Title: Challenges in Estimating Effectiveness of 2 Doses of COVID-19 Vaccines Beyond 6 Months in England

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Data Availability Statement: All data were linked, stored and analysed securely within the OpenSAFELY platform: https://opensafely.org/. Data include pseudonymised data such as coded diagnoses, medications and physiological parameters. No free text data are included. Detailed pseudonymised patient data is potentially re-identifiable and therefore not shared. Primary care records managed by the GP software provider, TPP/EMIS were linked to COVID-19 test results, hospital admissions, hospital deaths (COVID-19 only), and registered deaths through OpenSAFELY. Data management was performed using Python 3.8.10, with analysis carried out using R version 4.0.2. All code is shared openly for review and re-use under MIT open license https://github.com/opensafely/waning-ve-2dose-1year.

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Running Head: Estimating effectiveness of COVID-19 vaccines

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Abbreviations: vaccine effectiveness (VE); hazard ratio (HR); clinically vulnerable (CV)

Understanding how effectiveness of COVID-19 vaccines changes over time and in response to new SARS-CoV-2 variants is crucial to scheduling subsequent doses. A previous study quantified vaccine effectiveness (VE) over six consecutive 4-week periods from 2 to 26 weeks after second dose (1). Waning of hazard ratios (HRs) comparing vaccinated with unvaccinated individuals was approximately log-linear over time, and consistent across COVID-19-related outcomes and risk-based subgroups. To investigate waning beyond 26 weeks and in the omicron era, we extended follow-up to the earliest of 50 weeks after second dose or 31 March 2022.

METHODS

The data source, study design and statistical analysis are described in Web Appendix 1 and Web Table 1. Ethical approval and data protection are detailed in Web Appendix 2. Eligible individuals were aged ≥18 years; registered at an English primary care practice using TPP SystmOne; not in a care home or medically housebound; and had complete demographic data with no evidence of prior SARS-CoV-2 infection.

We estimated VE across 12 consecutive 4-week comparison periods in risk-based subgroups: ages 65+, 18-64 and clinically vulnerable (CV), 40-64 and 18-39 years. We estimated VE of two doses of the BNT162b2 and ChAdOx1 vaccines (versus no vaccine) in the 65+ and 18-64 CV subgroups. VE could only be estimated for ChAdOx1 in the 40-64 subgroup, and BNT162b2 in the 18-39 subgroup.

Unvaccinated individuals were eligible for vaccination throughout follow up. From the later of mid-September 2021 and six months after second dose, individuals at highest risk of severe COVID-19 were offered a third dose (2,3). Third dose eligibility was progressively extended based on risk of severe COVID-19 until mid-December 2021, when concerns about the omicron variant led to third doses being made available to all adults, with the required interval reduced to three months (4–6). In our VE models, unvaccinated individuals who received a first dose or vaccinated individuals who received a third dose were followed up for the remainder of that 4-week comparison period, then excluded. We fitted additional models to investigate factors associated with uptake of third dose (Web Appendix 3).

RESULTS

There were 1,990,562, 3,281,054 and 1,227,170 eligible individuals in the BNT262b2, ChAdOx1 and unvaccinated groups respectively. Subgroup characteristics were described previously (1). Earliest follow-up dates in the 65+, 18-64 CV, 40-64 and 18-39 subgroups were 15 March, 21 April, 18 May and 23 July 2021 respectively. Individuals were followed for up to 50 weeks in the 65+ and 18-64 CV subgroups, and 47 and 38 weeks in the 40-64 and 18-39 subgroups respectively. The latest follow-up date in all subgroups was 31 March 2022. Web Figure 1 shows the distribution of follow-up time per comparison period. Web Tables 2-21 show the number of events during each comparison period across subgroups and outcomes.

Cumulative incidence of third dose increased rapidly during the eight weeks following eligibility (Figure 1A). In the 65+ subgroup, incidence increased from 1% 23 weeks after second dose to ≥93% by 31 weeks. Trends were similar in the 18-64 CV and 40-64 subgroups, reaching ≥90%. In the 18-39 subgroup, incidence increased from 1% after 15 weeks to 62% after 23 weeks and 73% after 38 weeks. Uptake of third dose was over five times lower in those with, compared to without, a recent positive SARS-CoV-2 test, and also lower in those who were in hospital after unplanned admission, particularly if the admission included a COVID-19 code, and those who initiated end-of-life care (except the 18-39 subgroup in whom such events were rare; Web Figures 2-5).

Because of high uptake of third dose, estimated effectiveness of two doses during later comparison periods was based on highly selected individuals who had received two but not three doses. Estimated HRs for non-COVID-19 death in the 65+, 18-64 CV and 40-64 years subgroups changed markedly over the comparison periods during which most third doses occurred (Figure 1B). In the 65+ subgroup, estimated HRs comparing non-COVID-19 death in individuals with two BNT162b2 versus no vaccine doses increased from 0.61 (95% CI 0.51,0.73) to 2.40 (2.02,2.85) during weeks 27-30 and 35-38 respectively. Trends were similar for ChAdOx1 and the 18-64 CV and 40-64 subgroups. Because estimated HRs for non-COVID-19 death strongly suggest selection bias arising from deferred vaccination in people with a recent SARS-CoV-2 infection or in poor health, we did not attempt to interpret estimated HRs beyond 26 weeks for COVID-19-related outcomes in the 65+, 18-64 CV and 40-64 subgroups.

In the 18-39 subgroup, estimated HRs for non-COVID death (BNT162b2 only), although imprecisely estimated, did not change markedly during the rollout of third vaccine doses (Figure 1B). The cumulative incidence of third dose was lower in this than other subgroups, and postponement of vaccination because of ill-health was rare. Waning of HRs for COVID-19 hospitalisation was approximately log-linear over time, from 0.04 (0.03,0.07) during weeks 3-6 to 1.48 (0.69,3.17) by weeks 35-38. Waning of HRs for positive SARS-CoV-2 test was approximately log-linear up to weeks 23-26 after second dose. Estimated HRs were 0.25 (0.24,0.26) during weeks 3-6, with HRs greater than 1 by weeks 5-18. By weeks 23-26, the HR for positive SARS-CoV-2 test (1.97 (1.91,2.02)) was close to the HR for any SARS-CoV-2 test (2.16 (2.12,2.19)). HRs for any SARS-CoV-2 test remained close to 2 throughout follow-up (Web Figure 6). Waning of HRs against positive SARS-CoV-2 test and COVID-19 hospitalisation in this subgroup did not appear to be affected by the emergence of the omicron variant.

DISCUSSION

Cumulative incidence of third dose in the 65+, 18-64 CV and 40-64 subgroups reached ≥90%. In these subgroups, vaccinated individuals who did not receive a third dose were at higher risk of non-COVID-19 death than unvaccinated individuals, due to postponement of vaccination because of SARS-CoV-2 infection, or acute illness requiring an unplanned hospital admission. In these subgroups, estimates of effectiveness of second dose against COVID-19-related outcomes are unlikely to be meaningful beyond six months, because they are based on highly selected individuals. In these subgroups, it is difficult to disentangle the effect of the omicron variant from depletion of the two-dose group due to third dose.

In the 18-39 subgroup the maximum cumulative incidence of third dose was 73%, and there was no evidence that individuals who remained in the two-vaccine-dose group were at greater risk of non-COVID-19 death than unvaccinated individuals. Waning of HRs against COVID-19 hospitalisation in this subgroup was approximately log-linear, and VE was negligible by weeks 35-38 after second dose. Waning of HRs against positive SARS-CoV-2 test was approximately log-linear until weeks 23-26, and VE was negligible by weeks 15-18. This finding should be interpreted with caution, as it may have been due to higher uptake

and reporting of SARS-CoV-2 tests in vaccinated than unvaccinated individuals. Waning HRs in the 18-39 group did not appear to be affected by emergence of the omicron variant.

An Australian survey found that unvaccinated individuals reported lower intentions to test for SARS-CoV-2 when symptomatic and to report a positive SARS-CoV-2 test than vaccinated individuals (7). While estimated HRs reported here were adjusted for characteristics including previously reported SARS-CoV-2 tests (Web Table 1), unmeasured confounding by testing behaviour likely remains given that HRs against any SARS-CoV-2 test were approximately 2 throughout follow-up. Waning of HRs for positive SARS-CoV-2 test in the 18-39 subgroup was approximately log-linear until weeks 23-26, then plateaued and was close to the HRs for any SARS-CoV-2 test for the remaining comparison periods (except weeks 31-34). A tentative interpretation is that estimated VE against positive SARS-CoV-2 test does not become negligible until weeks 23-26 (the inflection point in log-linear waning), while HRs ≥1 were a result of uncontrolled confounding relating to differences in testing behaviour between vaccinated and unvaccinated individuals. Follow-up from week 23 in this subgroup (Web Figure 1) coincided with changes to testing policy in early January 2022 (8), and the announcement in February that freely available mass testing would stop on 1 April 2022 (9). End of follow-up for this study was 31 March 2022, but changes to testing behaviours are likely to have preceded this.

Third doses should be deferred until four weeks after the start of a SARS-CoV-2 infection (10), consistent with our finding that uptake of third dose was five times lower in those with than without a recent positive SARS-CoV-2 test (Web Appendix 3). Consequently, a high proportion of individuals remaining in two-vaccine-dose groups after widespread uptake of third dose may have had current or recent SARS-CoV-2 infection. Individuals who reported a positive SARS-CoV-2 test were removed from subsequent comparison periods where the outcome was SARS-CoV-2-test-related. However, they remained in subsequent comparison periods for all other outcomes. Thus, higher prevalence of recent or current positive SARS-CoV-2 test in two-vaccine-dose groups due to delayed vaccination could have resulted in higher rates of COVID-19 hospitalisation or death and underestimates of VE against these outcomes following widespread uptake of third doses.

Previous studies reported estimates of effectiveness of second dose beyond six months (11–13) and reduced VE against the omicron variant (11). However, the impacts of third dose uptake on estimated second dose VE, and of changes in testing policy and behaviours, are rarely discussed. This study demonstrated the importance of these factors in interpreting estimated VE. Studies increasingly focus on incremental effectiveness of additional doses, rather than using unvaccinated individuals as the comparator. Investigators of such studies should carefully consider reasons why eligible individuals may not have received additional doses, particularly when the cumulative incidence of additional doses is high. We explored this by fitting models to investigate the baseline and time-updating characteristics associated with uptake of third dose. However, HRs from these models may be biased by time-dependent confounding, so should not be interpreted as estimating causal effects. Reporting non-COVID-19 outcomes may also provide important insights into potential biases impacting interpretation of estimated VE.

It is challenging to estimate long-term effectiveness of two COVID-19 vaccine doses in populations in which uptake of third doses was high. These challenges also impact investigations of VE against the omicron variant, whose emergence coincided with rapid uptake of third doses, and of incremental effectiveness of third dose against second dose. The uptake of third dose was sufficiently high that we do not believe that, for the data analysed here, much could be done to address the biases that we have identified beyond constraining timeframes over which VE is estimated. However, in situations when uptake was more gradual, weighting observations by the inverse probability of censoring due to vaccination is a useful way to address informative censoring.

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Figure 1. (A) Cumulative incidence of third dose in the vaccinated groups and first dose in the unvaccinated groups throughout follow-up time. Cumulative incidence lines are dashed before and solid after omicron became dominant. (B) Hazard ratios (HR) for BNT162b2 vs unvaccinated and ChAdOx1 vs unvaccinated. Shapes are hollow before and solid after omicron became dominant. Y-axes for HRs and estimated vaccine effectiveness (VE) are on the log scale. The plot background is shaded where the cumulative incidence of third dose is >80%. Data are from OpenSAFELY-TPP, England, 2020-2021.