Effectiveness of COVID-19 vaccines: findings from real world studies

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Competing interests: No relevant disclosures

Word Count 1505 (excluding abstract table and references)

1 Table

16 references

Intro Line *Community-based studies in five countries show consistent strong benefits from early rollouts of COVID-19 vaccines.*

Abstract

Researchers in five countries analysed multiply linked health datasets to measure effectiveness of the COVID-19 vaccines being deployed in their communities. They used different techniques to adjust for factors that likely confound the relationship between vaccination and COVID-19 complications. The studies were consistent in finding greater than 80% reductions in rates of infection and hospitalisation, and these appeared unaffected by age. Two studies documented substantial reductions in mortality. Follow up times were short, data on viral variants were confined to the B.1.1.7 (UK) strain; viral transmission was not assessed directly, and serious vaccine harms were not evaluated. Although Australia collects the necessary information researchers do not have ready access to the multiply linked data needed to perform community-based studies of the benefits and harms of COVID-19 vaccines.

Background

By the end of April 2021, over 600 million individuals had received at least one dose of a coronavirus disease 2019 (COVID-19) vaccine internationally.[1] This represents an extraordinary scientific and logistical achievement, where in around 12 months researchers, manufacturers and governments collaborated to produce and distribute vaccines that appear effective and acceptably safe in preventing COVID-19 and its complications. [2,3]

The initial randomized trials confirmed immunological responses and generated unbiased evidence of vaccine efficacy. They were conducted in selected populations with limited numbers of participants in high-risk groups, such as the elderly and those with serious underlying medical conditions.[2,3] They provided sparse information on the impact of vaccination on transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were too small to quantify rare but serious harms and did not take account of the logistical obstacles encountered during the community-wide roll-out of new vaccines. While large cluster randomized trials could address some of these concerns [4], large observational studies have used large linked routinely collected population datasets in 5 countries to address important knowledge gaps. [5,6,7,8,9]

The purpose of this Perspective article is to highlight these important studies and stress that at present researchers in Australia do not have timely access to the linked Commonwealth and state datasets needed to perform such analyses.

Real world studies

In five countries (Israel, England, Scotland, ~~the United Kingdom~~, Sweden and the United States of America) researchers have analysed routinely collected data to report the early outcomes of community-wide vaccination programs with three of the first vaccines to reach market – the BNT162b2 mRNA (Pfizer/BioNTech) mRNA-1273 (Moderna) and ChAdOx1 adenoviral vector (Oxford/AstraZeneca) vaccines.[5,6,7,8,9]

At this time only two of the papers (from Israel and Scotland) have been peer reviewed[5,6], so details reported here may change after revisions to the other reports.[7,8,9] There is a rapidly growing literature on community impact of COVID-19 vaccines that have provided very consistent evidence of substantial vaccine effectiveness. We think it is unlikely that these findings will be change significantly with future research.

The vaccination programs against COVID-19 commenced in December 2020 in the study countries, so follow-up is limited. Most of the investigators used rigorous designs and statistical methods to analyse linked routinely collected person-level data from large community-wide databases that tracked outcomes in vaccinated and unvaccinated individuals (Table). Importantly, allocation to vaccines was not by randomization and vaccinated and unvaccinated populations differed in respect of factors that were associated with both the probability of vaccination and with the severe outcomes of COVID-19. Information that featured in most studies included demographic details, a vaccine register, results of laboratory polymerase chain reaction (PCR) testing, records of hospitalisation and death, and some geographic measures of social deprivation. In addition, the Israeli, United States and Scottish studies included linkage to clinical records from which to quantify co-morbidities.[5,6,8] The Israeli study included information on previous adherence to influenza vaccination schedules.[5]

Study designs and adjustments for confounding

The studies had used different approaches to adjust for confounding (Table). The most advanced design was used to analyse the linked data from members of the Clalit Health Services integrated health care organisation in Israel, which covers around 4.7 million people Israel.[5] The investigators extracted data on matched cohorts of vaccinees and non-vaccinated controls and analysed study endpoints using rules that emulated the steps taken in a randomized trial. [10] These steps minimised selection or measurement biases and controlled for potential confounders through precise 1:1 matching of vaccinated and non-vaccinated subjects across 7 domains. The investigators took the additional step of calibrating their statistical model against the results of the pivotal Phase 3 randomized trial, which found no benefit during the first 2 weeks after vaccination.[2] In contrast, this observational study found lower rates of infection in the first 2 weeks after vaccination, which remained after matching for age and sex – illustrating the potential for confounding. Only after full matching on seven factors was this source of bias eliminated.[5]

In England, investigators linked data from a national vaccine register to laboratory PCR swab results, emergency department admissions, demographic and ethnicity data, care home status and deaths, in subjects aged 70 years and over (Table).[7] The first part was a test negative case-control design, which compared vaccination status in subjects who received a positive PCR swab result with contemporaneous controls who returned a negative result. That both cases and controls had been tested for SARS-CoV-2 should have controlled for clinical and behavioral factors that influence the probability of having a test. The second part of the study followed subjects aged 80 years and over who had a positive PCR test and

analysed them according to vaccination status. The investigators calculated adjusted hazard ratios for death up to and beyond 14 days from the first vaccine dose.

A study in Scotland used an unmatched cohort design comparing clinical endpoints in subjects who received either the Pfizer/BioNTech or Oxford/ Astra Zeneca vaccines with an unvaccinated control group.[6] The Oxford/Astra Zeneca vaccine was given later to an older population. The study adjusted for age and sex, frequency of prior PCR tests and clinical risk groups extracted from linked health records. The statistical model generated unexpectedly strong protective effects of the vaccines on hospitalisation rates in the first 2 weeks after vaccination in subjects aged 65 + years and the opposite effect in younger subjects, possibly indicating age-related residual confounding.

In the USA researchers working within the Mayo Clinic heath system used post code and propensity scores (based on age, sex, race, ethnicity and records of PCR testing) to match a cohort of individuals who received the Pfizer BioNTech or Moderna mRNA vaccine with unvaccinated controls to measure impact on infections and hospitalisations.[8]

A simple unmatched cohort design using linkage of routinely collected administrative data measured infection rates in a cohort who received the Pfizer/BioNTech vaccine in a single county in Sweden.[9] The unvaccinated population acted as controls (Table). Confounding adjustments in this study were limited to age and sex.

The Table summarises the results of these studies. All included at least one mRNA vaccine and the reductions in infections and hospitalisations were consistent and large. Two studies reported on mortality and the reductions were substantial, although based on small numbers of deaths in Israel (Table).[5,7] The studies did not directly compare vaccines, but the Oxford/Astra Zeneca vaccine appeared to perform as well as the mRNA vaccines in reducing hospitalisations.

Other approaches to estimating vaccine effectiveness

In the UK over 600,000 volunteers using a COVID-19 symptom phone App recorded adverse events after vaccination with either the Pfizer BioNTech or Oxford Astra Zeneca vaccines.[11] Based on post-vaccination self-reports of infections and after adjustment for age sex obesity and co-morbidities they estimated effectiveness rates of 60 to 70% beyond 21 days after administration of either vaccine. Three studies measured the effectiveness of COVID-19 vaccines in care home, healthcare, and other frontline workers in the UK, Israel, and USA. [12,13,14] These projects enrolled smaller numbers of participants than the community-based studies but used similar designs and adjustment techniques. Importantly, workers

in these settings undergo routine PCR testing for SARS-CoV-2, which enabled detection of asymptomatic infections. These studies also found large protective effects and a potential to reduce viral transmission. This latter possibility has been investigated directly in a study conducted in Scotland that showed that 14 days or more after healthcare workers received a second dose of vaccine their household members had a 54% lower rate of COVID-19 than individuals who shared households with non-vaccinated healthcare workers. [15]

Conclusions

We can draw important conclusions from these non-randomised studies of vaccine effectiveness. Most importantly the currently available COVID-19 vaccines appear to be effective in preventing severe complications and deaths from COVID-19 in adults of all ages. Follow-up periods are short, and these reports do not provide information on rare but serious adverse events, such as cerebral venous thrombosis. The use of sophisticated trial emulation methods in the study from Israel replicated some key features of the pivotal randomized trial of the Pfizer vaccine, particularly by controlling for an early healthy cohort effect that probably confounded the incompletely adjusted endpoint analyses. This design should prove useful in enabling direct head-to-head comparisons of effectiveness and safety of vaccines, studies of the duration of clinical immunity, studies of the degree to which vaccines prevent transmission and their impacts on 'long COVID'.

These studies exemplify the value of advanced analyses of large multiply linked routinely collected community datasets. This resource is not yet readily available to researchers in Australia due to continued lack of agreement on the governance of linked state and commonwealth datasets.[16] While Australia's low rates of community transmission of SARS-CoV-2 reduce the feasibility of observational studies of vaccine effectiveness, the available data can provide important information on potential harms of vaccines. With continuing questions about the comparative safety of vaccines, the long-term effects of COVID-19 and the likelihood of future epidemics, it is essential that Australia urgently removes barriers to allowing pre-qualified researchers to safely access the linked de-identified population datasets that are needed to expeditiously conduct the types of studies reviewed here.

Table: Characteristics of five 'real world' community-based studies of effectiveness of SARS-CoV-2 vaccines

Author	Dagan et. al. (2021)[5]	Bernal et. al. (2021)[7]	Vasileiou et. al. (2021)[6]	Bjork et. al. (2021)[9]	Pawlowski et. al. (2021)[8]
Country	Israel	England	Scotland	Sweden	USA
Vaccine	BNT162b2*(1 or 2 doses)	BNT162b2* (2 doses) or ChAdOx1* (1 dose)	BNT162b2* or ChAdOx1* (1 dose)	BNT16b2*(1 or 2 doses)	BNT162b2* or mRNA-1273*(2 doses)
Study Design	Target trial emulation using 1:1 individual matching of vaccinated and unvaccinated subjects	Hybrid of (1) Test negative case-control followed by (2) cohort analysis of PCR +ve individuals	Controlled cohort study	Controlled cohort study	Controlled cohort study with 1:1 individual matching of vaccinated and unvaccinated subjects
Source Population	Aged 16 + years 1,503,216 vaccinated 1,655,920 unvaccinated enrolled with single state-mandated healthcare provider	Aged 70+ years >7.5 million enrolled with UK National Health Service	Aged 15+ years 1,137,775 vaccinated 3,271,836 unvaccinated enrolled with UK National Health Service	Aged 18-64 years 26,587 vaccinated 779,154 unvaccinated enrolled with single regional health service	Aged 18+ years 249,708 enrolled with single non-profit healthcare provider who had PCR test for SARS-CoV-2
Numbers analysed	596,618 vaccinated; 596,618 matched unvaccinated controls	1. Cases (PCR+ve) 44,590 Controls (PCR-ve) 112,340 2. Vaccinated 1846 Unvaccinated 8096	Same as source population	Same as source population	31,069 vaccinated 31,069 unvaccinated
Analysis methods	Kaplan-Meier analysis	Logistic regression analysis	Time-dependent Cox regression / Poisson regression adjusting for time at risk	Incidence rate ratios	Kaplan-Meier analysis
Study endpoints included in analyses (n)	Infections (10,561) Hospitalisations (369) Deaths (41)	Infections (32,832) Hospitalisations (1,859) Deaths (1,228)	Hospitalisations (7,914)	Infections (4228) Deaths (36)	Infections (924) Hospitalisations (224)

Confounder adjustments	1:1 matching on day of vaccination on 7 features - *age, sex, place, ethnicity, past flu vaccine, pregnancy, number of pre-existing medical conditions*	Adjusted for 5 features: *age, sex, ethnicity, NHS region, deprivation*	Adjusted for 5 features: *age, sex, deprivation score, number of prior PCR tests, number of medical conditions*	Adjusted for *age and sex*	Propensity-matched based on *sex, age, ethnicity, location and number of prior SARS-CoV-2 PCR tests*
Check on residual confounding[#]	Yes - calibrated to check no effect in first 14 days	Yes – used immediate post vaccination period as reference	No – significant benefit noted prior to day 14	No – did not evaluate endpoints before day 14	No - significant benefit noted prior to day 14
Vaccine Effectiveness: selected measures (95% CI)	**BNT162b2** Days 14-20 Infection 46% (40-51%) Hospitalisation 74% (56-86%) Death 72% (19-100%) Day 7+ after second dose Infection 92% (88-95%) Hospitalisation 87% (55-100%)	**BNT162b2** Days 28-34 Infection 61% (51-69%) Hospitalisation^ 43% (33-52%) Death^ 51% (37-62%) **ChAdOx1** Days 28-34 Infection 60% (41-73%) Hospitalisation^ 37% (3-59%)	**BNT162b2** Days 28-34 Hospitalisation 86% (76-91%) **ChAdOx1** Days 28-34 Hospitalisation 94% (73-99%)	**BNT162b2** Day 14+ Infection 42% (14-63%) Death not calculated[$] Day 7+ after second dose Infection 86% (72–94%) Death not calculated[$]	**BNT162b2 or mRNA-1273** Day 14+ Infection 75.0% (67.4-81.1%) Hospitalisation 60% (14.0-79.0%) Day 36+ (2 doses only) Infection 88.7% (68.4-97.1%)
Viral variants of concern	B.1.1.7. common during follow up	B.1.1.7 was the dominant virus during the study period	B.1.1.7 common during study period	B.1.1.7. common during follow up	No mention of variants

* BNT162b2 (Pfizer/BioNTech mRNA vaccine); ChAdOx1 (Oxford/Astra Zeneca adenoviral vector vaccine); mRNA-1273 (Moderna mRNA vaccine)
^ Reductions in risk of hospitalisation and death were **additional** to the reduction in infection risk, equivalent to an overall reduction in hospitalisation of 80% and 85% reduction for death (BNT162b2 only)
# It is assumed that an apparent protective effect before day 14 reflects residual confounding
$ No deaths recorded in vaccinated subjects

References

1. Our world in numbers. Statistics and research Coronavirus (COVID-19) Vaccinations https://ourworldindata.org/covid-vaccinations (accessed 19 May 2021)
2. Polack FP, Thomas SJ, Kitchin N, Absalon J, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; 383: 2603-15.
3. Voysey M, Clemens SA, Madhi SA, Weckx LY, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* 2021;397: 881-91.
4. Bell K J L, Glasziou P, Stanaway F, Bossuyt P, et al. Equity and evidence during vaccine rollout: stepped wedge cluster randomised trials could help *BMJ* 2021;372: n435. doi:10.1136/bmj.n435
5. Dagan N, Barda N, Kepten E, Miron O, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021; 384: 1412-23
6. Vasileiou E, Simpson CR, Shi T, Kerr S, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet 2021*; doi.org/10.1016/S0140-6736(21)00677-2
7. Bernal JL, Andrews N, Gower C, Stowe J, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. medRxiv 02 March 2021. doi.org/10.1101/2021.03.01.21252652 (accessed 19 May 2021)
8. Pawlowski C, Lenehan P, Puranik A, Agarwal V, et al. FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system. medRxiv 27 Feb 2021. doi.org/10.1101/2021.02.15.21251623 (accessed 19 May 2021)
9. Bjork J, Inghammar M, Moghaddassi M, Rasmussen M, et al. Effectiveness of the BNT162b2 vaccine in preventing COVID-19 in the working age population - first results from a cohort study in Southern Sweden. medRxiv 21 April 2021. doi.org/10.1101/2021.04.20.21254636 (accessed 19 May 2021)
10. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol* 2016; 183:758-64.
11. Menni C, Klaser K, May A, Polidori L, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. *Lancet Infect Dis* 27 Apr 2021. doi.org/10.1016/S1473-3099(21)00224-3 (accessed a9 May 2021)
12. Hall VJ, Foulkes S, Saei A, Andrews N, et al. Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN Study). Preprints with The Lancet 22 Feb 2021. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3790399 (accessed 19 May 2021)
13. Amit S, Regev-Yochay G, Afek A, Kreiss Y, et al. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *Lancet* 2021; 397: 875-7.
14. Thompson MG, Burgess JL, Naleway AL, Tyner HL, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers—eight US locations, December 2020–March 2021. *MMWR Morb Mortal Wkly Rep* 2021; 70: 495 - 500.

15. Shah AS, Gribben C, Bishop J, Hanlon P et al. Effect of vaccination on transmission of COVID-19: an observational study in healthcare workers and their households. medRxiv 21 March 2021. doi.org/10.1101/2021.03.11.21253275 (accessed 19 May 2021)
16. Henry D, Stehlik P, Camacho X, Pearson SA. Access to routinely collected data for population health research: experiences in Canada and Australia. *Aust N Z J Public Health* 2018; 42: 430 - 433