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Influenza epidemics in Europe, nursing homes and vaccination of healthcare workers

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Abstract

During the 2022-2023 season, influenza circulation levels in the European Union (EU) have increased substantially compared to the 2021-2022 season but were still generally somewhat lower compared to pre-pandemic influenza seasons. Studies have shown that influenza epidemics in the EU countries were associated with a heavy toll of mortality for different principal causes of death including respiratory, cardiac and other causes. Mortality data also suggest that residents of long-term care facilities represent a sizeable share of all cases of death in the EU, and an even higher share among deaths stemming from infections with respiratory viruses, including influenza. Influenza vaccination coverage for healthcare workers in nursing homes in many EU countries is moderate to low, whereas evidence in the literature suggests that higher influenza vaccination coverage levels for healthcare workers result in a significant reduction in all-cause mortality during influenza seasons, both in nursing home residents as well as in hospital patients, though the magnitude of that effect varies with influenza season. Here, we review the above evidence, and as well as the effect of different strategies for boosting influenza vaccination coverage in healthcare workers, such as mandatory vaccination, educational initiatives/outreach activities and availability of on-sight vaccination.

During the period prior to the COVID-19 pandemic, annual influenza epidemics in the European Union (EU) were associated with a heavy mortality toll. For example, study¹ estimated that for the 2012-2013 through the 2017-2018 seasons, influenza circulation was associated with an annual average of 16.1 all-cause deaths per 100,000 EU residents. While influenza incidence levels have declined during the early stages of the COVID-19 pandemic, during the most recent, 2022-2023 season, influenza circulation levels in the EU have rebounded, though they still were generally somewhat lower compared to pre-pandemic influenza seasons². Long-term care facilities (LTCFs) for older individuals are responsible for a sizeable share of deaths in the whole population associated with epidemics of different respiratory viruses. Studies during the early stages of the COVID-19 pandemic in the EU found that deaths among LTCF residents accounted for 37–66% of all COVID-19-related deaths in EU/EEA countries³. Studies have also shown that introduction of influenza infections into LTCFs results in high rates of infection and death in residents. For examples, for the 49 outbreaks caused by influenza in study⁴, the median attack rate in residents was 33%, range 4-94%, with a median case-fatality rate for residents being 6.5%. In France, residents of establishments for dependent elderly persons (EHPAD) made up about a 1/4 of all deaths in the French population in the pre-pandemic period^{5,6}. During influenza and Omicron epidemics, the relative contribution of EHPAD to all-cause

mortality in France increased, as suggested e.g. by the data for the 2022-2023 season⁷.

Studies have shown that vaccination of healthcare workers (HCWs) in LTCFs against influenza has a strong effect on all-cause mortality and other outcomes in LTCF residents⁸⁻¹⁰. We also note that the effect of HCW vaccination on mortality outcomes in residents varies from one influenza season to another, as suggested e.g., by the results for two consecutive influenza seasons in the study¹⁰. That study found that during the first, strong influenza season there were 5 fewer deaths per 100 residents in intervention nursing homes compared to control homes (95% Confidence Interval (CI) 2-7 deaths), with no significant decreases in any of any of the studied outcomes, including mortality, influenza-like illness etc. during periods when influenza was not circulating in the community or in the second year when influenza rates were substantially lower than the first¹⁰. At the same time, rates of influenza vaccination of HCWs in a number of EU countries are relatively low, under 40% and lower in most countries in the survey¹¹. In France, influenza vaccination coverage for HCWs in nursing homes during the 2022-2023 season was 24.7%¹². Experience from Austria, Germany and Greece suggests that educational interventions and on-sight vaccination campaigns can result in substantial increases in influenza vaccination coverage in HCWs in both long-term care facilities and hospitals¹³⁻¹⁵. In this review, we spell out the evidence for the benefits of HCW vaccination against influenza for all-cause mortality and other outcomes in LTCF residents, as well as in hospital patients, and discuss strategies for boosting influenza vaccination coverage in HCWs.

A systematic literature review that included 4 cluster randomized trials and 4 observational studies on influenza vaccination in HCWs conducted in long-term care or hospital settings found that pooled risk ratios across trials for all-cause mortality and influenza-like illness in patients/residents were 0.71 (95% CI, .59-.85) and 0.58 (95% CI, .46-.73), respectively⁸. The earlier version of the Cochrane review by Thomas et al. on the same subject⁹ found that vaccination of HCWs was associated with a reduction in all-cause mortality in residents/patients, with the effectiveness of HCW vaccination against all-cause mortality in residents/patients being 40% (95% CI, 27% to 50%) and deaths from pneumonia, with the effectiveness of HCW vaccination being 39% (95% CI, 2% to 62%), with a somewhat smaller reduction in lower respiratory tract infections that failed to reach significance (odds ratio (OR) 0.70, 95% CI 0.41 to 1.20). However, the estimation of the effect of influenza vaccination of HCWs on mortality in patients and in nursing home residents was excluded from the later version of the Cochrane review by Thomas et al.¹⁶. We will argue that the above estimates, particularly ones

suggesting a significant benefit of HCW vaccination for all-cause mortality in nursing home residents during influenza seasons are sensible and should support the case for initiating various measures to boost influenza vaccination coverage in HCWs.

First, several studies have shown that only 23%-38% of all influenza-associated deaths are for respiratory causes depending on the circulating influenza strain and practices for coding deaths in different countries¹⁷⁻¹⁹. Thus, excluding non-respiratory outcomes ignores most of the mortality benefit offered by influenza vaccination, with other benefits being related to myocardial infarctions and other outcomes, e.g.²⁰.

Secondly, the magnitude of the effect of influenza vaccination for HCWs on all-cause mortality in residents plays a role in the decision to boost influenza vaccination coverage in HCWs. Studies^{8,9,21} found that 20%-40% of all deaths in nursing home residents during influenza seasons were prevented by HCW vaccination against influenza. Studies of the effect of influenza epidemics on mortality in the whole population found that up to 10% of all-cause deaths during influenza seasons are associated with influenza infections^{22,23}. While the 10% estimate applies to the whole population, influenza outbreaks in nursing homes are more explosive compared to infection rates in the overall population of elderly individuals (e.g the median attack rate of 33% for the 49 influenza outbreaks in nursing homes in study⁴). Study²⁴ found a 9-fold higher COVID-19 attack rates in nursing homes for dependent persons (EHPAD) compared to the attack rates in Residential Care Facilities for older individuals who were not dependent. Additionally, study²⁴ noted that for EHPAD, there are 64 staff per 100 residents, while in other Residential Care Facilities for older individuals in France, there are 13 staff per 100 residents. All of this supports the notion that infection rates for respiratory virus epidemics can be much higher in establishments for dependent older persons compared to other populations of older individuals, and that HCWs play a substantial role in the spread of respiratory infections in nursing homes. Compared to the 10% estimate for influenza's contribution to all-cause mortality for the entire population during influenza epidemics^{22,23}, it could well be that 20%-40% or more of all deaths in nursing homes during select influenza seasons are triggered by influenza infections, which are listed as a cause of death only in a small minority of cases of influenza infection.

Thirdly, limited-to-no effect of HCW vaccination on to lab-confirmed influenza illness in patients/residents was found in some studies, e.g.^{9,16}, and this is sometimes cited as suggesting lack of clear evidence for the effect of vaccinating HCWs against influenza on illness outcomes in residents/patients^{16,4}. For example, recent recommendations from

the French Health Authority (HAS) suggest that further studies are needed to better understand the effect of vaccination of caregivers on influenza-related illness in LTCF residents and hospital patients²⁵. We note, however, that lab-confirmed influenza illness is *not* an objective outcome as most episodes of influenza infection are not being tested for/detected, and the volume of detected influenza is a correlate of the policies for testing for influenza infection in respiratory illness episodes in a given institution. Moreover, in the studies that examine the effect of influenza vaccination in HCWs, some of the facilities were randomized to receive influenza vaccination in HCWs, while others did not receive a placebo; it is not unlikely that facilities randomized for HCW vaccination also started to test for influenza infection more frequently as a result of being selected for HCW vaccination, whereas facilities that weren't selected for HCW vaccination might have tested their residents less frequently so not to exhibit a high burden of influenza infection compared to facilities that were selected for vaccination in those trials. Overall, it is difficult to interpret the estimates of the effect of vaccination of HCWs on lab-confirmed influenza infection as inclusion/lack of inclusion in the vaccination category may result in changes in testing practices for influenza infection in the different arms of the trials.

Fourthly, there is evidence that influenza vaccination may increase the risk of respiratory illness due to other respiratory viruses during select seasons^{26,27}. Mechanisms have been proposed for that phenomenon, from lack of non-specific short-term immunity due to prevented influenza infections in vaccinated persons to skewed immune responses for related epitopes following influenza vaccination, which may be relevant during select influenza seasons²⁸. Thus, some of the benefit of influenza vaccination against influenza-associated respiratory illness can be reversed through excess respiratory illness due to other viruses. This may explain the results of ⁹ that found a smaller effect of HCW vaccination on respiratory illness in residents/patients compared to the effect on all-cause mortality, with the latter effect being more representative of the impact of HCW vaccination against influenza.

Finally, a study of influenza vaccination of HCWs in the Paris area²¹ showed a 20% reduction in mortality only after adjustment for the different covariates. However, supporting information for that paper shows that there was a big epidemic due to different respiratory viruses, including RSV in the control nursing homes prior to the study period, but not the vaccination arm. That prior epidemic in the control arm created short term immunity to influenza infection and biased the results of the paper because the study period did not include the preceding epidemic during the same winter season. The period preceding the study period in²¹ should have also been included in the study as

the preceding epidemic in the vaccination vs. control arm was likely affected by influenza vaccination as a result of possible influenza outbreaks in studied nursing homes during the earlier period, as well as non-specific short-term immunity rendered by influenza vaccination²⁹ that affects susceptibility to infection for different respiratory viruses. Overall, it is difficult to interpret the findings in²¹ due to the exclusion of the preceding epidemic in the study period.

In summary, there is evidence that influenza epidemics are associated with a significant burden of all-cause mortality in the EU^{1,30}, that nursing home residents represent a sizeable share of all-cause mortality^{5,6} and influenza-associated mortality⁴ in the EU, and that influenza vaccination for HCWs results in a significant reduction in all-cause mortality during influenza seasons in nursing home residents⁸⁻¹⁰, as well as in hospital patients³¹. Various strategies are available for boosting influenza vaccination coverage for HCWs in different settings, e.g. hospitals^{14,15} vs. nursing homes¹³. Finland has introduced a semi-mandatory approach whereas it is the employer's responsibility to appoint only vaccinated staff for servicing vulnerable populations³², with influenza vaccination rates in HCWs in Finland having reached 87.6% in seasons 2019-2022. Experience from other countries in the EU, e.g. Austria¹³, Germany¹⁴ and Greece¹⁵ suggests that educational interventions and on-sight vaccination campaigns can result in substantial increases in influenza vaccination coverage in HCWs in both long-term care facilities and hospitals. Efforts should be undertaken to increase awareness and accessibility for influenza vaccines for HCWs in different settings to mitigate the mortality burden of influenza epidemics in residents in long-term care facilities, as well as in hospital patients.

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Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

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