely increase in case numbers in the coming season as seen in the SH
	Harmonisation, coordination, and integration of purchase and delivery models are needed to improve logistic simplicity and increase assess points for vaccination
Operational aspects and co-administration	Operational aspects of COVID-19 booster and seasonal flu vaccinations must be brought into alignment as much as possible
	Facilitation of co-administration through advance planning should be encouraged to ensure that vaccines are available in clinics attended by people eligible for both vaccines.
	Facilitating co-administration by improving compatibility of IT systems, will help ensure availability of critical patient data across sites.
	Determining the future role of the vaccination hub concept: should those continue? If so, how do they best integrate into the existing programs and distributed delivery models? The answers to these questions will likely differ between jurisdictions and health care environments, thus lessons must be learnt from the last two years and any reform should be implemented in a way that uptake of both vaccines is facilitated

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Author's contribution

All authors conceived the idea and contributed equally to writing. All authors have seen and approved the final manuscript.

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