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STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER

Department of Global Health | University of Washington

VACCINE DELIVERY RESEARCH DIGEST

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH, & TRAINING (START) CENTER

REPORT TO THE BILL & MELINDA GATES FOUNDATION

DECEMBER 15, 2016

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1. **Optimal vaccine schedules to maintain measles elimination with a two-dose routine policy.**

McKEE A, Shea K, Ferrari MJ.

Epidemiol Infect. 2016 Oct 20:1-9. [Epub ahead of print]

PMID:27760574

ABSTRACT

Measles was eliminated in the Americas in 2002 by a combination of routine immunizations and supplementary immunization activities. Recent outbreaks underscore the importance of reconsidering vaccine policy in order to maintain elimination. We constructed an age-structured dynamical model for the distribution of immunity in a population with routine immunization and without disease, and analyzed the steady state for an idealized age structure and for real age structures of countries in the Americas. We compared the level of immunity maintained by current policy in these countries to the level maintainable by an optimal policy. The optimal age target for the first routine dose of measles vaccine depends on the timing and coverage of both doses. Similarly, the optimal age target for the second dose of measles vaccine depends on the timing and coverage of the first dose. The age targets for the first and second doses of measles vaccine should be adjusted for the post-elimination era, by specifically accounting for current context, including realized coverage of both doses, and altered maternal immunity. Doing so can greatly improve the proportion immune within a population, and therefore the chances of maintaining measles elimination, without changing coverage.

WEB: http://dx.doi.org/10.1017/S0950268816002296

IMPACT FACTOR: 1.31

CITED HALF-LIFE: 6.6

START SCIENTIFIC COMMENT: Authors recommend that in settings where first dose coverage is poor, the timing of the second dose should be adjusted to compensate by offering second dose earlier, because otherwise a large proportion of children will be susceptible before reaching the age target for the second dose, which would result in lower herd immunity. Similarly, in settings where coverage of the second dose is poor, authors recommend adjusting the timing of the first dose to ensure maximum protection (and thus delaying until maternal antibody has sufficiently waned), since many children will not receive a second dose.

Figure 2 depicts the optimal age for the first and second doses for each individual country in the Americas, at coverages ranging from 80% to 100% for both doses (assuming equal coverage for both doses), as well as the optimal age target for a single-dose strategy to maximize population immunity in each setting.

For two-dose strategies, authors point out that regardless of the age structure of a country, "the higher the coverage, the longer the recommended time between doses." For single-dose strategies, authors note that current policy recommendations for the first dose timing are close to ideal for most settings.

Figure 3 depicts the population immunity achieved by current policy or 'optimal' strategy for first and second dose targets for countries the Americas with a range of age structures and current coverage proportions. The figure emphasizes the difference in population immunity achieved by current policy versus an 'optimal' strategy, particularly in countries with low coverage of first and/or second dose and countries with a large proportion of the population < 5 years.

2. **What vaccine product attributes do immunization program stakeholders value? Results from interviews in six low- and middle-income countries.**

Kristensen DD, Bartholomew K, Villadiego S, Lorenson K.

Vaccine. 2016 Nov 8. [Epub ahead of print]

PMID:27836438

ABSTRACT

This study attempts to capture the opinions of stakeholders working in immunization programs in low and middle-income countries to understand how vaccine products could be improved to better meet their needs and to obtain feedback on specific vaccine product attributes including the number of doses per container and ease of preparing a dose for administration. We also reviewed how procurement decisions are made within immunization programs. Semi-structured interviews were undertaken with 158 immunization stakeholders in Brazil, China, India, Peru, the Philippines, and Tanzania. Interviewees included national decision-makers and advisors involved in vaccine-purchasing decisions (n = 30), national Expanded Programme on Immunization managers (n = 6), and health and logistics personnel at national, subnational, and health-facility levels (n = 122). Immunization stakeholders at all levels of the supply chain valued vaccine product attributes that prevent heat damage, decrease vaccine wastage, and simplify delivery. Minimizing the time required to prepare a dose is especially valued by those closest to the work of actually administering vaccines. Respondents appreciated the benefits of lower-multi-dose presentations on reducing wastage but seemed to prefer single-dose vials even more. They also expressed concern about the need for training and the potential for confusion and vial contamination if opened vials of liquid preservative-free vaccines are not handled properly. Procurement decision-making processes varied widely between countries, though most relied heavily on international agencies and vaccine manufacturers for information.

WEB: http://dx.doi.org/10.1016/j.vaccine.2016.10.057

IMPACT FACTOR: 3.62

CITED HALF-LIFE: 5.50

START SCIENTIFIC COMMENT: Authors point out that user preferences regarding specific vaccine attributes varied across countries, but these differences did not appear to be related to a country's economic resources. Different stake-holder types tended to value similar vaccine product attributes. Conversely, different types of stakeholders valued the amount of time required/ease of preparation of dose delivery very differently, with front line health workers indicating this was of very high importance and national policy or procurement personnel equating less value to ease of preparation (Figure 2). Table 2 summarizes the proportion of respondents who indicated each specific improvement/specific product attribute that was important (not disaggregated by country of type of respondent).

The sources of information used for national decision-making and procurement also varied substantially by country (Figure 3).

3. Manufacturing costs of HPV vaccines for developing countries.

Clendinen C, Zhang Y, Warburton RN, Light DW.

Vaccine. 2016 Nov 21;34(48):5984-5989.

PMID:27771183

ABSTRACT

Background: Nearly all of the 500,000 new cases of cervical cancer and 270,000 deaths occur in middle or lower income countries. Yet the two most prevalent HPV vaccines are unaffordable to most. Even prices to Gavi, the Vaccine Alliance, are unaffordable to graduating countries, once they lose Gavi subsidies. Merck and Glaxosmithkline (GSK) claim their prices to Gavi equal their manufacturing costs; but these costs remain undisclosed. We undertook this investigation to estimate those costs.

Methods: Searches in published and commercial literature for information about the manufacturing of these vaccines. Interviews with experts in vaccine manufacturing.

Findings: This detailed sensitivity analysis, based on the best available evidence, finds that after a first set of batches for affluent markets, manufacturing costs of Gardasil for developing countries range between $0.48 and $0.59 a dose, a fraction of its alleged costs of $4.50. Because volume of Cervarix is low, its per unit costs are much higher, though at comparable volumes, its costs would be similar.

Interpretation: Given the recovery of fixed and annual costs from sales in affluent markets, Merck's breakeven price to Gavi could be $0.50–$0.60, not $4.50. These savings could support Gavi programs to strengthen delivery and increase coverage. Outside Gavi, prices to lower- and middle-income countries, with profit, could also be lowered and made available to millions more adolescents at risk. These estimates and their policy implications deserve further discussion.

WEB: http://dx.doi.org/10.1016/j.vaccine.2016.09.042

IMPACT FACTOR: 3.62

CITED HALF-LIFE: 5.50

START SCIENTIFIC COMMENT: Accounting for vaccine yield, cost estimates included annualized capital costs, raw materials, factory and administrative overheads, and labor costs of manufacturing, filling and packaging the vaccine. Authors estimated separate costs for producing the first and second 15.4 million doses total costs as well as cost per dose of single-fill and 10-fill preparations, assuming differences in the relative efficiencies of earlier versus later production. Sensitivity analysis were used to estimate 'high', 'medium' and 'low' cost estimates. The authors cautioned that estimates are not based on manufacturing data from companies themselves, and thus are best estimates of actual costs experienced.

4. **Cholera cases cluster in time and space in Matlab, Bangladesh: implications for targeted preventive interventions.**

Debes AK, Ali M, Azman AS, Yunus M, Sack DA.

Int J Epidemiol. 2016 Oct 27. [Epub ahead of print]

PMID:27789673

ABSTRACT

Background: Cholera remains a serious public health threat in Asia, Africa and in parts of the Americas. Three World Health Organization (WHO) pre-qualified oral cholera vaccines are now available but their supply is limited, so current supplies must be administered strategically. This requires an improved understanding of disease transmission and control strategies.

Methods: We used demographics and disease surveillance data collected from 1991 to 2000 in Matlab, Bangladesh, to estimate the spatial and temporal extent of the zone of increased risk around cholera cases. Specifically, we compare the cholera incidence among individuals living close to cholera cases with that among individuals living close to those without medically-attended cholera in this rural endemic setting.

Results: Those living within 50 m of a confirmed cholera case had 36 times (95% confidence interval: 23–56) the risk of becoming a cholera case in the first 3 days (after case presentation) compared with risk elsewhere in the community. The relative risk gradually declined in space and time, but remained significantly high up to 450me away within 3 days of case presentation, and up to 150 m away within 23 days from the date of presentation of the case.

Conclusion: These findings suggest that, if conducted rapidly, vaccinating individuals living close to a case (ring vaccination) could be an efficient and effective strategy to target vaccine to a high-risk population in an endemic setting.

WEB: http://dx.doi.org/10.1093/ije/dyw267

IMPACT FACTOR: 2.63

CITED HALF-LIFE: 8.40

START SCIENTIFIC COMMENT: The relative risk for cholera among those exposed to a cholera case ("case cohort") compared with those unexposed to a cholera case ("control cohort") are presented at a range of different distances and time points from exposure (Figure 3). Authors note that while results from this study indicate "case-based" intervention strategies (such as "ring vaccination" approaches) can identify individuals at high risk for infection, the impact of this approach in preventing early cases will be limited due to the time needed to generate an immune response following vaccination. Authors emphasize the need to vaccinate quickly and the need for additional strategies to prevent early cases.

5. Fractional dosing of yellow fever vaccine to extend supply: a modelling study.

Wu JT, Peak CM, Leung GM, Lipsitch M.

Lancet. 2016 Nov 9. [Epub ahead of print]

PMID:27837923

ABSTRACT

Background The ongoing yellow fever epidemic in Angola strains the global vaccine supply, prompting WHO to adopt dose sparing for its vaccination campaign in Kinshasa, Democratic Republic of the Congo, in July–August, 2016. Although a 5-fold fractional-dose vaccine is similar to standard-dose vaccine in safety and immunogenicity, efficacy is untested. There is an urgent need to ensure the robustness of fractional-dose vaccination by elucidation of the conditions under which dose fractionation would reduce transmission.

Methods We estimate the effective reproductive number for yellow fever in Angola using disease natural history and case report data. With simple mathematical models of yellow fever transmission, we calculate the infection attack rate (the proportion of population infected over the course of an epidemic) with various levels of transmissibility and 5-fold fractional-dose vaccine efficacy for two vaccination scenarios, ie, random vaccination in a hypothetical population that is completely susceptible, and the Kinshasa vaccination campaign in July–August, 2016, with different age cutoff for fractional-dose vaccines.

Findings We estimate the effective reproductive number early in the Angola outbreak was between 5.2 and 7.1. If vaccine action is all-or-nothing (ie, a proportion of vaccine recipients receive complete protection [VE] and the remainder receive no protection), n-fold fractionation can greatly reduce infection attack rate as long as VE exceeds 1/n. This benefit threshold becomes more stringent if vaccine action is leaky (ie, the susceptibility of each vaccine recipient is reduced by a factor that is equal to the vaccine efficacy). The age cutoff for fractional-dose vaccines chosen by WHO for the Kinshasa vaccination campaign (2 years) provides the largest reduction in infection attack rate if the efficacy of 5-fold fractional-dose vaccines exceeds 20%.

Interpretation Dose fractionation is an effective strategy for reduction of the infection attack rate that would be robust with a large margin for error in case fractional-dose VE is lower than expected.

WEB: http://dx.doi.org/10.1016/S0140-6736(16)31838-4

IMPACT FACTOR: 8.04

CITED HALF-LIFE: 9.20

START SCIENTIFIC COMMENT: Authors assumed prior vaccination of 28% before the outbreak, and note that the basic reproductive number in populations with different prior partial immunity could range from 4 - 12. Figure 2 depicts the effect on the attack rate of 5-fold fractional-dose vaccination with different vaccine efficacy and reproductive numbers, under different coverage assumptions. Under scenarios where the vaccination protection is leaky, dose fractionation is less beneficial, vaccine efficacy (VE) is “modest” and basic reproductive number is higher. To be beneficial compared with standard dosing, VE of a fractional dose would need to be 80-90%. 5-fold fractionation was used in the models because this strategy had the most available data, but authors point out that other approaches for higher than 5-fold fractionation could potentially be feasible and efficacious. Authors emphasize the benefit of high population immunity via vaccine coverage before the peak in transmission, to maximize the efficacy of a fractional dose strategy.

6. **Presentation matters: Buffers, packaging, and delivery devices for new, oral enteric vaccines for infants.**

Lal M, Jarrahian C.

Hum Vaccin Immunother. 2016 Nov 7:0. [Epub ahead of print]

PMID:27819524

ABSTRACT

Oral administration of vaccines is simpler and more acceptable than injection via needle and syringe, particularly for infants (Figure 1.) This route is promising for new vaccines in development against enterotoxigenic *Escherichia coli* (ETEC) and *Shigella* that cause childhood diarrhea with devastating consequences in low-resource countries. However, vaccine antigens and adjuvants given orally need buffering against the degradative effects of low stomach pH, and the type and volume of antacid buffer require special attention for infants. In addition, container/closure systems must be compatible with vaccine formulations, protect against water and gas transfer, and have minimal impact on the cold chain. Health care workers in demanding low-resource settings need an administration device that is easy to use, yet will accurately measure and safely deliver the correct vaccine dose. Developers must consider manufacturing capabilities, and immunization program managers want affordable vaccines. As new combination enteric vaccine candidates advance into clinical evaluation, features of the final vaccine presentation—liquid or dry format, diluent, buffer, primary and secondary packaging, and administration device—should be taken into account early in product development to achieve the greatest possible impact for the vaccine.

WEB: http://dx.doi.org/10.1080/21645515.2016.1238536

IMPACT FACTOR: 2.37

CITED HALF-LIFE: 1.80

START SCIENTIFIC COMMENT: Authors discuss the following "key features" of effective containers and delivery devices for oral enteric vaccines:

- *Protection of and compatibility with vaccine formulation*
- *Performance and ease of use in dose administration*
- *Safety for recipients and health care workers*
- *Manufacturing feasibility*
- *Immunization program suitability*
- *Cost containment*

Each of the aforementioned features must be considered during the development stages of both the vaccine and the container/delivery device to ensure the vaccine is suitable and appropriate for delivery and scale in low-resource settings.

7. **National legislation and spending on vaccines in Latin America and the Caribbean.**

McQuestion M, Garcia AG, Janusz C, Andrus JK.

J Public Health Policy. 2016 Oct 27. [Epub ahead of print]

PMID:27789905

ABSTRACT

This study examined the dynamics of vaccine spending and vaccine legislation in the Americas Region over the period 1980–2013. Annual vaccine expenditures from thirty-one countries were extracted from the Pan American Health Organization Revolving Fund database. Information on vaccine laws and regulations was provided by the PAHO Family, Gender, and Life Course Unit. Both time series and event history models were estimated. The results show that passing an immunization law led a representative country to increase its vaccine spending, controlling for income, infant mortality, population size, and DPT3 vaccine coverage. Countries with higher vaccine coverage were also more likely to have passed laws. Conversely, higher income countries were less likely to have vaccine laws. Vaccine legislation will likely play a similarly important role in other regions as more countries move towards immunization program ownership.

WEB: http://dx.doi.org/10.1057/s41271-016-0052-x

IMPACT FACTOR: 0.91

CITED HALF-LIFE: 5.50

START SCIENTIFIC COMMENT: The following factors were hypothesized to affect a country's vaccine spending or passage of a vaccine law: progress against vaccine-preventable diseases including polio; introduction of new technologies and practices; and public involvement in immunization campaigns. Authors also considered that countries were likely influenced by the laws and practices of other countries.

It is important to note that the analyses focused specifically on countries in the Latin American context, which are not necessarily representative of countries in other regions. GDP was considered as a possible explanatory factor for the association between legislation and spending, but should be noted that most countries in Latin America fall into lower-middle-income or middle-income categories, and thus the influence of the distribution of GDP may not be applicable to countries that fall within the low-income category.

Authors were interested in evaluating temporal trends and causal relationships between immunization law and spending, but no costing data was available prior to 2000 and thus ability to evaluate temporality or causation is limited. Thus expenditures on vaccine programs could not be evaluated as a possible predictor of vaccination legislations

Authors note that laws are generally a reflection of social norms and conditions, and may thus serve as a proxy for (versus cause of) other social factors which are not evaluated in this analysis.

Higher-income countries tended to be less likely to have passed vaccine legislation. Authors attribute this to less perceived need in the public for vaccination programs in countries where burden of disease may be lower (since higher income countries tend to have lower disease burden independent of vaccination spending and legislations) or the greater availability of funding for vaccination programs within the better-financed general public health program budgets, which would attenuate the need for legislation to 'ear-mark' funding for vaccination.

8. **Revitalizing the home-based record: Reflections from an innovative south-south exchange for optimizing the quality, availability and use of home-based records in immunization systems.**

Hasman A, Rapp A, Brown DW.

Vaccine. 2016 Nov 11;34(47):5697-5699.

PMID:27743647

ABSTRACT

N/A

WEB: http://dx.doi.org/10.1016/j.vaccine.2016.09.064

IMPACT FACTOR: 3.62

CITED HALF-LIFE: 5.50

START SCIENTIFIC COMMENT: A commentary about the importance and opportunity of home-based records for improving coverage, quality and efficiency of vaccine programs in low-resource settings.

Authors note that to be beneficial, home-based records maintained by caregivers must be well-designed, available in adequate supply, adopted and utilized appropriately. Such records can help prevent missed opportunities for vaccination and avoid unnecessary re-vaccination when registries or health facility documentation is lacking, incomplete or inaccurate. Authors point out the potential limitations in validity of coverage estimates and program monitoring from surveys based on care-giver recall alone in areas of home-based records are rare. Authors emphasize the importance of ongoing research to inform the optimization of home based strategies to improve availability, adoption and utilization for care-givers, health workers and public health programs.

9. **The impact of assumptions regarding vaccine-induced immunity on the public health and cost-effectiveness of hepatitis A vaccination: Is one dose sufficient?**

Curran D, de Ridder M, Van Effelterre T.

Hum Vaccin Immunother. 2016 Nov;12(11):2765-2771.

PMID:27428611

ABSTRACT

Hepatitis A vaccination stimulates memory cells to produce an anamnestic response. In this study, we used a mathematical model to examine how long-term immune memory might convey additional protection against clinical/icteric infections. Dynamic and decision models were used to estimate the expected number of cases, and the costs and quality-adjusted life-years (QALYs), respectively. Several scenarios were explored by assuming: (1) varying duration of vaccine-induced immune memory, (2) and/or varying levels of vaccine-induced immune memory protection (IMP), (3) and/or varying levels of infectiousness in vaccinated individuals with IMP. The base case analysis assumed a time horizon of 25 y (2012 – 2036), with additional analyses over 50 and 75 y. The analyses were conducted in the Mexican public health system perspective. In the base case that assumed no vaccine-induced IMP, the 2-dose hepatitis A vaccination strategy was cost-effective compared with the 1-dose strategy over the 3 time horizons. However, it was not cost-effective if we assumed additional IMP durations of at least 10 y in the 25-y horizon. In the 50- and 75-y horizons, the 2-dose strategy was always cost-effective, except when 100% reduction in the probability of icteric Infections, 75% reduction in infectiousness, and mean durations of IMP of at least 50 y were assumed. This analysis indicates that routine vaccination of toddlers against hepatitis A virus would be cost-effective in Mexico using a single-dose vaccination strategy. However, the cost-effectiveness of a second dose depends on the assumptions of additional protection by IMP and the time horizon over which the analysis is performed.

WEB: http://dx.doi.org/10.1080/21645515.2016.1203495

IMPACT FACTOR: 2.37

CITED HALF-LIFE: 1.80

START SCIENTIFIC COMMENT: Authors point out that the superiority of a 2-dose strategy versus a one-dose strategy primarily arises when analyses are based on longer time horizons (75 years or longer). This is attributed in part to a shift in age distribution of infectious cases resulting from vaccination strategy. With single dose strategy, mean age of infection shifts upwards in the population, and older individuals are more likely to have hospitalization and death associated with infection.

Authors note their models are based on data from a population that may not be reflective of current or future Hepatitis A transmission dynamics; the unvaccinated population from which the models are derived would tend to have younger age of infection than would be expected in a population in which the coverage of vaccination was greater. With greater coverage, the mean infection age would likely be older, which would influence transmission dynamics. The lack of a comprehensive understanding of the long-term immunity and protection provided by a single dose also introduces uncertainly into the results.

10. Macromolecular systems for vaccine delivery.

MuzikovÃ G, Laga R.

Physiol Res. 2016 Oct 20;65(Supplementum 2):S203-S216.

PMID:27762586

ABSTRACT

Vaccines have helped considerably in eliminating some life threatening infectious diseases in past two hundred years. Recently, human medicine has focused on vaccination against some of the world's most common infectious diseases (AIDS, malaria, tuberculosis, etc.), and vaccination is also gaining popularity in the treatment of cancer or autoimmune diseases. The major limitation of current vaccines lies in their poor ability to generate a sufficient level of protective antibodies and T cell responses against diseases such as HIV, malaria, tuberculosis and cancers. Among the promising vaccination systems that could improve the potency of weakly immunogenic vaccines belong macromolecular carriers (water soluble polymers, polymer particles, micelles, gels etc.) conjugated with antigens and immune-stimulatory molecules. The size, architecture, and the composition of the high molecular-weight carrier can significantly improve the vaccine efficiency. This review includes the most recently developed (bio)polymer-based vaccines reported in the literature.

WEB: http://www.biomed.cas.cz/physiolres/pdf/65%20Suppl%202/65_S203.pdf

IMPACT FACTOR: 0.59

CITED HALF-LIFE: 6.90

START SCIENTIFIC COMMENT: Authors discuss developments in the following synthetic or natural macromolecular carriers and adjuvants for vaccine delivery:

Synthetic:

Poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) poly(oxazoline); poly(acrylate); polyethylenimine-based (PEI); poly(glycerol; monomethacrylate) (PGMMA); poly(ethylene glycol)- block-poly(propylene sulfide) polymersomes.

Natural:

Poly(ethylene glycol)-block-poly(propylene sulfide) polymersomes; poly((R)-3-hydroxybutyrate) (PHB) to produce PHB beads; ISCOM (immunostimulating complex) made up of saponin, phospholipids, and cholesterol to form forms micelles; ISCOM with the A1 subunit from cholera toxin and a dimer of the Dfragment of Staphylococcus aureus (CTA1-DD); chitosan; acetylated dextran.

Non- polymer:

Gold nanoparticles; carbon nanoparticles.

APPENDIX: PUBMED SEARCH TERMS

(((((vaccine[tiab] OR vaccines[tiab] OR vaccination[tiab] OR immunization[tiab] OR immunisation[tiab] OR vaccine[mesh] OR immunization[mesh]) AND (logistics[tiab] OR supply[tiab] OR "supply chain"[tiab] OR implementation[tiab] OR expenditures[tiab] OR financing[tiab] OR economics[tiab] OR "Cost effectiveness"[tiab] OR coverage[tiab] OR attitudes[tiab] OR belief[tiab] OR beliefs[tiab] OR refusal[tiab] OR "Procurement"[tiab] OR timeliness[tiab] OR systems[tiab])) OR ("vaccine delivery"[tiab])) NOT ("in vitro"[tiab] OR "immune response"[tiab] OR gene[tiab] OR chemistry[tiab] OR genotox*[tiab] OR sequencing[tiab] OR nanoparticle*[tiab] OR bacteriophage[tiab] OR exome[tiab] OR exogenous[tiab] OR electropor*[tiab] OR "systems biology"[tiab] OR "animal model"[tiab] OR cattle[tiab] OR sheep[tiab] OR goat[tiab] OR rat[tiab] OR pig[tiab] OR mice[tiab] OR mouse[tiab] OR murine[tiab] OR porcine[tiab] OR ovine[tiab] OR rodent[tiab] OR fish[tiab])) AND (English[LA]) AND ("2016/10/15"[PDAT] : "2016/11/14"[PDAT]))

* On November 29, 2016, this search of English language articles published between October 15, 2016 and November 14, 2016 and indexed by the US National Library of Medicine resulted in 196 unique manuscripts.