Health impact and cost-effectiveness of COVID-19 vaccination in Sindh Province, Pakistan

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Research in context

Evidence before this study

Searching PubMed, medRxiv, and econLit using the search term ("coronavirus" OR "covid" OR "ncov") AND ("vaccination" OR "immunisation") AND ("model" OR "cost" OR "economic") for full text articles published in any language between 1 January 2020 and 20 January 2021, returned 29 (PubMed), 1,167 (medRxiv) and 0 (econLit) studies, of which 20 were
relevant to our study. Four of these studies exclusively focused on low- or middle-income countries (India, China, Mexico), while 3 multi-country analyses also included low- or middle-income settings. The majority of studies overall conclude that targeting COVID-19 vaccination to older age groups is the preferred strategy to minimise mortality, particularly when vaccine supplies are constrained, while other age- or occupational risk groups should be priorities when vaccine availability increases or when other policy objectives are pursued. Only three studies considered economic outcomes, all of them comparing the costs of vaccination to the costs of other non-pharmaceutical interventions and concluding that both are necessary to reduce infections and maximise economic benefit.

Added value of this study

Our study provides the first combined epidemiological and economic analysis of COVID-19 vaccination based on real-world disease and programmatic information in a low- or middle-income country. Our findings suggest that vaccination in this setting is highly cost-effective, and even cost saving, as long as the vaccine is reasonably priced and efficacy is high. Unlike studies in high-income settings, we also found that vaccination programmes targeting all adults may have similar impact to those initially targeted at older populations, likely reflecting the higher previous infection rates and different demography in these settings.

Implications of all the available evidence

LMICs and international bodies providing guidance for LMICs need to consider evidence specific to these settings when making recommendations about COVID-19 vaccination. Further data and model-based analyses in such settings are urgently needed in order to ensure that vaccination decisions are appropriate to their contexts.
Abstract

Background

Multiple COVID-19 vaccines appear to be safe and efficacious, but only high-income countries have the resources to procure sufficient vaccine doses for most of their eligible populations. The World Health Organization has published guidelines for vaccine prioritisation, but most vaccine impact projections have focused on high-income countries, and few incorporate economic considerations. To address this evidence gap, we projected the health and economic impact of different vaccination scenarios in Sindh province, Pakistan (population: 48 million).

Methods

We fitted a compartmental transmission model to COVID-19 cases and deaths in Sindh from 30 April to 15 September 2020 using varying assumptions about the timing of the first case and the duration of infection-induced immunity. We then projected cases and deaths over 10 years under different vaccine scenarios. Finally, we combined these projections with a detailed economic model to estimate incremental costs (from healthcare and partial societal perspectives), disability adjusted life years (DALYs), and cost-effectiveness for each scenario.

Findings

A one-year vaccination campaign using an infection-blocking vaccine at $3/dose with 70% efficacy and 2.5 year duration of protection is projected to avert around 0.93 (95% Credible Interval: 0.91, 1.0) million cases, 7.3 (95% Crl: 7.2, 7.4) thousand deaths and 85.1 (95% Crl: 84.6, 86.8) thousand DALYs, and be net cost saving from the health system perspective. However, paying a high price for vaccination ($10/dose) may not be cost-effective. Vaccinating the older (65+) population first would prevent slightly more deaths and a similar number of cases as vaccinating everyone aged 15+ at the same time, at similar cost-effectiveness.

Interpretation

COVID-19 vaccination can have a considerable health impact, and is likely to be cost-effective if more optimistic vaccine scenarios apply. Preventing severe disease is an important contributor to this impact, but the advantage of focusing initially on older, high-risk populations may be smaller in generally younger populations where many people have already been infected, typical of many low- and -middle income countries, as long as vaccination gives good protection against infection as well as disease.

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has resulted in over 50 million cases and nearly 2 million deaths in 2020, with cases in nearly every country (1). To reduce transmission of the causal SARS-CoV-2 virus, many countries have imposed physical distancing measures such as closure of schools and workplaces, and restrictions on public gatherings (2). Such measures often incur socioeconomic costs that are not indefinitely sustainable, particularly in resource poor settings (3), and, when these measures are lifted, transmission has readily resumed in most places (4).

Vaccination may provide a durable option to protect individuals. If a vaccine also reduces transmission (e.g., by preventing infection or limiting infectiousness of disease), even unvaccinated individuals would have reduced infection risk. As of January 2021, 3 vaccines have completed phase III trials and at least 20 other vaccine candidates were in phase III trials, with over 250 in earlier trials or pre-clinical studies (5,6).

Many high-income and large middle-income countries have signed bilateral agreements with manufacturers, pre-ordering enough vaccines to cover their populations, some multiple times (7). However, many small and/or lower income countries individually lack the resources for such arrangements. The World Health Organization (WHO); Gavi, the Vaccine Alliance; and the Coalition for Epidemic Preparedness Innovations (CEPI) launched the COVAX Facility to enable these countries to pool their purchasing power. To date, 141 countries and territories have started the COVAX participation process, which will distribute vaccines to participating countries according to population size (8,9). This distribution will cover a small proportion (3%) of those populations in the months following vaccine approval, aiming to expand to 20% by the end of 2021 (10). Additionally, they face substantial other health sector resource constraints that may require external funding including scale-up of vaccine delivery infrastructure and workforce, and continued care and treatment of those with COVID-19.

The WHO’s Strategic Group of Experts on Immunization (SAGE) has issued a roadmap to help countries prioritise distribution of these limited doses. This roadmap draws from work across multiple disciplines, including modelling to project the health outcomes, health sector financing and broader economic consequences of different vaccine prioritisation strategies, but much of the available research has focused on high-income settings (11–14).

To address this gap, we assessed the health impact, economic impact and cost-effectiveness of COVID-19 vaccination in Sindh province, Pakistan, using a combined epidemiological and economic model. We chose a specific setting to ensure our model could incorporate local mobility and cost data. Sindh province initially confirmed a large number of cases, followed by declining incidence after a nationwide lockdown. Our analysis addresses vaccine prioritisation questions faced by both global (WHO) and national (Pakistan Ministry of Health) decision-makers, and illustrates the decision support analysis that should be applied more broadly in low- and middle-income countries.
Methods

Epidemiological model

To capture the natural history and transmission of SARS-CoV-2, we used a previously published compartmental model (15–17) tailored to the population of Sindh using population data from WorldPop (18) and assumed baseline population contact rates from previously estimated national patterns for Pakistan (19).

Briefly, the model compartments are an extended SEIRS+V (Susceptible, Exposed, Infectious with multiple sub-compartments, Recovered and Vaccinated, both returning to Susceptible) system with births, deaths, and age structure. For all compartments other than Recovered and Vaccinated, we use event-time distributions derived from global observations (Table 1). For Recovered and Vaccinated, we consider multiple characteristic protection durations, given the uncertainty in these durations. For the Recovered compartment, we assume perfect protection; we address the Vaccinated compartment protection along with the vaccination programme details in the “Vaccine Programme” section.

We assumed that contact patterns changed over the course of the epidemic, and estimated these changes using Google Community Mobility indicators (20) for Sindh and school closures as reflected in the Oxford Coronavirus Government Response Tracker (2). For projections, we assume that contact patterns return to the baseline contract matrix at the end of May 2021, and no further physical distancing interventions are imposed.

Model fitting and projections

Using Bayesian inference via Markov Chain Monte Carlo, we fit five elements of the model: the effective introduction date, $t_0$, as number of days after 1 January 2020; the basic reproduction number in Sindh without any interventions, $R_0$; a time-varying ascertainment rate for both COVID-19 deaths and cases; and the standard deviation characterising the distribution of reported data points around the model-predicted mean value. We fitted the model to the new daily cases and deaths in Sindh reported by the Government of Pakistan COVID-19 Dashboard (21) from 30 April to 14 September 2020 (Figure 1A-B).

As a validation, we compared model outputs to three reports of SARS-CoV-2 seroprevalence (Figure 1C), all from Karachi (22–24). Two concerned broad population samples over an extended period (23,24): these generally overlap with model estimates, but are aggregated over time making precise comparison difficult. The third conducted repeat surveys in two specific regions (22), finding clear qualitative trends which match model trends - limited exposure pre-May, rapid rise through July and subsequent plateau - but recorded lower levels. Additional figures in that study, however, indicate that the specific study sites recorded lower positivity trends generally than their broader districts, and particularly during the case surge in June, suggesting the measured values may be lower than those in the broader population. As another out-of-sample validation, we also compared forward projections to Sindh data for 15 September 2020 to 15 January 2021.
Since the waning rate of infection-acquired immunity is unknown and the benefits of vaccination highly sensitive to this parameter, we repeated the fitting exercise with four assumptions for waning of infection-acquired immunity: life-long, and exponentially waning immunity with expected durations of 1, 2.5, and 5 years.

Vaccine programme

We assumed vaccination distribution consistent with the availability of doses indicated by WHO SAGE’s Working Group on COVID-19 Vaccines (25). We assumed that vaccination required two doses per course, since this is true of most vaccines in the COVAX portfolio.

The number of full courses available each month was assumed to be divided among all COVAX participating countries proportional to population, and likewise for subnational regions. In addition we assumed 10% of courses would be wasted for reasons such as cold chain failures and incorrect use. Hence we assumed that Sindh would complete 4000 courses/day in the first three months (with a 30 day delay accounting for timing of second dose) after a vaccine is approved. We assumed availability would increase in subsequent quarters using the schedule suggested by WHO SAGE (25) and modified to update to the current vaccine landscape (See SI Section 5).

For all vaccine scenarios, we assumed the vaccine provides protection against infection (not just disease) and that protection is tested with each exposure in the model (i.e. “leaky” protection). Vaccine doses are distributed amongst individuals in the Susceptible and Recovered compartments; Susceptible individuals become Vaccinated, while Recovered are unchanged.

We considered different durations of protection: once vaccinated in the model, individuals lose vaccine protection with an exponentially distributed duration. Finally, we considered different efficacy levels of protection. A wide variety of COVID-19 vaccines are available to Pakistan via COVAX, which have reported different efficacy levels (26). Instead of modelling a particular vaccine, for our base case scenario, we assume a vaccine with 70% efficacy that protects for 2.5 years on average. As alternatives, we considered a higher efficacy (90%) or longer duration of protection (5 years). See SI for more combinations.

We track vaccine impact for 10 years, and assume that vaccination continues at the same volume for 1 (base case), 5 or 10 years. For simplicity, vaccination occurs at the same rate on every day in the model, rather than excluding weekends and holidays. We assume that vaccination cost does not fundamentally change as the programme continues and coverage increases; this implicitly assumes a linear average in the costs of vaccination across groups and time.

Given the emphasis on prioritising older adults in WHO’s vaccine prioritisation roadmap (27), we considered two scenarios for distribution: either individuals 15+ years old for the duration or individuals 65+ years old for the first quarter before shifting to 15+. For all scenarios, we assume vaccine doses are uniformly (i.e., proportional to fraction of population) distributed in the targeted populations.
Health and economic outcomes

We modelled the impact of COVID-19 vaccination on cases, deaths and Disability Adjusted Life Years (DALYs) compared to counterfactual scenarios with no vaccination over a 10 year time-horizon. For different vaccination scenarios the averted DALYs were combined with the costs of the vaccination programme and any reduction in COVID-19 case management costs from vaccination to calculate incremental cost-effectiveness ratios (ICERs). Our analysis followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS; for checklist see SI section 10) and base case model parameters are listed in Table 1.

DALYs

For each scenario we modelled the health burden in Disability Adjusted Life Years (DALYs) for symptomatic cases, non-fatal hospitalisations, non-fatal admissions to critical care, and premature death due to COVID-19. For the non-fatal outcomes, and in the absence of specific DALY data, we used Quality Adjusted Life Years (QALYs) reported by Sandmann et al. (28) based on pandemic influenza studies treated one QALY as equivalent to one DALY averted.

For COVID-19 deaths we estimated age-specific DALYs using the premature-death method by Briggs (29,30) which builds on standard life-table methods to estimate the discounted years of life lost adjusting for age-related quality-of-life (QoL) in the general population, and also allows for inclusion of different baseline morbidity and mortality assumptions. We used national life-tables for Pakistan (United Nations estimates for 2015-2020 (31) and based QoL population norms on EQ-5D data from Zimbabwe (32)) since all other countries with available data were high-income. We calculated the average DALYs per deaths for each age-band in our epidemiological model using 0% and 3% discounting (SI Table S7).

In our base case analysis we assumed COVID-19 deaths occurred among individuals with the same baseline QoL and life expectancy as the general population. However, since risk of severe COVID-19 is higher for people with comorbidities (33) we also explored an alternative scenario that assumed 50% of deaths were amongst individuals with higher baseline mortality (Standardised Mortality Ratio = 1.5) and 10% reduction in baseline QoL compared to population norms.

Costs

We estimated annual economic costs of vaccine introduction and of diagnosis and treatment in 2020 values, using an exchange rate of 155 PKR for one USD on 1 January 2020 (34) and adjusting earlier data by the Gross Domestic Product (GDP) deflator for Pakistan (35). Following WHO guidelines, we used a 3% discount rate for future costs and for annualising capital investments, while health outcomes are discounted at either 0% (base case) or 3% (36). The costing was carried out from a health system (vaccination, testing and care and treatment costs) and partial societal perspective (including household costs incurred by COVID-19 illness and case management or costs of illness, but excluding benefits of reduced NPIs), using a bottom-up ingredients-based approach.
Costs of COVID-19 vaccine introduction

Vaccine and immunisation costs, including supplies costs per dose with freight charges and wastage are in Table 1. Full costing details are given in SI section 6.

The price of the COVID-19 vaccine itself was set at USD 3 per dose, at which the Serum Institute of India has capped prices for low- and middle-income countries (37). The cost per dose of expanding national and provincial level cold chain equipment was obtained from a model of the costs of delivering COVID-19 vaccines in the 92 COVAX countries developed by UNICEF (38). The additional cold chain costs at the facility level were calculated by allocating a proportion of existing equipment and electricity costs to the COVID-19 vaccine relative to the volume of other vaccines in the immunisation programme.

We estimated vaccine delivery costs via a state-wide campaign by adding together the costs of human resources, social mobilization, and transport. We assumed nurses and vaccinators would deliver the vaccines. We carried out a microcosting of human resource costs using data from the Disease Control Priorities project (39,40). Social mobilisation costs were obtained from budgets from a poliovirus campaign (41). Transportation costs of delivering vaccines to the distribution sites were obtained from the UNICEF model (38). Transportation costs associated with campaigns originating at facilities were calculated by estimating the catchment areas for facilities and assuming daily vehicle journeys corresponding to the radius of the catchment area.

Our delivery costs did not include additional health system activities, such as planning and coordination, pharmacovigilance and waste management. Accordingly, we added a 31% mark-up on the delivery costs, obtained from the UNICEF model (38).

Table 1. Summary of epidemiological, vaccine and economic parameters used in the base case analysis.

| Parameter                          | Value                              | Source |
|------------------------------------|------------------------------------|--------|
| **Epidemiological parameters**     |                                    |        |
| Latent period                      | Gamma(mean = 2.5, k = 5)           | (42,43)|
| Contact rates                      | Age-dependent synthetic contact matrix for Pakistan | (19)   |
| Proportion asymptomatic            | age-specific                       | posterior from (15) |
| Duration of infectiousness         | Gamma(mean = 5, k = 4)             | (42,43)|
| Duration of natural immunity       | 2.5 years                          | Assumed|
| **Vaccine-related parameters**     |                                    |        |
| Duration of vaccine-induced immunity| 2.5 years                         | Assumed|
| Number of courses administered     | Based on COVAX availability, see SI | (25)   |
| Number of doses per course         | 2                                  | (25)   |
| Efficacy                           | 70%                                | Assumed|
Costs of COVID-19 diagnosis and treatment

The economic impact of COVID-19 on the health system includes diagnosis and clinical management. Costing methods and estimates are reported in full elsewhere (17,44). Briefly, unit costs of outputs, such as bed-days or outpatient visits, were sourced from a range of primary published and unpublished sources in Pakistan. These estimates represent the economic cost of all resources required to deliver health services, including staff time, capital and equipment, drugs, supplies and overhead costs. Quantities of resources used were defined following WHO guidelines and refined based on expert advice to identify less-resource intensive activities in the area of case management that were more feasible in low- and middle-income settings. More information on unit costs calculations can be found in SI sections 6-7.

Household costs of COVID-19 diagnosis and treatment include out-of-pocket expenses for care seeking, funeral expenses and productivity losses due to lost income from isolation of cases, and were sourced from previously published work (17).

Results

Fit to data and epidemic projections without vaccination

Our transmission model is able to fit reported COVID-19 cases and deaths in Sindh for April to September 2020 for different infection-induced immunity assumptions; each gives comparable quality fits (DIC values: no waning protection, 2771; expected protection 5 years, 2772; 2.5 years, 2778; 1 year, 2766). The model also produces seropositivity comparable to three serosurveys in Karachi. At the end of the fitting period, we estimate...
48.1K deaths (95% CrI: 45.3-49.7K) and 10.5M cases (95% CrI: 9.9-10.9M), with ascertainment of 5.3% (95% CrI: 4.8-5.8%) of deaths and 1.4% (95% CrI: 1.2-2.0%) of cases. Figure 1 shows our baseline assumption of 2.5 years for infection-derived immunity. When the best fitting parameters are used to project cases and deaths beyond September 2020, however, only the shorter durations of protection appear to give a reasonable fit (SI Figure 3).

In forward projections of epidemics between 2022-2030 in the absence of vaccination, we found that the duration of immunity following infection is the major determinant of the size of epidemics, as measured by annual incidence (Figure 2). If immunity largely wanes within a year, the region will rapidly settle into recurring epidemics of comparable scale to the 2020 waves. For longer durations of protection, there will tend to be some inter-annual oscillation. Life-long immunity results in transmission only at very low residual levels, though we do not consider external re-introductions. This is consistent with epidemic theory, where low immunity duration leads to a rapidly stabilizing endemic disease burden while intermediate durations lead to a series of shrinking epidemic waves settling eventually to lower endemic transmission.
Figure 1: Outcomes for fitted model ascertained outcomes compared to data. Sample ascertained trajectories (n=250) from the posterior of model parameters (blue) compared to observed outcomes (black). For observed cases and deaths, the solid line is the seven-day average, with points corresponding to daily reports. For the limited serological data, the crosshairs show the collection period and binomial confidence interval on the seropositivity estimates. The serial study results with expected low seropositivity are faded. Expected duration of infection-derived immunity assumed to be 2.5 years; other immunity assumptions in SI Figure S3. All of the assumptions considered produce comparable fits to reported cases and deaths through September 2020.
Figure 2: Long term baseline projections without vaccination for different assumptions about the duration of natural immunity. Black line shows median simulation, and grey windows mark 50 and 95% simulation intervals.

Impact of vaccination on projected cases and deaths

In our base case scenario vaccination averts 0.93 (95% CrI: 0.91, 1.0) million cases, 7.3 (95% CrI: 7.2, 7.4) thousand deaths over 10 years (Table 2.) The distinct scenarios caused by the current uncertainty in the duration of infection-induced immunity also directly affected the impact of a 1 year vaccine campaign. We found that the annual cases averted by vaccination are higher for longer duration of vaccine-induced immunity, in scenarios targeting people aged over 15 or over 65 for vaccination (Figure 3). For 70% efficacious vaccines that generated 1, 2.5, and 5 years of protection the median cumulative cases averted was negative in 2022, and for vaccines of 1 and 2.5 years protection, also negative in 2023. Only duration of immunity of 1 and 2.5 years showed negative deaths averted in 2022 when targeting 15+, and duration of 1 year when targeting 65+.

These temporary negative years are an outcome of delaying a wave of infections, leading to offset epidemic years which ultimately has some net reduction in cases and deaths, but in the short term experiences an epidemic when with no intervention the infection-induced immunity would be preventing that epidemic. In general, a vaccine with low duration of immunity delayed and slowed the oscillation of epidemics, but does not substantially reduce
total burden because rapid waning leads to relatively low effective coverage.

**Figure 3: Cumulative cases and deaths averted by the end of each year.** For a vaccine efficacy of 70%, delivered in a 2 dose schedule over a 1 year vaccine campaign, and expected duration of infection-derived immunity assumed to be 2.5 years, the median averted disease (lines; darker ribbon 50% IQR, lighter ribbon 95% IQR) with varying vaccine protection duration (from dark to light, increasing vaccine protection duration) and initial target age group (either 15+ or 65+; after the first quarter of vaccination, 15+ is targeted in both cases); full combinations and projection intervals in SI Figures SY-SZ.

**Economic outcomes of vaccination strategies**

The cost of delivery per dose was estimated to be $0.95 for campaign delivery and $0.98 for delivery at fixed sites, excluding vaccine procurement, immunisation supplies procurement and freight charges. Based on a vaccine price of $3 per dose the total undiscounted cost of the vaccination programme was estimated to be $64.1 million, $496 million and $1.04 billion for a 1-year, 5-year and 10-year campaign respectively.

The incremental cost, taking into account cost savings from reduced COVID-19 burden, was influenced by the duration of infection-induced immunity (Figure 4). When this duration was short (1-2.5 years), then annual incremental costs are likely to be cost-saving in the long run. For longer durations of infection-induced immunity, the duration of the campaign affected the annual incremental costs, with the potential for negative costs at the cessation of 5-year campaigns from a health sector perspective. If the infection-induced immunity is life-long, then the extra protection from the vaccine is of limited benefit. The cumulative number of DALYs averted over the entire 10 year time horizon is positive for all vaccine strategies, although it is especially high for a short duration of natural immunity and long vaccine campaign (Figure 5).
Figure 4: Annual incremental costs of vaccination programme (compared to no vaccination) for different vaccination strategies and assumptions about the duration of infection-induced immunity. Results are shown for vaccination using a 2-dose vaccine regimen with 70% efficacy and 2.5 year duration. The societal perspective includes household out-of-pocket payments and lost income, but excludes wider economic impacts of the pandemic. Red lines show different vaccine prices, and the solid and dashed lines show health system costs and with societal costs respectively.
Cost-effectiveness of vaccination scenarios

Over 10 years our base case vaccination scenario averts 85.1 (95% CrI: 84.6, 86.8) thousand DALYs, and saves the health sector 0.4 (95% CrI: -0.9, 3.7) million USD after deducting the cost of the vaccination programme (Table 2). These results are relatively stable when vaccination is not age-targeted (i.e. the entire population 15 years and older are given vaccination from the outset), DALYs are discounted at 3%, or COVID-19 patients are assumed to have a higher rate of comorbidities.

A one dose regimen (assuming no loss in efficacy) with twice the rate of people vaccinated results in both greater health gains and increased costs with an ICER of USD 65.9 per DALY averted. Similarly, extending the length of the vaccination campaign to 5 or 10 years substantially increases health benefits, but also leads to a net increase in costs yielding ICERs of USD 126.1 and USD 271.9 respectively.

Increasing the vaccine price to $10 per dose would dramatically increase the net costs leading to an ICER of USD 1391 per DALY averted. On the other hand, a vaccine with higher efficacy, longer duration of vaccine protection, or using a societal perspective would make vaccination even more cost saving.
| No. | Description                                                                 | Cases Averted (millions) | Deaths Averted (thousands) | Difference in Cost (USD millions) | DALYs Averted (thousands) | Cost per DALY Averted (USD) |
|-----|------------------------------------------------------------------------------|--------------------------|----------------------------|----------------------------------|---------------------------|---------------------------|
|     | Base case                                                                    |                          |                            |                                  |                           |                           |
| 1   | Vaccine base case                                                            | 0.9 (0.9, 1.0)           | 7.3 (7.2, 7.4)             | -0.4 (-3.7, 0.9)                 | 85.1 (84.6, 86.8)         | dom (dom, 10.3)           |
|     | Vaccination strategy                                                         |                          |                            |                                  |                           |                           |
| 2   | Not age targeted (vaccinate everyone 15+ from outset)                        | 0.9 (0.9, 1.0)           | 6.4 (6.3, 6.5)             | 0.4 (-3.4, 1.6)                  | 80.9 (80.3, 83.0)         | 5.1 (dom, 19.7)           |
| 3   | 5 year campaign                                                              | 6.2 (6.1, 6.2)           | 39.1 (38.5, 39.7)          | 63.5 (62.8, 66.5)                | 504.9 (498.3, 506.9)      | 126.1 (124.4, 133.5)      |
| 4   | 10 year campaign                                                             | 11.0 (11.0, 11.2)        | 65.3 (64.5, 66.4)          | 234.2 (227.8, 236.0)             | 861.6 (857.4, 872.4)      | 271.9 (261.1, 274.2)      |
|     | Immunity characteristics                                                      |                          |                            |                                  |                           |                           |
| 5   | 1 year vaccine & natural immunity duration                                   | 1.0 (1.0, 1.0)           | 7.6 (7.5, 7.7)             | -6.5 (-6.8, -6.2)                | 87.1 (86.4, 87.8)         | dom (dom, dom)            |
| 6   | 5 year vaccine & 2.5 year natural immunity duration                          | 1.8 (1.7, 1.9)           | 13.4 (13.3, 13.6)          | -56.0 (-58.6, -54.2)            | 159.7 (159.5, 160.5)      | dom (dom, dom)            |
|     | Vaccine characteristics                                                       |                          |                            |                                  |                           |                           |
| 7   | 1 dose regimen (twice rate of people vaccinated)                             | 1.7 (1.7, 1.8)           | 13.0 (12.9, 13.3)          | 10.2 (4.9, 11.4)                 | 154.2 (153.2, 156.6)      | 65.9 (31.0, 74.3)         |
| 8   | 30% vaccine efficacy                                                         | 0.4 (0.4, 0.4)           | 3.4 (3.3, 3.4)             | 34.5 (33.3, 35.3)                | 38.9 (38.6, 39.3)         | 887.5 (847.2, 914.8)      |
| 9   | 90% vaccine efficacy                                                         | 1.2 (1.1, 1.3)           | 9.0 (9.0, 9.2)             | -16.3 (-20.6, -15.2)            | 106.1 (105.5, 108.3)      | dom (dom, dom)            |
| 10  | $10 price per dose                                                           | 0.9 (0.9, 1.0)           | 7.3 (7.2, 7.4)             | 118.4 (115.0, 119.6)             | 85.1 (84.6, 86.8)         | 1391.1 (1325.2, 1411.5)   |
|     | Economic methodology choices                                                 |                          |                            |                                  |                           |                           |
| 11  | DALYs discounted at 3%                                                        | 0.9 (0.9, 1.0)           | 7.3 (7.2, 7.4)             | -0.4 (-3.7, 0.9)                 | 59.5 (59.0, 61.0)         | dom (dom, 14.8)           |
| 12  | DALYs based on higher comorbidities                                          | 0.9 (0.9, 1.0)           | 7.3 (7.2, 7.4)             | -0.4 (-3.7, 0.9)                 | 65.6 (65.2, 67.0)         | dom (dom, 13.3)           |
| 13  | Societal perspective                                                         | 0.9 (0.9, 1.0)           | 7.3 (7.2, 7.4)             | -20.6 (-24.9, -19.0)            | 85.1 (84.6, 86.8)         | dom (dom, dom)            |

Table 2: Costs, DALYs averted, Cost-Effectiveness Ratio, Cases averted and Deaths averted for different vaccination programme scenarios compared to a counterfactual scenario without vaccination. The base case vaccination scenario assumes: a 1 year campaign using a 2-dose vaccine regimen with 70% efficacy at a price of $3 per dose; 2.5 year duration of natural and vaccine induced immunity; and costing from a health-care perspective. dom=dominant (less costly & more effective); DALY=Disability Adjusted Life Year; USD=United States Dollars

Discussion

Our modelling suggests that COVID-19 vaccination in Sindh province, Pakistan could have a
substantial health impact, particularly if the vaccine campaign can be sustained for 5-10 years. Assuming that SARS-CoV-2 does not produce life-long infection-induced immunity, a highly efficacious vaccine (with 70% efficacy for 2.5 years) may avert 900,000 cases and 7300 deaths after a year of vaccination.

Under base case assumptions, a single year of vaccination would be cost saving if the vaccine was priced at below USD 3 a dose. This assumes that vaccination can be delivered at USD 1 a dose, in line with incremental economic cost estimates from the EPIC vaccine delivery costs catalogue, which range between USD 0.48-1.38 for new vaccines (45). A vaccination campaign extended to 5 years or 10 years would no longer be cost saving, but would still have an ICER well below USD 300 per DALY averted. Pakistan does not have a fixed cost-effectiveness threshold. However, a recently conducted exercise defining Pakistan’s Essential Package of Health Services found that over half of the interventions included had an ICER higher than USD 500 per DALY averted (39,40).

However, vaccination would look less cost-effective if the vaccine could only be procured at USD 10 a dose or had efficacy as low as 30%. Also, even if a large-scale multi-year mass-vaccination programme is cost-effective, it may drain scarce financial and human resources from other essential health services. In addition, there are many non-financial constraints (e.g. trained personnel), meaning that health opportunity cost may be higher without careful delivery planning. Decisions about vaccination should also take account of other factors besides cost-effectiveness, such as the disproportionately high burden of COVID-19 and related interventions on socio-economically marginalised groups, and the urgent need to return the economy and society to normal. To effectively inform policy decisions, analyses such as this should be combined with analyses of macro-economic impact and data on broader societal impacts in a transparent decision framework (e.g. health technology assessment).

We found that vaccinating 65+ year olds would save about 14% more lives compared to vaccinating everyone 15+ years, although the two strategies had similar cost-effectiveness since the broader strategy would prevent more non-fatal cases. This differs sharply from model-based analyses set in high-income countries (11,12,28,46), which find targeting older adults initially would save far more lives and be much more cost-effective. Potential reasons for these differences include the younger age structure of Sindh compared to high-income countries, and the inferred seroprevalence which was greater than 50% by September 2020. Initial epidemic waves in Sindh (and other settings) may have raised population-level immunity to a point where transmission-reducing vaccination in high transmission subgroups (i.e. younger, working age) can indirectly protect subgroups at high risk of severe disease (i.e. older, comorbid). Targeting that population could also enable relaxation of physical distancing, enabling resumption of other activities that contribute to health and well-being. However, our findings rely on the assumption that vaccination protects equally well against infection and disease; a vaccine that protects only against disease but does not prevent infection may still be better targeted at the older age groups most at risk of severe disease.

In general, our epidemiological projections have relatively narrow uncertainty intervals. While there remains substantial uncertainty on a daily basis, this tends to be off-setting: cases may shift a little in time, but an annual aggregation results in fairly narrow estimates. These
relatively small intervals propagate through the rest of the analysis. These narrow intervals are an accurate reflection of the model assumptions, but the model is fixing many aspects of the real world that are likely to shift unpredictably over the next several years. As demonstrated by recent emergence of novel variants, the underlying epidemiology may shift, as will technological and social trends, including the relative prices of the inputs to the economic estimation. Given that core uncertainty, the intervals ought to be thought of as on our estimate of the central trend, rather than as reflecting the volatility in the system.

We used a range of scenarios for the duration of natural immunity, although the shortest duration (1 year) best fitted case and death data. This is because the apparent loss of natural immunity may be driven by other factors we did not consider such as behaviour change or emergence of escape variants. If natural immunity is indeed short-lived, this will further strengthen the conclusion that vaccination is likely to be cost saving.

Our findings provide an example of the type of analysis that low- and middle-income countries can employ to inform vaccination strategies in terms of target populations and financing requirements. While the economic and societal impact of COVID-19 is substantial, the real resource constraints within the health sector in many low- and middle-income countries mean that vaccination strategies need to balance the current emergency and the longer term needs of the health sector. The slow rate of vaccine distribution is the major impediment to larger health impact. Administering 4000 doses/day in a province of roughly 50 million people would need to be continued for a long time for vaccination to have a large impact. Such a long-term programme may not be feasible if vaccine delivery disrupts delivery of other health services, which is a possibility given that the vaccine is targeted at an age group outside the usual Expanded Program on Immunization (EPI). Hence both short-term rapid response and longer-term consideration about how COVID-19 vaccination can be incorporated in the broader package of essential health services are important in Pakistan and beyond.

Declaration of Interests

The authors have no interests to declare.

Data Sharing

Model code is available at: https://github.com/cmmid/vaxco
Data from Sindh province is publicly available data but is included in the repository.

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**Ethics**

All clinical data used were obtained from publicly available sources, so no ethical approval was required for this study.

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