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Commentary

Use of seasonal influenza and pneumococcal polysaccharide vaccines in older adults to reduce COVID-19 mortality

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1. Background and aim

SARS-CoV-2 that causes COVID-19 has emerged as a pandemic with all continents now reporting cases, most of them community acquired [1]. Many COVID-19 infections cause pneumonia and some are fatal, predominantly among older adults [2]. Co-infection with other viruses or bacteria, particularly those that similarly cause inflammation of the respiratory tract would likely enhance the risk for severe COVID-19 disease. Such disease enhancing co-infections have been frequently reported for respiratory pathogens [3–5], most notably so for the 1918 influenza pandemic [6,7]. Vaccinating older adults at elevated risk of severe COVID-19 disease against vaccine preventable diseases may therefore not only help to reduce the strain on the healthcare system from those diseases during a pandemic, but also alleviate some of the potential COVID-19 mortality due to co-infecting pathogens [8].

Vaccines that can prevent respiratory tract infections in adults and particularly in older adults, either through direct protection or indirectly through high coverage childhood immunisation programmes, include vaccines against seasonal influenza, *Streptococcus pneumoniae*, measles, *Bordetella pertussis* and *Haemophilus influenzae* type b (Hib). Measles, pertussis and Hib vaccines are already included in almost all routine infant immunisation programmes globally and have largely eliminated the targeted pathogens as a risk to the older adult population through indirect protection [9]. Hence, they have limited scope for use in older adults in order to limit COVID-19 morbidity and mortality. Pneumococcal conjugate vaccine (PCV), either 10- or 13-valent, is used in three-quarters of routine infant immunisation programs globally; in countries that use PCV, the burden of adult pneumococcal disease due to PCV serotypes has also substantially decreased [10]. These considerations mean there is a relatively small preventable disease burden in countries routinely using PCV in children. As vaccine costs are relatively high and there is no current World Health Organisation recommendation regarding PCV use in adults, PCVs are not considered further here. Two vaccines that target a large burden of the remaining respiratory disease in older adults are seasonal influenza vaccines and 23-valent pneumococcal polysaccharide vaccine (PPV23). These vaccines are only included in routine adult immunisation in some countries and even there with only moderate coverage [11]. We conducted a non-systematic review of the published, pre-print and grey literature to evaluate whether vaccination of older adults with seasonal influenza vaccine or PPV23 could help reduce COVID-19 mortality.

2. Seasonal influenza vaccines

The World Health Organization recommends seasonal influenza vaccine use for pregnant women as well as older adults (>65yrs),

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Table 1
Estimating COVID-19 death attributable to influenza and pneumococcal coinfection.

Parameter description	Minimum value	Maximum value	Reference
Seasonal influenza vaccine efficacy	20%	60%	[17,18]
COVID-19 deaths attributable to influenza coinfection (assuming it is similar to COVID-19 cases attributable to influenza co-infection)	0%	60%	[19–24][†]
Preventable COVID-19 deaths due to influenza co-infection	0 * 0.2 = 0%	0.6 * 0.6 = 36%	
PPV23 vaccine efficacy	20%	60%	[28–30]
PPV23 preventable serotypes in older adults	48%	66%	[26]
COVID-19 deaths attributable to pneumococcal co-infection (assuming it is similar to influenza A (H1N1) deaths attributable to pneumococcal co-infection)	0%	25%	[6][‡]
Preventable COVID-19 deaths due to pneumococcal co-infection	0.2 * 0.48 * 0 = 0%	0.6 * 0.66 * 0.25 = 10%	

[†] In five studies, co-infection occurred in 41/68, 0/20, 11/127, 0/99 and 5/115 cases.
[‡] In seven studies, co-infection occurred in 0/100, 2/182, 2/45, 13/585, 20/199, 2/585 and 5/21 cases.

health care workers and persons with specific chronic illnesses (particularly HIV) [12]. In 2014, 45% of countries globally had established a seasonal influenza vaccine programme that targets older adults, hardly any of them are in low or middle income countries [13].

Seasonal influenza as a risk factor for COVID-19 could be an important consideration in tropical climates and the southern hemisphere, and potentially during future waves of COVID-19 in the northern hemisphere [14–16]. Inactivated influenza vaccine effectiveness varies markedly by season from about 20% in seasons with a poor match to the circulating strains to up to 60% for closer matched seasons [17,18]. Hence, influenza vaccination could prevent 20% to 60% of influenza infections and thereby potentially a similar percentage of influenza-attributable COVID-19 morbidity and mortality (Table 1).

A number of studies to date have tried to assess the percentage of influenza-attributable COVID-19 morbidity and mortality. Some reported the occurrence of co-infection of COVID-19 inpatients with influenza viruses, although the proportion of co-infections varies by study, from no influenza coinfection identified to more than 60% of PCR positive COVID-19 patients being currently or having been recently infected with influenza [19–25]. Whether this co-occurrence is co-incidental, or indeed influenza contributes to the clinical severity of COVID-19 presentation is not yet clear. However, to date there is no evidence that would suggest clinical manifestations in COVID-19 patients with influenza co-infection differ from those without co-infection [19].

3. Pneumococcal polysaccharide vaccine

PPV23 targets 23 of the over 90 serotypes that are responsible for most adult pneumococcal disease. In countries with an infant PCV program, about 48–66% of invasive pneumococcal disease (IPD) in older adults is caused by serotypes that PPV23 is effective against [26]; in countries without an infant PCV programme this percentage is likely about 20% higher (details see Appendix). PPV23 is recommended for routine use in older adults in most high-income countries, but rarely in low and middle-income countries [27]. It provides short-term protection against IPD caused by vaccine serotypes in healthy older adults with a pooled efficacy across targeted serotypes of about 60% [28–30]. However, PPV23's effectiveness is much lower among high risk groups including the immunocompromised [31–33], who may be at particular risk for severe COVID-19. Consequently, PPV23 use in older adults could prevent up to 33–40% of pneumococcal disease and thereby potentially pneumococcal-attributable COVID-19 morbidity and mortality (Table 1).

The extent of pneumococcal-attributable COVID-19 morbidity and mortality is largely unknown. Pneumococci have been identified as a major source for often fatal secondary bacterial infections during pandemic and seasonal influenza infections. Estimates for the proportion of pneumococcal co-infections among pandemic influenza deaths range from about 7% during the 2009 H1N1 pandemic to more than 50% during the 1918 pandemic [6,34–37]. Few studies so far have tried to identify bacterial co-infections among COVID-19 cases, and those that did found very few bacteria and only a limited number of cases with pneumococci [23,38,39]. This may be due to the empirical treatment with antimicrobials for the majority of severely ill suspected COVID-19 patients, or because bacterial infection plays little role in the severity of COVID-19 disease [23,40]. However, elevated procalcitonin levels, a sensitive but not very specific biomarker for bacterial infections, have been reported in 13% of severe and 25% of fatal COVID-19 infections, but largely absent in COVID-19 infected persons with less severe outcomes, which may suggest some role for bacterial coinfection [41,42].

4. COVID-19 associated risk of attending clinics to receive PPV23 or influenza vaccination

Attending a vaccination clinic during the COVID-19 pandemic will likely come with an excess risk of SARS-CoV-2 infection. This risk may be small, particularly if physical contact reducing interventions are implemented. To illustrate the potential magnitude of such excess risk, we assume a reasonably high COVID-19 burden scenario: contact reducing interventions can be implemented and upheld to substantially slow COVID-19 spread but not contain it, so that after 6 months and in the absence of a COVID-19 vaccine herd immunity will end the outbreak [43]. Assuming a basic secondary attack rate of R_0 = 2.5 and that contact-reducing interventions spread the COVID-19 infection risk equally across that 6-month time period, the increase in risk for COVID-19 acquisition attributable to the vaccination clinic visit would be roughly 0.3–1.3%, depending on the effectiveness of transmission-reducing measures during the vaccination visits (details see Appendix) [44]. This implies, that if either seasonal influenza vaccine or PPV23 reduces COVID-19 morbidity and mortality by a similar amount or more, their benefit on COVID-19 alone would outweigh the risk associated with the vaccination visit in this scenario, while also preventing morbidity from influenza and pneumococcal disease.

5. Conclusion

Both seasonal influenza vaccine and PPV23 can prevent a substantial burden of targeted disease and mortality among older adults and adults at-risk. Despite a potential collateral reduction in influenza and pneumococcal circulation due to contact reducing interventions, in countries where the COVID-19 pandemic coincides with the season of high risk for pneumococcal and/or influ-

enza disease, vaccination at high coverage will have added benefits: minimising the number of pneumococcal and influenza hospital admissions reduces the resources needed to care for non-COVID-19 patients and minimises the risk of health-care acquired COVID-19 infection. For influenza, the similarity of symptoms with COVID-19 cases also suggests that vaccination will increase the specificity of syndromic COVID-19 surveillance. Similarly, maintaining high vaccine coverage of existing PCV and live attenuated influenza vaccine programmes in children reduces the associated disease burden in older adults through herd effects, and will further enhance benefits for limiting COVID-19 risks.

The magnitude of COVID-19 morbidity and mortality prevented by influenza vaccine and PPV23 is probably relatively small, although at present we cannot exclude the possibility of either preventing a considerable amount of COVID-19 related mortality (Table 1). This uncertainty highlights the importance for detailed monitoring and additional studies where possible, in both high and low income settings. The proportion of vaccine preventable COVID-19 morbidity and mortality could be assessed, for example, by post mortem examinations or test-negative case-control studies [45].

In summary, where already in routine use among older adults and/or adults at-risk, maintaining both seasonal influenza and PPV23 at high coverage have the potential to not only reduce the burden of the targeted diseases but also prevent a proportion of COVID-19 morbidity and mortality, if they can be delivered while minimising the risk for SARS-CoV-2 transmission. However, for countries who previously decided that seasonal influenza vaccine or PPV23 programmes for older adults are not a priority, there is currently little evidence to encourage implementation of either during the COVID-19 pandemic solely for the purpose of reducing COVID-19 mortality.

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CRediT authorship contribution statement

Deus Thindwa: Writing - original draft, Writing - review & editing. **Maria Garcia Quesada:** Writing - review & editing. **Yang Liu:** Writing - review & editing. **Julia Bennett:** Writing - review & editing. **Cheryl Cohen:** Writing - review & editing. **Maria Deloria Knoll:** Writing - review & editing. **Anne von Gottberg:** Writing - review & editing. **Kyla Hayford:** Writing - review & editing. **Stefan Flasche:** Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix

Proportion of PPV23 serotypes among older adults

The PSERENADE project aims to understand the impact of PCV10/13 on invasive pneumococcal disease (IPD) incidence and serotype distribution using IPD data contributed by surveillance sites across the world. In settings with mature PCV10/13 infant immunization programmes, the estimated proportion of IPD in older adults (≥65 years of age) attributable to PPV23 serotypes is 67–79% for countries using PCV10 in infants and 68–71% for countries using PCV13. Excluding ST3 (PPV23-minus-ST3), these proportions drop to 48–66% and 51–57% respectively. Because effectiveness against ST3 has not been observed in all countries, the proportion of IPD in older adults attributable to PPV23-minus-ST3 is used here as a more conservative estimate of preventable disease. In the time period prior to PCV use in children, the estimated proportion of IPD in older adults attributable to PPV23-minus-ST3 serotypes was about 20% higher; this can be a proxy for countries without an infant PCV programme. However, most of the data included comes from high-income countries and may not be entirely representative of the serotype distribution in countries without a PCV programme, which are mostly low and middle income.

Risk of SARS-CoV-2 infection during a vaccination clinic visit

Assume that contact reducing interventions spread the risk of COVID-19 out roughly equally over a 6 month period. This scenario is in line with model predictions for SARS-CoV-2 spread in the presence of a 50% reduction in contacts for the duration of 6 months. Assuming an R_0 of 2.5 and a duration of infectiousness of 1 week means that about 60% of the population will have been infected at the end of the pandemic and that at any one time about 2% of the population is infectious. Further, assume that an adult attends a vaccination clinic and makes a total of 2–10 contacts (hereby 2 may reflect a scenario of effective measures to avoid contacts) related to that visit and that the probability of infection per potentially infectious contact is about 10% (R_0 attributed over the number of contacts during the infectious period e.g. 2.5 transmissions during the two days before symptom onset and self-isolation, with 12 contacts per day before isolation). Then the probability for SARS-CoV-2 infection during that vaccine clinic visit is $P = 1 - (1–10\%)^{\#contats * 2\%} = 0.4$ to 2%. Hence, the excess absolute risk for SARS-CoV-2 infection over the pandemic baseline risk is

P*(1–60%) and corresponds to a relative risk increase over the pandemic baseline risk of 0.3 to 1.3%.

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