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Characteristics and risk of COVID-19-related death in fully vaccinated people in Scotland

Vaccines are highly effective in preventing COVID-19 hospitalisations and deaths.[1,2] COVID-19-related deaths in fully vaccinated individuals have, however, been reported. To inform public health strategy and vaccination policy, it is vital to characterise these post-vaccination COVID-19 fatalities.

We used EAVE II, a national, individual-level surveillance system, to estimate the frequency of COVID-19-related deaths among fully vaccinated individuals and to describe the clinical and demographic characteristics of COVID-19-related deaths among fully vaccinated individuals since the start of the COVID-19 vaccination programme in Scotland.[2] We also conducted survival analyses to understand predictors for death among fully vaccinated individuals who tested positive for SARS-CoV-2. Ethical approval was granted by the National Research Ethics Service Committee, Southeast Scotland 02 (12/SS/0201). Approval for data linkage was granted by the Public Benefit and Privacy Panel for Health and Social Care (1920-0279). Individual written patient consent was not required for this project.

COVID-19-related deaths in fully vaccinated individuals were defined as death in those who tested positive by RT-PCR for SARS-CoV-2 at any timepoint more than 14 days after receiving their second dose of BNT162b2 (Pfizer–BioNTech) or ChAdOx1 nCoV-19 (AZD1222; Oxford–AstraZeneca) vaccines[3] and subsequently died with COVID-19 listed as an underlying or contributory cause of death on the death certificate (appendix p 1).

Of the 3 273 336 individuals in Scotland who were fully vaccinated by Aug 18, 2021 (73·6% of the eligible population), 1 205 642 individuals received two doses of BNT162b2 and 2 026 198 individuals received two doses of ChAdOx1 nCoV-19. As there were no deaths among the 41 496 individuals who received two doses of mRNA-1273 (Moderna) vaccine during the study period, they were not further considered in this analysis.

236 deaths in fully vaccinated people were recorded (0·007% of the total vaccinated): 47 (0·004%) of those individuals had received BNT162b2 (median age 74·0 years [IQR 69·0–89·0]), and 188 (0·009%) individuals had received ChAdOx1 nCoV-19 (80·0 years [73·0–86·0]). One death was in an individual who received a first dose of ChAdOx1 nCoV-19 followed by a second dose of BNT162b2. 195 (82·6%) individuals had COVID-19 as the underlying cause of mortality, and 41 (17·4%) individuals had COVID-19 as a contributing cause of mortality.

We calculated age-stratified death rates per 10 000 person-years in each vaccine group to describe differences in death rates between unvaccinated and fully vaccinated individuals in the age groups 18–64 years, 65–79 years, and older than 80 years (appendix p 3).

Within the vaccine-eligible population of Scotland aged 65–79 years, the death rate per 10 000 person-years was 64·8 for unvaccinated individuals and 4·2 for fully vaccinated individuals. This difference in death rate was most marked in the population older than 80 years (14·0 deaths per 10 000 person-years for fully vaccinated *vs* 420·1 deaths per 10 000 person-years for unvaccinated individuals older than 80 years) but attenuated in individuals aged 18–64 years (0·8 deaths per 10 000 person-years for fully vaccinated *vs* 3·1 deaths per 10 000 person-years for unvaccinated individuals aged 18–64 years). For

	All laboratories	Lighthouse laboratories	NHS laboratories
Place of test			
Community cases (Lighthouse laboratory)	1·0	..	..
Hospital cases (NHS laboratory)	10·20 (7·17–14·51)	..	..
Sex			
Female	1·0	1·0	1·0
Male	1·93 (1·46–2·54)	2·74 (1·49–5·01)	1·77 (1·29–2·41)
Deprivation status			
1 (most deprived)	1·0	1·0	1·0
2	1·02 (0·70–1·48)	1·03 (0·49–2·17)	1·03 (0·67–1·59)
3	0·90 (0·61–1·34)	0·58 (0·23–1·45)	1·03 (0·66–1·59)
4	0·79 (0·51–1·21)	0·49 (0·19–1·29)	0·90 (0·56–1·46)
5 (least deprived)	0·79 (0·52–1·20)	0·83 (0·37–1·86)	0·80 (0·49–1·33)
Number of comorbidities			
0	1·0	1·0	1·0
1	1·56 (0·85–2·86)	2·21 (0·74–6·58)	1·21 (0·58–2·51)
2	1·87 (1·04–3·37)	2·25 (0·73–6·90)	1·48 (0·75–2·94)
3–4	3·35 (1·95–5·77)	4·75 (1·69–13·39)	2·49 (1·33–4·65)
≥5	3·15 (1·73–5·72)	10·01 (3·15–31·79)	2·09 (1·06–4·14)

Data are adjusted hazard ratios (95% CI). Cox regression was used to model the hazard ratio for a COVID-19-related death following a positive test in fully vaccinated individuals, accounting for age, sex, number of comorbidities and deprivation quintile. Age and date of death were included as spline terms. Tests undertaken in symptomatic individuals in the community were analysed in Lighthouse laboratories whereas those attending Accident and Emergency or admitted to hospital were tested in NHS laboratories. Deprivation status was measured with the Scottish Index of Multiple Deprivation 2020. NHS=National Health Service.

Table: **COVID-19-related death in fully vaccinated individuals in Scotland who test positive for SARS-CoV-2**

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fully vaccinated individuals who subsequently tested positive, there was a median of 8·0 days (IQR 5–13) between a positive test and dying of COVID-19.

The median age at death was 79·5 years (IQR 72·0–87·0), with 146 (61·8%) deaths occurring in men. 184 (78·0%) individuals were admitted to hospital before dying, and 63 (34·2%) individuals tested positive before hospital admission. 101 (54·9%) individuals tested positive on admission to hospital or during their stay, suggesting that they did not seek or receive treatment for COVID-19 before hospital admission. 41 individuals were admitted to an intensive care unit or high-dependency unit after testing positive for SARS-CoV-2 and before dying. A limitation of our analysis includes being unable to discern why an individual with a positive COVID-19 PCR test was admitted to hospital.

230 (97%) individuals had at least one cause of death listed in addition to COVID-19. A mean of 2·9 causes of death (excluding COVID-19) were listed on death certificates (range from one to eight other causes of death). The most common non-COVID-19 causes of death were chronic heart disease, chronic kidney disease, diabetes, chronic obstructive pulmonary disease, and atrial fibrillation (appendix p 4). Additional clinical and sociodemographic characteristics of individuals who died are summarised in the appendix (p 5).

Viral sequencing data were available for 106 deaths. Five individuals died with the alpha variant of concern (VOC), and 101 individuals died with the delta VOC. Sequencing data were not available for 130 deaths.

A Cox proportional hazard model was used to understand predictors of mortality for fully vaccinated individuals who tested positive (table). We linked 225 (95%) of 236 deaths to general practice records, and these individuals were subsequently included in the Cox regression model. The risk of COVID-19-related mortality among community-tested (ie, tested in Lighthouse laboratories) double-vaccinated individuals increased with number of comorbidities: people with five or more comorbidities were at substantially higher risk of COVID-19-related death than people with no comorbidities, although CIs were very wide (adjusted hazard ratio 10·01; 95% CI 3·15–31·79). Men also had a higher risk of COVID-19-related death than women (2·74; 1·49–5·01). Among all cases, those individuals who were identified in hospital had a much higher risk of death than individuals who were identified in the community (10·20; 7·17–14·51).

In summary, COVID-19-related deaths were extremely uncommon in those fully vaccinated with either BNT162b2 or ChAdOx1 nCoV-19. Most individuals who died after two doses of COVID-19 vaccine were older than 75 years and had multiple comorbidities. These results are similar to the risk profile for mortality in unvaccinated individuals with COVID-19 infection[3,4] and in vaccinated individuals who have received one dose of vaccine.[5] Risk of COVID-19-related death is therefore not completely eliminated when fully vaccinated; the results of this study suggest the importance of continued caution and non-pharmaceutical interventions, in particular for older adults with multiple comorbidities.

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