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Real world effectiveness of covid-19 vaccines

Rigorous studies of these vaccines in action are an urgent priority globally

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Post-introduction vaccine studies provide practitioners and policy makers with the kind of evidence that clinical trials cannot—including real world vaccine effectiveness against multiple clinical outcomes. Two linked studies[1][2] that together examined three covid-19 vaccines, add to mounting evidence that efficacy reported in clinical trials translates well to the real world.[3 -7] The studied vaccines—CoronaVac (Sinovac Biotech), BNT162b2 (Pfizer-BioNTech), and mRNA-1273 (Moderna)—performed well in preventing severe covid-19 and deaths in adults after two doses; a single dose was significantly less effective, and all three vaccines were effective (although demonstrably less so) against milder disease.

Both studies used test negative case-control designs to estimate effectiveness—comparing vaccination history among people with symptoms who tested either positive (cases) or negative (controls) for SARS-CoV-2. Ranzani and colleagues (doi:10.1136/bmj.n2015) evaluated CoronaVac in adults aged 70 or older in Brazil during a gamma variant epidemic and report an effectiveness after two doses of 42% against symptomatic covid-19 of any severity.[1] Chung and colleagues (doi:10.1136/bmj.n1943) evaluated two mRNA vaccines (BNT162b2 and mRNA-1273) in adults in Canada, reporting point estimates of greater than 80% effectiveness after two doses against symptomatic covid-19 caused by several variants—including alpha, beta, and gamma—but lower effectiveness (43-61%) after a single dose.[2] Additional studies of delta and other variants will be needed as SARS-CoV-2 continues to evolve.[8]

Vaccine performance is highly context dependent, influenced by population risk of infection and disease, so assessment is required among multiple different subgroups. Importantly, the Brazilian study added to age restricted clinical trials by including only adults aged 70 or older, reporting 80% effectiveness against hospital admissions after two doses in 70-74 year olds but declining effectiveness with increasing age. Both new studies provide evidence that delaying the second dose beyond manufacturers' recommended schedules might be beneficial for some subgroups. For example, populations at low risk of complicated covid-19 benefit because protection against severe disease increases with time after the first dose.

The need to evaluate different covid-19 vaccines against multiple endpoints and variants in a range of subgroups means that effectiveness studies will be a staple of public health and academic workload for the foreseeable future. We need to ensure that methodological approaches such as test negative case-control designs can be delivered through common protocols using routine, quality controlled, health and surveillance data systems. Harmonisation will minimise the proliferation of expensive bespoke studies with individualised designs requiring different approaches to data collection and ethical approval, thereby protecting scarce resources for other public health priorities.

Additionally, as countries reach high levels of vaccine coverage and case rates fall, case-control designs will become more challenging.[9] Alternative approaches such as cohort studies offer opportunities to explore indirect effects of vaccination, including herd protection, and the effects of covid-19 vaccines on non-specific outcomes, such as absenteeism from work or school and symptoms such as gastrointestinal illness. These designs have limitations, however, including the potential for confounding as a result of important differences between unvaccinated and vaccinated groups—differences in health status, access to healthcare, and health seeking behaviour, for example.[10][11] Ultimately, vaccine effectiveness studies are only as good as the data available, and measures to capture high quality, timely data must be prioritised, particularly in low and middle income countries where disease burdens are high and systems for routine data collection can be suboptimal.

Since covid-19 vaccines were authorised for use on accelerated regulatory pathways with comparatively little supportive clinical data, robust and timely real world safety data are critical to inform risk, minimise harm, and maintain public confidence. This was recently highlighted in the context of the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine by the paucity of accurate data on background rates of thromboembolic events to inform the response to an emerging safety signal.[12][13]

In some countries, vaccines are offered to most of the population, including both high risk individuals and those targeted primarily because of their role in transmission. This latter group includes children in Canada, the USA, Indonesia, Chile, and Malta.[14 -16] Data on the short term safety of covid-19 vaccines in young children are emerging from clinical studies.[17] Nevertheless, considering that severe covid-19 is less common in children than in adults, it is imperative that rigorous long term safety and effectiveness studies are conducted in children to quantify risk-benefit balance and inform vaccine policy and choices.

The success of any vaccine programme depends on the quality of real world evaluations. Decisions on which vaccines to purchase and which groups to target must be based on the highest quality analyses of vaccines in action, fully contextualised according

to place and population and accounting for all relevant biases. We must also facilitate timely access to expertise and data in countries with greatest disease burden, to ensure optimal performance of covid-19 vaccines and equity globally.

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