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Review

Cost-effectiveness of sub-national geographically targeted vaccination programs: A systematic review

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ABSTRACT

Immunization is an essential component of national health plans. However, the growing number of new vaccine introductions, vaccination campaigns and increasing administrative costs create logistic and financial challenges, especially in resource-limited settings. Sub-national geographic targeting of vaccination programs is a potential strategy for governments to reduce the impact of infectious disease outbreaks while optimizing resource allocation and reducing costs, promoting sustainability of critically important national immunization plans. We conducted a systematic review of peer-reviewed literature to identify studies that investigated the cost-effectiveness of geographically targeted sub-national vaccination programs, either through routine immunization or supplementary immunization activities. A total of 16 studies were included in our review, covering nine diseases of interest: cholera, dengue, enterotoxigenic *Escherichia coli* (ETEC), hepatitis A, Japanese encephalitis, measles, rotavirus, *Shigella* and typhoid fever. All studies modelled cost-effectiveness of geographically targeted vaccination. Despite the variation in study design, disease focus and country context, studies generally found that in countries where a heterogenous burden of disease exists, sub-national geographic targeting of vaccination programs in areas of high disease burden was more cost-effective than a non-targeted strategy. Sensitivity analysis revealed that cost-effectiveness was most sensitive to variations in vaccine price, vaccine efficacy, mortality rate, administrative and operational costs, discount rate, and treatment costs. This systematic review identified several key characteristics related to geographic targeting of vaccination, including the vaccination strategy used, variations in modelling parameters and their impact on cost-effectiveness. Additional research and guidance is needed to support the appropriateness and feasibility of geographically targeted vaccination and to determine what country context would make this a viable complement to routine immunization programs.

Contents

Abbreviations: CASP, Critical Appraisal Skills Programme; DALY, disability adjusted life year; ETEC, enterotoxigenic *Escherichia coli*; GNI, gross national income; GDP, gross domestic product; HepA, hepatitis A; HIC, high income country; ICER, incremental cost-effectiveness ratio; LIC, low income country; LMIC, lower middle income country; MIC, middle income country; OCV, oral cholera vaccine; QALY, quality adjusted life year; RI, routine immunization; SIA, supplementary immunization activities; UMIC, upper middle income country; WHO, World Health Organization.

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1. Introduction

Immunization is regarded as one of the most cost-effective public health interventions [1,2]. Several studies on the economic costs of immunization [3,4] suggest financing requirements increase as new vaccines are introduced into routine immunization systems [5–7] by national governments. This creates challenges for the sustainability of immunization programs in resource-limited settings, compounded by the fact that vaccine delivery costs are often underestimated [8].

Geographic targeting of vaccination may be done globally with a focus on certain countries, or sub-nationally in specific districts or regions within a country. For example, at the global level, targeted strategies may involve eradication of measles in high burden countries[9], or the introduction of new vaccines in low-income countries[10]. In contrast, this paper is focused on sub-national targeting of vaccination programs within a country, as a potential complement to routine immunization with the aims of optimizing resource allocation, reducing costs, and promoting the effectiveness of national immunization plans.

The papers included in this systematic review have modelled sub-national geographic targeting of vaccination across a range of different diseases, different country contexts, and implemented using existing routine immunization (RI) systems and/or supplementary immunization activities (SIAs). RI in this paper is defined to include fixed sites, outreach, mobile units, or school-based services. As a complement to RI, SIAs, or mass-immunization campaigns, are conducted to deliver vaccines to children who have been missed by RI. For example, WHO recommends that SIAs for measles-containing vaccines be conducted when the number of susceptible individuals approaches the size of one birth cohort, usually every 2 – 5 years, depending on the strength of a country's RI system.[11].

However, outside an outbreak response situation, there is a lack of clear guidance to support decision making on when to conduct sub-national geographic targeting. Given the high costs of national level SIAs, WHO guidelines state that sub-national SIAs that target geographical high-risk areas or accumulating susceptible populations may be considered in settings with limited program capacity, settings with substantial heterogeneity in the immunity profiles, or in response to small, localized outbreaks.[11] Moreover, unlike SIAs, RI is often focused nationally, with no guidance on potential for sub-national geographic targeting. Epidemiologically, there is also a lack of guidance on which diseases or vaccine programs would be best suited to geographic targeting. Economic evaluation of these different variables within different country contexts can help provide data for evidence-based decision making on the most efficient application of geographic targeting of vaccination programs.

Existing studies on vaccine cost-effectiveness are often focused on vaccine introduction, investigating the effects of variation in target population, such as by age or risk rating[12,13], or variation in vaccination delivery strategy, such as through RI or SIA[14,15]. However, studies have rarely explored the effects of geographic targeting. Similarly, several studies have looked at geographic targeting through modelling techniques but have not measured the cost-effectiveness or economic implications of these targeted strategies[16,17]. While other systematic reviews have explored cost-effectiveness of different vaccination strategies, these have been disease-specific and have not assessed geographic targeting as a specific vaccination strategy.[18–20].

This systematic review adds value to existing research as it explores evidence on the cost-effectiveness of geographically targeted sub-national vaccination programs, either through routine immunization or supplementary immunization activities. The outcome of this review is intended to inform researchers and policy makers of the current evidence that exists in peer-reviewed literature regarding geographic targeting of vaccination programs as well as their associated costs and health benefits.

2. Methods

2.1. Search protocol

We conducted a systematic review of literature published in MEDLINE (PubMed), and EMBASE as of 1 December 2021. A search protocol was developed and registered on PROSPERO database on 1 January 2022. In order to account for changes to immunization strategies following recent vaccine introductions, publications were limited to those in the last 20 years (from 2001). Publications were also limited to those available in the English-language. Search terms included those relevant to immunization and geographic targeting, such as "vaccine*", "immuni*", "supplementa*", "routine", "campaign*", "geographic" and "sub-national". Search terms related to cost-effectiveness were based on the CADTH search filters for economic evaluations[21], including "cost*", "economic*", "model", "budget*", "fee*", "financ*", "price*", "pricing", "resource allocat*", "cost-effective*", "cost-utilit*", "cost-benefit*", "cost-minimi*", "value", "monetary" and "money". For full details on the search protocol see PROSPERO registration: (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=286731).

2.2. Exclusion criteria

In the first round of the review, three authors (MG, EM, KY) independently reviewed titles and abstracts to identify studies where the immunization strategy demonstrated geographic targeting and also reported cost-effectiveness. To maintain applicability of interventions to the routine immunization schedule, we excluded studies on vaccines administered outside of childhood (0–18 years), studies that focused only on outbreak response, and studies on animal vaccination. Studies on vaccine introduction or

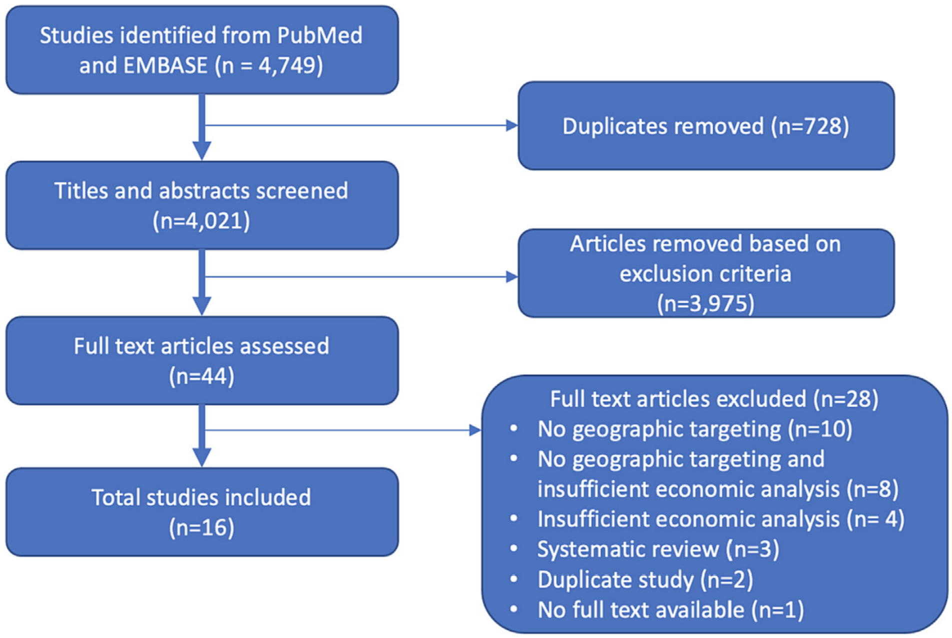

Fig. 1. Literature review process.

vaccine efficacy that did not demonstrate geographic targeting or cost measurements were excluded. For the full list of exclusion criteria, see PROSPERO registration. The authors discussed any discrepancies in their selection and reached consensus on studies to include in the second round for full text review. In the second round, all authors independently screened the shortlisted studies using the Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist[22], discussed discrepancies and reached consensus on the final set of studies. All authors performed independent data extraction on the selected studies while one author (EM) compiled extracted data. For both rounds of review, the first author reviewed all studies while the second and third authors each reviewed half the studies. References from short-listed studies were reviewed for any relevant papers not captured in the database search, but this did not result in the inclusion of any additional studies.

2.3. Data extraction and analysis

For each included study, data was extracted on country, vaccine, geographic targeting, study design, study population, time horizon, discount rate, health measure, currency, price year, cost-effectiveness threshold, cost perspective and sensitivity analysis. Countries were coded as either Low-Income Country (LIC), Lower-Middle Income Country (LMIC), Middle-Income Country (MIC), Upper-Middle-Income Country (UMIC) or High-Income Country (HIC) according to the 2022 World Bank country classifications by income.[23] The vaccine intervention was coded as either delivered through routine immunization (RI), supplementary immunization activity (SIA) or both. Cost-effectiveness calculations were conducted from different perspectives and were categorized into five main groups by the reviewers according to the reported costs included in each study; healthcare payer (government or third party healthcare payer), health care sector (all costs regardless of payer, including out of pocket costs), societal (including external costs such as productivity losses from illness), donor perspective and vaccination programme.[24] Due to the heterogeneity in study designs, target populations, interventions and health outcomes, a meta-analysis was not conducted.

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3. Results

Fig. 1 summarizes the literature review and final study selection process. A total of 4,021 articles were identified for title and abstract review, with 44 selected for full text review after application of exclusion criteria. Of these, 16 studies satisfied the requirement for geographic targeting and fulfilled the CASP Economic Evaluation Checklist screening for final selection.

For the full text review, reviewers applied the exclusion criteria to the 44 shortlisted papers, coding excluded papers as having insufficient geographic targeting, insufficient economic analysis, or both. Ten papers (n = 10) were excluded due to lack of sufficient geographic targeting. Of these, four studies involved vaccination strategies which focused on targeting high-risk populations and selected age groups, while six studies compared different vaccine delivery strategies and combinations of strategies including RI, SIA, and follow-up campaigns, but without geographic targeting. Studies that were geographically targeted but did not conduct a cost-effective analysis or include information on cost of interventions were excluded for having insufficient economic analysis (n = 4), along with studies that were found to have neither geographic targeting nor sufficient economic analysis (n = 8). The remaining studies were excluded as they were either a systematic review (n = 3), were a duplicate study already included as another journal publication (n = 2) or had no full text available (n = 1). Following the review of 44 full text articles, 16 were eventually selected for final inclusion in this review.

3.1. Country and disease focus

Table 1 summarizes the key characteristics across the final list of 16 studies, listed alphabetically by author and publication year. The 16 studies selected represent geographic targeting of vaccines for a range of diseases, including: rotavirus (n = 4), measles (n = 3), hepatitis A (n = 2), dengue (n = 2), Japanese encephalitis (n = 2),

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Table 1
Summary of key characteristics from selected studies.

Author, Year	Setting	World Bank classification, 2022	Disease studied	Intervention category	Model type	Study population age	Time horizon	Discount rate	Model includes herd immunity	Health measure
Anderson, JD; 2019[37]	Africa, multi country	LIC, LMIC	ETEC and Shigella	RI only	dynamic, cohort	0 – 4 years	10 years	3 %	No	DALY
Anderson, JD; 2020[38]	Nigeria	LMIC	Rotavirus	RI only	dynamic, cohort	0 – 5 years	5 years	3 %	No	DALY
Dhankhar, P; 2015[27]	USA	HIC	Hepatitis A	RI only	dynamic, individual	12 – 18 months	100 years	3 %	Yes	QALY
Flasche, S; 2016 [26]	Latin America and Southeast Asia	LIC, LMIC, UMIC	Dengue	RI only	dynamic, cohort and individual*	9 years	30 years	3 %	Yes	DALY
Jacobs, RJ; 2003[45]	USA	HIC	Hepatitis A	RI only	static, cohort	2000 US birth cohort	84 years	3 %	No	QALY
Lee, EC; 2019[29]	Sub-Saharan Africa	LIC, LMIC, UMIC	Cholera	SIA only	dynamic, cohort	Not specified**	13 years	3 %	Yes	DALY
Lo, NC; 2018[33]	LMIC	LMIC	Typhoid	RI and RI + SIA	dynamic, cohort	<1 year (RI), 5 – 14 (SIA)	10 years	3 %	No	DALY
Rheingans, R; 2014[39]	India	LMIC	Rotavirus	RI only	dynamic, cohort	0 – 5 years	5 years	3 %	No	DALY
Rheingans, R; 2018[40]	Pakistan	LMIC	Rotavirus	RI only	dynamic, cohort	0 – 5 years	5 years	3 %	Yes	DALY
Rheingans, R; 2018[41]	Lao	LMIC	Rotavirus	RI only	dynamic, cohort	0 – 5 years	5 years	3 %	Yes	DALY
Shafie, AA; 2017[31]	Malaysia	UMIC	Dengue	RI + SIA	dynamic, cohort	9 – 30 years†	10 years	3 %	Yes	DALY
Suraratdecha, C; 2006[32]	India	LMIC††	Japanese Encephalitis	RI and RI + SIA	static, cohort	9 months (RI), 2 – 12 years (SIA)	15 years	3 %	No	DALY
Uzicanin, A; 2004[46]	South Africa	UMIC††	Measles	SIA only	static, cohort	9 mo. – 14 years	20 years	2 %	No	Measles cases averted
Verguet, S; 2013[35]	South Africa	UMIC	Measles	SIA only	static, cohort	6 mo. – 15 years	3 years	3 %	No	DALY
Vodicka, E; 2020[28]	Philippines	LMIC	Japanese Encephalitis	RI and RI + SIA	dynamic, cohort	9 months (RI), 1 – 5 years (SIA)	20 birth cohorts over lifetime	3 %	No	DALY
Zimmermann, M; 2019[34]	Nigeria	LMIC	Measles	SIA only	dynamic, individual	0 – 10 years	10 years	3 %	No	DALY

* Eight different models were used in this study. All were dynamic transmission models. Four models were deterministic compartmental models (categorised as "cohort") and the other four were stochastic simulation models (categorized as "individual").
** This study used a phenomenological model targeting vaccines geographically to high risk areas and not to specific age groups within those areas.
† Ages varied according to different program scenarios: 9 – 17 (school-based), 18 – 30 (community-based). Ages also varied by strategy: RI (ages 9 or 13) and SIA (ages 14 – 30, 10 – 30, or 10 – 17).
†† A change in World Bank classification is noted from year of original study publication to 2022: India was classified as a LIC in 2006 and South Africa was classified as a LMIC in 2004.

cholera (n = 1), ETEC/Shigella (n = 1), and typhoid (n = 1). Eight of the studies were conducted in LMICs, three in UMICs, and three were multi-country studies conducted across LIC, LMIC and UMICs. The two HIC studies were conducted in the USA and both focused on geographical targeting of hepatitis A vaccination as compared to a nationwide vaccination policy. All studies (N = 16) mentioned heterogeneity of disease burden across the sub-national geographical units used in the study (e.g., district, province or region).

3.2. Vaccination delivery strategy

Half of the studies (n = 8) explored geographical targeting of vaccination through routine immunization, while four studies explored a combination of routine and SIA strategies. Four studies looked exclusively at campaign strategies for geographic targeting, all of which were focused on measles or cholera.

3.3. Study design

All studies conducted modelling in order to estimate the health and economic effects of geographic targeting. There were variations in the types of models used, which were grouped by two criteria as either "dynamic" or "static" and as "cohort" or "individual," based on previously established model taxonomy.[25] Dynamic models allow for interactions and feedback loops between individuals and their environment over time while static models do not. Cohort models follow population groups over time while individual-level models simulate each individual independently. Most studies conducted dynamic modelling (n = 12), taking into account changes in system properties over time, such as transitions through health states, healthcare utilization, burden of disease and mortality rates. Most studies conducted modelling at the cohort level (n = 14), as opposed to performing individual, or agent-based, modelling. The study conducted by *Flasche et al. 2016* included eight dynamic models, half of which were deterministic compartmental models (defined as "cohort" in Table 1) while the other half were stochastic simulation models (defined as "individual" in Table 1).[26].

There were wide variations in the modelling timeframe used to estimate health benefits and cost-effectiveness, which ranged from 3 to 100 years. Five studies (n = 5) looked at a timeframe of 5 years or less, seven studies (n = 7) looked at a timeframe of 10 – 20 years, and the remaining studies (n = 4) looked at a longer timeframe between 30 and 100 years. A 3 % discounting rate was used in all studies except for one which used 2 %. Some studies (n = 6) incorporated herd immunity into the model. Nearly all studies (n = 15) used a standardized measure for health outcomes; 13 studies used the DALY and two studies used the QALY. One study used disease burden (i.e., number of measles cases averted) to estimate cost-effectiveness.

3.4. Cost-effectiveness

Table 2 summarizes the model parameters and conclusions related to cost-effectiveness across the final set of 16 studies. Studies estimated cost-effectiveness from different perspectives. Accounting for the fact that some studies focused on multiple perspectives, the most common perspective taken was the healthcare payer (n = 8), followed by the societal perspective (n = 6), healthcare sector (n = 5), vaccination program perspective (n = 3) and donor perspective (n = 2).

Many of the studies (n = 10) compared cost findings to an established cost-effectiveness threshold of 1x or 3x the gross domestic product (GDP) or gross national income (GNI) per capita. Two studies set their own thresholds of USD$2,000 per DALY and USD $50,000 per QALY. The remaining studies (n = 4) did not specify a predetermined threshold although they did report incremental cost-effectiveness ratios (ICERs) for different vaccination strategies.

All studies conducted a sensitivity analysis to test the effect of varying parameters of their models on cost-effectiveness. Given the differences in study design and target diseases, these variables differed across studies, but the most commonly cited variables with the greatest influence on cost-effectiveness (listed here in order of frequency) included vaccine price, vaccine efficacy, mortality rate, administrative and operational costs such as vaccine delivery or personnel time required, discount rate, and treatment costs such as hospitalization costs and outpatient costs.

All studies reviewed found geographic targeting of vaccination programs, either through RI or SIA, to be cost-effective according to the willingness to pay thresholds indicated in the study. Most of the studies (n = 14) found geographic targeting of vaccination in areas of higher disease incidence or higher mortality to be more cost-effective than a non-targeted strategy. However, two studies (*Dhankhar et. al., 2015* and *Vodicka et. al., 2020*) found nationwide vaccination to be more cost-effective than regionally targeted vaccination. *Dhankhar et. al.* took a societal perspective over a time period of 100 years, was conducted in a high income country and also incorporated herd immunity into their model. [27] *Vodicka et. al.* also used a relatively long timeframe (20 birth cohorts over their lifetime) compared to other studies and estimated costs from both the healthcare payer and societal perspectives.[28].

4. Discussion

This study systematically reviewed available evidence on the cost-effectiveness of sub-national geographic targeting of vaccination programs. We included 16 modelling studies in our analysis, comparing country context, disease focus, model type, sensitivity analysis and cost-effectiveness. Despite the variation in study design across these different characteristics, studies generally found that in countries with heterogenous burden of disease, sub-national geographic targeting of vaccination programs in areas of high disease incidence or high mortality was more cost-effective than a non-targeted strategy. Several information gaps have also been highlighted regarding the application and feasibility of geographically targeted vaccination, such as which vaccine delivery strategy to use and the comparative cost-effectiveness of other types of targeted vaccination strategies.

4.1. Cost-effectiveness of geographically targeted vaccination

Of the 14 studies that found geographic targeting to be more cost-effective than a non-targeted strategy, studies compared vaccination cost-effectiveness in high burden sub-national areas to either a nationwide strategy (n = 9) or to vaccination in other sub-national areas (n = 4). The exception was a study by *Lee et. al.* which modelled allocation of limited vaccines using an untargeted strategy, compared to different types of campaign targeting strategies. The study concluded that geographic targeting of vaccination to districts according to cholera incidence rate was the most cost-effective strategy, outperforming other strategies such as targeting of districts based on access to water and sanitation.[29].

An important caveat to geographic targeting is that while it can be cost-effective, national level vaccination may be equally cost-effective or cost saving, which would support a nationwide vaccination strategy.[27,28] While most studies in this review used dynamic, cohort based models, the use of different modelling

Table 2
Cost-effectiveness of geographically targeted vaccination.

Author, Year	Conclusion	Perspective	Price year ($USD)	Cost-effectiveness threshold	Most sensitive parameters
Anderson, JD; 2019[37]	Vaccination for ETEC/Shigella is more cost-effective in higher burden sub-national areas.	Healthcare sector	2016	1x GDP and 3x GDP	price per dose, efficacy and etiological fractions (mortality attributed to ETEC/Shigella), administration cost, mortality change over time
Anderson, JD; 2020[38]	ICERs are lower in areas with higher burden of rotavirus mortality.	Healthcare sector and donor	2019	Not mentioned	vaccine efficacy, administrative costs, rotavirus mortality rates, vaccine price
Dhankhar, P; 2015[27]	Nationwide HepA vaccination is more cost saving than a regional vaccination policy.	Societal	2013	Not mentioned	discount rate, vaccine uptake rate, outpatient days lost to work, outpatient cost, median weekly earnings, hospitalization cost, public health cost, cost of vaccine administration, cost of treating a fulminant case, vaccine efficacy
Flasche, S; 2016 [26]	Dengue vaccination is cost-effective in moderate to high transmission settings, and most cost-effective in highest transmission settings.	Healthcare payer and societal	2014	$2,000 per DALY	using societal perspective, no discounting of health effects, cost per DALY averted
Jacobs, RJ; 2003[45]	HepA vaccination is cost-effective, with lower cost per QALY gained, in regions with higher incidence.	Healthcare payer and societal	2002	$50,000 per QALY	vaccination costs and rates of disease transmission
Lee, EC; 2019[29]	It is more cost-effective to target districts with highest cholera incidence rate.	Vaccination program	2017	1x GDP and 3x GDP	vaccine deployment strategy, vaccine efficacy, indirect vaccine protection (herd immunity)
Lo, NC; 2018[33]	Vaccination was more cost-effective in settings with high endemicity of typhoid.	Healthcare payer and Vaccination program	2016	1x GDP and 3x GDP	Case-fatality rate, cost of vaccines and delivery, vaccine efficacy, duration of immunity, carrier contribution, range of willingness-to-pay thresholds
Rheingans, R; 2014[39]	Lowest ICER was shown in regions with high rotavirus mortality.	Healthcare sector	2013	1 × GDP	vaccine administration cost, rotavirus mortality, vaccine price
Rheingans, R; 2018[40]	Vaccination is most cost-effective in high burden areas and among the poorest quintile.	Healthcare sector and Donor	2017	1xGNI	vaccine effectiveness, mortality, administration costs, dose price
Rheingans, R; 2018[41]	Vaccination is most cost-effective in high burden areas and among the poorest quintile.	Healthcare sector	2017	2xGNI and 3xGDP	vaccine effectiveness, coverage equity, low efficacy for poor, mortality, administrative costs, dose price
Shafie, AA; 2017[31]	The most cost-effective vaccination program for dengue was through routine immunization with catch-up campaign in targeted hotspots.	Healthcare payer and Societal	2013	1x GDP and 3x GDP	ambulatory under-reporting, vaccine protection duration, hospitalized under-reporting, model time horizon and discount rate
Suraratdecha, C; 2006[32]	Vaccination was more cost-effective in high incidence districts.	Societal	2000	3x GDP	JE incidence rate, vaccine cost, vaccine efficacy, booster requirements
Uzicanin, A; 2004[46]	Vaccination campaign was cost-saving in areas with higher disease incidence and lower routine vaccination rates.	Healthcare payer	1996	Not mentioned	personnel time required, reporting efficiency, social promotion costs, operational costs, discount rate
Verguet, S; 2013[35]	Vaccination was more cost-effective in provinces with a higher measles case fatality rate.	Healthcare payer	2010	1x GDP	case fatality rate, number of measles cases averted, hospitalization costs
Vodicka, E; 2020[28]	Although regional targeting was cost-effective, national vaccination was more cost-effective (lower cost per DALY).	Healthcare payer and societal	2017	1x GDP	rate of asymptomatic JE, total cost of treatment for acute JE, vaccine efficacy, case fatality rate, vaccine delivery costs, vaccine costs per dose
Zimmermann, M; 2019[34]	It is cost-effective to conduct more frequent SIAs in regions with higher burden of measles. This strategy also reduces overall number of measles cases.	Healthcare payer and Vaccination programme	2018	Not mentioned	changing SIA frequency, % measles patients seeking care, SIA coverage rates

parameters may affect cost-effectiveness findings. As such, the range of different model parameters used across the studies, and the calibration of modelling data to country specific vaccination costs and disease burden, limits the generalizability of cost-effectiveness findings to other country contexts.

4.2. Cost-effectiveness of geographic targeting by vaccine delivery strategy

Regarding the vaccine delivery strategy, half the studies (n = 8) used RI to implement geographically targeted vaccination, likely due to the childhood focus of the study population, traditionally reached through RI during the first 5 years of life. The studies that used SIA exclusively in the targeted vaccination strategy (n = 4) were related to measles vaccination campaigns and oral cholera vaccine (OCV), both historically delivered through campaigns/SIAs.[29,30] However, as these studies do not compare RI and SIA strategies, it is difficult to determine which would be more cost-effective for geographic targeting. Of the four studies that modelled geographically targeted vaccine delivery using both routine and campaign strategies, one study used RI plus SIA in all scenarios preventing a direct comparison[31], while two studies found the combination of RI plus SIA to be more cost-effective than either strategy alone.[28,32] In contrast, *Lo et. al.* found delivery of typhoid vaccine through RI to be more cost-effective than a combined RI plus SIA strategy, although it is important to note that the combined strategy was also cost-effective and more impactful in reducing disease burden in areas of higher disease incidence, which is relevant to a geographically targeted strategy.[33].

The limited number of studies in this review that modelled both RI and SIA delivery strategies prevents any conclusions on the comparative cost-effectiveness of different vaccine delivery strategies for geographically targeted vaccination. However, the studies have clearly demonstrated that alternative delivery strategies, such as targeted SIAs or sub-national variation in SIA frequency, can be cost-effective or even cost saving, while also reducing the overall burden of disease.[29,34,35] Targeting SIAs towards hard-to-reach individuals provides greater benefit than non-targeted campaigns, especially in highly vaccinated populations where campaigns may be reaching those who have already been vaccinated.[36] Future studies on targeted vaccination or general vaccination introduction would benefit from exploring the use of different vaccination delivery strategies, or combination of strategies, to find scenarios that maximize health impact and cost-effectiveness within a given country context.

4.3. Geographic targeting for improved vaccine coverage and equity

Many studies have highlighted the overlap between geographic areas of high disease burden and low socio-economic status, raising the possibility for targeting vaccination strategies not only geographically but also to the lowest wealth quintiles.[37–41] For example, *Rheingans et al.* investigated the introduction of rotavirus vaccine in India, Pakistan and Lao through the existing routine immunization program, demonstrating the highest cost-effectiveness in regions with the highest disease burden and among the population in the lowest wealth quintile.[39–41].

Geographic targeting to areas of high disease burden can also produce significant reductions in disease incidence and mortality among vulnerable populations in underserved areas. Studies have shown that cost-effective vaccination strategies with the largest potential health impact are those that target areas of high burden and low coverage, provided that coverage can be increased through the targeted intervention.[34,37–41] A strategy for targeting geographic areas of high disease burden as well as vulnerable populations is in line with the coverage and equity goal of the Immunization Agenda 2030, which is to ensure access to immunization regardless of location, age, socio-economic status or gender-related barriers.[42].

4.4. Additional considerations for geographic targeting of vaccines

In line with WHO guidance, heterogenous burden of disease was demonstrated in all studies and appears to be a key precursor to the applicability of geographical targeting of vaccination strategies. Related to this, the capacity for geographic targeting is dependent on the strength of country surveillance data in order to accurately measure geographic heterogeneity of disease burden and maximize the impact of vaccination targeting.

Several studies referenced resource constraints related to limited vaccine availability or limited domestic funding for immunization as an incentive for considering geographic targeting, especially in the context of LICs and LMICs. For countries facing resource constraints, sub-national targeting of vaccination efforts presents a realistic option for cost-effective management of disease burden in the short- to medium-term.

4.5. Limitations of study

A key limitation of this review is the inability to conduct *meta*-analysis across the studies given the differences in modelling techniques, target populations and disease focus. The specificity of each model to the country context, such as health burden and vaccination costs, also limits the external validity of each study finding, making it difficult to determine if geographical targeting, even for that specific disease and target population, would be cost-effective in another country context. The search protocol for this study was limited to publications from the last 20 years and to publications available in the English-language, potentially limiting the inclusion of other relevant papers for this review.

The exclusive reliance on modelling techniques in this field demonstrates the potential for large-scale implementation research for building further evidence on the efficacy and cost-effectiveness of geographically targeted vaccination. For example, countries introducing a new vaccine or planning a national campaign may use a phased approach, documenting cost of vaccination according to geographic area (e.g., district level) during roll-out, as demonstrated through other large-scale effectiveness evaluations.[43,44] This costing information, coupled with sub-national coverage data, disease incidence and mortality, can be used to determine sub-national cost-effectiveness of vaccination which could then inform targeting of future SIAs.

5. Conclusion

This review suggests existing evidence points to the cost-effectiveness of geographic targeting of vaccination among high-incidence, high-risk populations in countries with a heterogenous disease burden. However, this review has also revealed the need for further research, including exploring the health impacts and cost-effectiveness of prioritized vaccine targeting based on age groups, socioeconomic status, country epidemiological contexts, and sub-national variation in timing and frequency of vaccination campaigns.

These findings are important for policy makers in shaping national immunization strategies, and are relevant for the effective allocation of donor funding. The potential for geographic targeting of vaccine strategies will influence planning for new vaccine introduction, and has implications on existing vaccines in the immunization schedule. Geographic targeting of vaccination is also especially important in resource limited settings, where a targeted approach can reduce costs, promote sustainability, increase vaccine coverage and equity, and improve health outcomes if successfully targeted to areas of high disease burden and low coverage. Finally, geographic targeting is a useful approach in cases of constrained vaccine availability for informing appropriate and efficient vaccine allocation in the short term, while working toward the long-term goal of meeting overall vaccine demand.

Authorship Statement

All authors attest they meet the ICMJE criteria for authorship.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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