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# VACCINE DELIVERY RESEARCH DIGEST

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

REPORT TO THE BILL & MELINDA GATES FOUNDATION

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PRODUCED BY: KIDANE, L; SLYKER, J.

TABLE OF CONTENTS

## 1. Quantitative assessment of the impact of partially protective anti-schistosomiasis vaccines

Alsallaq RA, Gurarie D, Ndeffo Mbah M, Galvani A, King C.
PLoS Neglected Tropical Diseases. 2017 Apr 14;11(4).
PMID: 28410369

**ABSTRACT**

**BACKGROUND:** Mass drug administration (MDA) of praziquantel has been the intervention of choice against schistosomiasis but with limited success in interrupting the transmission. The development of anti-Schistosoma vaccines is underway. Our objective is to quantify the population-level impact of anti-Schistosoma vaccines when administered alone and in combination with mass drug administration (MDA) and determine factors in vaccine design and public health implementation that optimize vaccination role in schistosomiasis control and elimination.

**METHODS AND FINDINGS:** We developed a deterministic compartmental model simulation of schistosomiasis transmission in a high-risk Kenyan community, including stratification by age, parasite burden, and vaccination status. The modeled schistosomiasis vaccines differed in terms of vaccine duration of protection (durability) and three biological efficacies. These are vaccine susceptibility effect (SE) of reducing person's susceptibility to Schistosoma acquisition, vaccine mortality effect (ME) of reducing established worm burden and vaccine fecundity effect (FE) of reducing egg release by mature worms. We quantified the population-level impact of vaccination over two decades under diverse vaccination schemes (childhood vs. mass campaigns), with different age-targeting scenarios, different risk settings, and with combined intervention with MDA. We also assessed the sensitivity of our predictions to uncertainties in model parameters. Over two decades, our base case vaccine with 80% SE, FE, and ME efficacies, 10 years' durability, provided by mass vaccination every 10 years, reduced host prevalence, mean intensity, incidence, and patent snail prevalence to 31%, 20 eggs/10-ml sample/person, 0.87 worm/person-year, and 0.74%, from endemic-state values of 71%, 152, 3.3, and 0.98%, respectively. Lower impact was found when coverage did not encompass all potential contaminators, and childhood-only vaccination schemes showed delayed and lower impact. In lower prevalence settings, the base case vaccine generated a proportionately smaller impact. A substantially larger vaccine program effect was generated when MDA + mass vaccination was provided every 5 years, which could be achieved by an MDA-only program only if drug was offered annually. Vaccine impact on schistosomiasis transmission was sensitive to a number of parameters including vaccine efficacies, human contact rates with water, human density, patent snails' rate of patency and lifespan, and force of infection to snails.

**CONCLUSIONS:** To be successful a vaccine-based control strategy will need a moderately to highly effective formulation combined with early vaccination of potential contaminators and aggressive coverage in repeated rounds of mass vaccination. Compared to MDA-only program, vaccination combined with MDA accelerates and prolongs the impact by reducing the acquisition of new worms and reducing egg release from residual worms.

**WEB:** https://dx.doi.org/ 10.1371/journal.pntd.0005544

**IMPACT FACTOR:** 3.95

**CITED HALF-LIFE:** 3.50

**START SCIENTIFIC COMMENT:** Key findings suggest mass coverage in repeated rounds is required at an interval less than the mean durability of the vaccine-induced immunity to minimize transmission. The most optimal impact at the population level includes vaccines that substantially reduce the acquisition of new worms, reduce shedding of eggs from residual worms, and achieve treatment effects comparable to PRZ. WHO asserts PRZ is contraindicated in children less than 4 years of age (or <94 cm in height) due to limited safety data. Unvaccinated children and livestock may act as reservoirs of infection in endemic settings. Though the model assumes universal coverage it does address how seasonal variations in transmission or zoonotic transmission impact vaccine effectiveness with or without MDA, future iterations of the model may include parameters addressing these factors.

## 2. The rotavirus vaccine development pipeline

Kirkwood CD, Ma LF, Carey ME, Steele AD.
Vaccine. 2017 Apr 7.
PMID: 28396207

**ABSTRACT**

Rotavirus disease is a leading global cause of mortality and morbidity in children under 5 years of age. The effectiveness of the two globally used oral rotavirus vaccines quickly became apparent when introduced into both developed and developing countries, with significant reductions in rotavirus-associated mortality and hospitalizations. However, the effectiveness and impact of the vaccines is reduced in developing country settings, where the burden and mortality is highest. New rotavirus vaccines, including live oral rotavirus candidates and non-replicating approaches continue to be developed, with the major aim to improve the global supply of rotavirus vaccines and for local implementation, and to improve vaccine effectiveness in developing settings. This review provides an overview of the new rotavirus vaccines in development by developing country manufacturers and provides a rationale why newer candidates continue to be explored. It describes the new live oral rotavirus vaccine candidates as well as the non-replicating rotavirus vaccines that are furthest along in development.

**WEB:** https://dx.doi.org/10.1016/j.vaccine.2017.03.076

**IMPACT FACTOR:** 3.62

**CITED HALF-LIFE:** 5.50

**START SCIENTIFIC COMMENT:** To date, a pentavalent human-bovine reassortant rotavirus vaccine (RV) developed by Merck & Co and a human univalent G1P[8] vaccine developed by GSK biologicals are the only two live oral RVs prequalified by the WHO, and have been incorporated into 82 national immunization programs. Three live attenuated oral RVs have been licensed for use in India. Vietnam and Indonesia have developed indigenous RVs, the most successful of which is ROTAVAC vaccine developed by Bharat Biotech International Ltd. A phase 3 clinical trial of the ROTAVAC vaccine demonstrated a vaccine efficacy of 53.6% against severe RV gastroenteritis in the first year of life, and 48.9% in the second. Beginning in March 2016 ROTAVAC was administered to over 1 million infants with no programmatic or safety issues reported. RV effectiveness ranges from 79%-100% in high-income settings and 53%-74% in LMIC settings across Latin America. In high burden settings in Africa and Asia clinical vaccine efficacy studies document considerably lower effectiveness. Several studies have reported a decline in vaccine effectiveness occurs during the second year of life. Authors suggest these differences may be attributable to variations in transmission rates, gut microbial composition unique to children residing in these regions, in addition to host factors inhibiting vaccine take and immune response.

A number of highly effective vaccines candidates developed for use in LMIC settings have also entered the RV pipeline. NIH has developed a quadrivalent UK-Compton (UK-BRV) bovine-human rotavirus reassortant vaccine and has also included components for G8 (strain 1290) and G9 (strain AU32) to address circulating strains in Africa and Asia. The Serum Institute of India (India), Shantha Biotechnics (India), Chengdu Institute of Biological Products (China), Wuhan Institute of Biological Products (China) and Instituto Butantan (Brazil) have all been granted non-exclusive licenses for the development and production of the UK-BRV vaccine. Table 2 lists details of these vaccines and their most current findings. As alternatives to live attenuated oral vaccines, several non-replicating, parenteral RVs comprised of inactivated rotavirus particles or proteins are also in the development pipeline and represent a promising cohort in the next generation of RVs (Table 3). Oral vaccine failure is of particular concern in LMICs in sub-Saharan Africa, South and Southeast Asia where environmental enteropathy may be a prevalent underlying concurrent disease process capable of compromising vaccine efficacy in children with poor gut function and integrity. The promise of non-replicating vaccines lies in their inability to trigger intussusception or revert to virulence, which may be particularly relevant to immunocompromised populations and children in LMICs in Africa and Asia.

## 3. Improving immunization in Afghanistan: results from a cross-sectional community-based survey to assess routine immunization coverage

Mugali RR, Mansoor F, Parwiz S, Ahmad F, Safi N, Higgins-Steele A, Varkey S.
BMC Public Health. 2017 Apr 4;17(1):290.
PMID: 28376806

**ABSTRACT**

**BACKGROUND:** Despite progress in recent years, Afghanistan is lagging behind in realizing the full potential of immunization. The country is still endemic for polio transmission and measles outbreaks continue to occur. In spite of significant reductions over the past decade, the mortality rate of children under 5 years of age continues to remain high at 91 per 1000 live births.

**METHODS:** The study was a descriptive community-based cross sectional household survey. The survey aimed to estimate the levels of immunization coverage at national and province levels. Specific objectives are to: establish valid baseline information to monitor progress of the immunization program; identify reasons why children are not immunized; and make recommendations to enhance access and quality of immunization services in Afghanistan. The survey was carried out in all 34 provinces of the country, with a sample of 6125 mothers of children aged 12–23 months.

**RESULTS:** Nationally, 51% of children participating in the survey received all doses of each antigen irrespective of the recommended date of immunization or recommended interval between doses. About 31% of children were found to be partially vaccinated. Reasons for partial vaccination included: place to vaccinate child too far (23%), not aware of the need of vaccination (17%), no faith in vaccination (16%), mother was too busy (15%), and fear of side effects (11%).

**CONCLUSION:** The innovative mechanism of contracting out delivery of primary health care services in Afghanistan, including immunization, to non-governmental organizations is showing some positive results in quickly increasing coverage of essential interventions, including routine immunization. Much ground still needs to be covered with proper planning and management of resources in order to improve the immunization coverage in Afghanistan and increase survival and health status of its children.

**WEB:** https://dx.doi.org/10.1186/s12889-017-4193-z

**IMPACT FACTOR:** 2.21

**CITED HALF-LIFE:** 4.30

**START SCIENTIFIC COMMENT:** Table 1 lists the complete routine childhood vaccination schedule in Afghanistan. Investigators obtained child immunization status for each of the provided antigens as well as the percentage of fully immunized children (either crude or valid coverage, overall and by the twelfth month of age). Vaccines recorded in the survey include: BCG; pentavalent Hib, pertussis, tetanus, hepatitis B and diphtheria; oral poliovirus vaccine (OPV); and the first dose of measles vaccine. Children who did not receive the next doses of the recommended antigens (three doses of Penta, OPV, and one dose of measles vaccine after taking BCG or Penta1) were recorded as dropouts. Correlates of childhood vaccine uptake included residence in an urban location, higher maternal education attainment, and increased wealth.

There are several methodological limitations to note. The sample was highly skewed, with 85% of the sample rural and 85% of mothers having no education. It is unclear how or whether confounding was addressed. Immunization status was determined using patient cards when available, but >30% relied on maternal recall, so information bias is likely. The investigators were unable to reach 16 (1.6%) clusters due to active security threats or geographical constraints; selection bias is likely as individuals living in these remote and/or high conflict settings may have lower vaccine coverage.

## 4. Country-level predictors of vaccination coverage and inequalities in Gavi-supported countries.

Arsenault C, Johri M, Nandi A, Rodríguez JM, Hansen PM, Harper S.
Vaccine. 2017 Mar 29.
PMID: 28365251

**ABSTRACT**

**BACKGROUND:** Important inequalities in childhood vaccination coverage persist between countries and population groups. Understanding why some countries achieve higher and more equitable levels of coverage is crucial to redress these inequalities. In this study, we explored the country-level determinants of (1) coverage of the third dose of diphtheria-tetanus-pertussis- (DTP3) containing vaccine and (2) within-country inequalities in DTP3 coverage in 45 countries supported by Gavi, the Vaccine Alliance.

**METHODS:** We used data from the most recent Demographic and Health Surveys (DHS) conducted between 2005 and 2014. We measured national DTP3 coverage and the slope index of inequality in DTP3 coverage with respect to household wealth, maternal education, and multidimensional poverty. We collated data on country health systems, health financing, governance and geographic and sociocultural contexts from published sources. We used meta-regressions to assess the relationship between these country-level factors and variations in DTP3 coverage and inequalities. To validate our findings, we repeated these analyses for coverage with measles-containing vaccine (MCV).

**RESULTS:** We found considerable heterogeneity in DTP3 coverage and in the magnitude of inequalities across countries. Results for MCV were consistent with those from DTP3. Political stability, gender equality and smaller land surface were important predictors of higher and more equitable levels of DTP3 coverage. Inequalities in DTP3 coverage were also lower in countries receiving more external resources for health, with lower rates of out-of-pocket spending and with higher national coverage. Greater government spending on heath and lower linguistic fractionalization were also consistent with better vaccination outcomes.

**CONCLUSION:** Improving vaccination coverage and reducing inequalities requires that policies and programs address critical social determinants of health including geographic and social exclusion, gender inequality and the availability of financial protection for health. Further research should investigate the mechanisms contributing to these associations.

**WEB:** https://dx.doi.org/10.1016/j.vaccine.2017.03.029

**IMPACT FACTOR:** 3.62
**CITED HALF-LIFE:** 5.50

**START SCIENTIFIC COMMENT:** DTP3 coverage was defined as the proportion of children 12-23 months having received the DPT3 vaccine at the time of the survey and was assessed using vaccination cards or maternal recall when vaccination cards were unavailable. The mean DPT3 coverage rate was 77.1% (95% CI [71.9, 82.3]) and 77.5% (95% CI [73.3, 81.7]) for MCV after pooling national DPT3 coverage rates across all 45 countries using random-effects meta-analyses weighted by the inverse variance of the individual estimates. The model assumed a linear relationship between inequality rankings and vaccination coverage rates. Authors chose to measure absolute inequalities in DTP3 coverage with respect to the wealth index, maternal education and the multidimensional poverty index (MPI). The investigators use the Slope Index of Inequality (SII) to predict the difference in DPT3 vaccination coverage among individuals across levels of maternal education, wealth, and multidimensional poverty indices. Across countries, comparing individuals in the highest and lowest levels of wealth, education and MPI resulted in a 20%-21% difference in DPT3 vaccination coverage. At the country level, political stability was the single greatest country level predictor of DPT3 coverage, was associated with a 10% increase in DTP3 coverage compared to instability (95% CI [0.04, 0.16]), and accounted for 21% of variation across the sample. The study does not adequately address confounding of gender inequality and vaccine coverage due to maternal education. It also does not include data from 28 GAVI-supported countries and is thus not representative of all GAVI supported LMICs.

## 5. Impact of high-intensity polio eradication activities on children's routine immunization status in Northern India.

Haenssgen MJ.
Health policy and planning. 2017 Mar 16.
PMID: 28335014

**ABSTRACT**

The objective of this article is to analyse and quantify the side effects of the Polio Eradication Initiative on routine immunization performance in India. Past studies have faced methodological challenges in assessing these side effects. This article offers a methodological alternative for health policy analysts. The research uses secondary household survey data from the Indian District-Level Household and Facility Survey (DLHS), focusing on children aged 10-30 months in the Northern Indian states of Uttar Pradesh (n = 34 327) and Bihar (n = 20 525). Covering the years 2002-08, this is the latest large-scale data from India that enables the matching technique used in this article. District-level programme intensity data of the Polio Eradication Initiative in India were reconstructed using publicly available resources. The methodological innovation compared with previous studies consists of matching each child in the DLHS data set with a child-specific value of programme exposure depending on its district of residence, its birth date, and the date of the survey interview. Average and age-specific associations between polio programme exposure and children's full immunization status were assessed using logistic regression, controlling for other determinants of immunization. The regression results show that the link is negative in Uttar Pradesh and positive in Bihar. Age-specific analysis shows that the positive association diminishes for older children in Bihar and that a negative association emerges and becomes increasingly pronounced for older children in Uttar Pradesh. This indicates that heterogeneous results emerge across two neighbouring states with similar programme intensity and suggests that the catch-up of unvaccinated older children may be a channel through which negative effects accrue. The method described in this article, based on an analytical focus on individual-level programme exposure, can therefore help health policy implementers and evaluators to illuminate positive or negative interactions between a health intervention and a health system.

**WEB:** https://dx.doi.org/10.1093/heapol/czx022

**IMPACT FACTOR:** 2.51
**CITED HALF-LIFE:** 7.40

**START SCIENTIFIC COMMENT:** Evidence documenting the positive and negative impacts of polio eradication efforts across a number of national health systems are primarily qualitative. Some research suggests that Polio Eradication Initiatives (PEIs) may work in tandem with national routine immunization (RI) to bolster childhood vaccination programs in some settings while diverting health systems resources and introducing logistical hurdles to the detriment of national RI programs in other settings. Data are sourced from a nationally representative survey and are supplemented with publicly available policy reports. The primary innovation of this study lies in the construction of a statistical model designed to predict the probability of full vaccination status for children ages 10-30 in Uttar Pradesh and Bihar without access to vaccine administration data. Since administrative program data were unavailable to the author at the time of this study, the investigator attempted to map immunization patterns and gaps using DLHS data on the child's district of residence, birthdate and date of the survey interview. The degree of exposure to polio mass immunization campaigns reflects the intensity of immunization campaigns and is defined as the number of polio immunization rounds a child would have ostensibly experienced given their birthdate and location, assuming universal vaccination of all children aged 10-30 months during immunization campaigns. Though exploratory in nature the volume of comparisons made in the study suggests multiple testing issues may compromise the reliability of the findings from the repeated cross-sectional analysis.

## 6. Mobile phone-delivered reminders and incentives to improve childhood immunisation coverage and timeliness in Kenya (M-SIMU): a cluster randomised controlled trial.

Gibson DG, Ochieng B, Kagucia EW, Were J, Hayford K, Moulton LH, Levine OS, Odhiambo F, O'Brien KL, Feikin DR.

The Lancet Global Health. 2017 Apr 30;5(4):e428-38
PMID: 28288747

**ABSTRACT**

**BACKGROUND:** As mobile phone access continues to expand globally, opportunities exist to leverage these technologies to support demand for immunisation services and improve vaccine coverage. We aimed to assess whether short message service (SMS) reminders and monetary incentives can improve immunisation uptake in Kenya.

**METHODS:** In this cluster-randomised controlled trial, villages were randomly and evenly allocated to four groups: control, SMS only, SMS plus a 75 Kenya Shilling (KES) incentive, and SMS plus 200 KES (85 KES = USD$1). Caregivers were eligible if they had a child younger than 5 weeks who had not yet received a first dose of pentavalent vaccine. Participants in the intervention groups received SMS reminders before scheduled pentavalent and measles immunisation visits. Participants in incentive groups, additionally, received money if their child was timely immunised (immunisation within 2 weeks of the due date). Caregivers and interviewers were not masked. The proportion of fully immunised children (receiving BCG, three doses of polio vaccine, three doses of pentavalent vaccine, and measles vaccine) by 12 months of age constituted the primary outcome and was analysed with log-binomial regression and General Estimating Equations to account for correlation within clusters. This trial is registered with ClinicalTrials.gov, number NCT01878435.

**FINDINGS:** Between Oct 14, 2013, and Oct 17, 2014, we enrolled 2018 caregivers and their infants from 152 villages into the following four groups: control (n=489), SMS only (n=476), SMS plus 75 KES (n=562), and SMS plus 200 KES (n=491). Overall, 1375 (86%) of 1600 children who were successfully followed up achieved the primary outcome, full immunisation by 12 months of age (296 [82%] of 360 control participants, 332 [86%] of 388 SMS only participants, 383 [86%] of 446 SMS plus 75 KES participants, and 364 [90%] of 406 SMS plus 200 KES participants). Children in the SMS plus 200 KES group were significantly more likely to achieve full immunisation at 12 months of age (relative risk 1·09, 95% CI 1·02-1·16, p=0·014) than children in the control group.

**INTERPRETATION:** In a setting with high baseline immunisation coverage levels, SMS reminders coupled with incentives significantly improved immunisation coverage and timeliness. Given that global immunization coverage levels have stagnated around 85%, the use of incentives might be one option to reach the remaining 15%.

**FUNDING:** Bill & Melinda Gates Foundation.

**WEB:** https://dx.doi.org/10.1016/S2214-109X(17)30072-4

**IMPACT FACTOR:** 14.72

**CITED HALF-LIFE:** 1.60

**START SCIENTIFIC COMMENT:** Upon receiving text notifications from village reporters via RapidSMS server, field-based community interviewers visited the homes of newborns to determine the caregiver's residency and age of the newborn. In doing so, Investigators were able to avoid selection bias seen in facility-based enrollment procedures in addition to securing a more representative sample by enrolling infants ages 0-34 prior to receipt of their first scheduled vaccination. Twenty-one percent of children were lost to follow up in the final analysis. Moreover, a comparison of the final analytic sample and the baseline sample revealed data were not missing at random. Caregivers with missing follow-up data were more likely to be <25 years old, have a single child aged <5 years in the household, and reside in Gem. Investigators conducted a per-protocol analysis of delivered SMS reminders, which makes it difficult to evaluate the effectiveness of the SMS platform since such an analysis cannot account for whether or not SMS reminders were received, read, or relayed to caregivers.

## 7. Geospatial Planning and the Resulting Economic Impact of Human Papillomavirus Vaccine Introduction in Mozambique.

Haidari LA, Brown ST, Constenla D, Zenkov E, Ferguson M, de Broucker G, Ozawa S, Clark S, Portnoy A, Lee BY.
Sexually transmitted diseases. 2017 Apr 1;44(4):222-6
PMID: 28282648

**ABSTRACT**

**BACKGROUND:** Research has shown that the distance to the nearest immunization location can ultimately prevent someone from getting immunized. With the introduction of human papillomavirus (HPV) throughout the world, a major question is whether the target populations can readily access immunization.

**METHODS:** In anticipation of HPV vaccine introduction in Mozambique, a country with a 2015 population of 25,727,911, our team developed Strategic Integrated Geo-temporal Mapping Application (SIGMA) to determine the potential economic impact of HPV immunization. We quantified how many people in the target population are reachable by the 1377 existing immunization locations, how many cannot access these locations, and the potential costs and disease burden averted by immunization.

**RESULTS:** If the entire 2015 cohort of 10-year-old girls goes without HPV immunization, approximately 125 (111-139) new cases of HPV 16,18-related cervical cancer are expected in the future. If each health center covers a catchment area with a 5-km radius (i.e., if people travel up to 5 km to obtain vaccines), then 40% of the target population could be reached to prevent 50 (44-55) cases, 178 (159-198) disability-adjusted life years, and US $202,854 (US $140,758-323,693) in health care costs and lost productivity. At higher catchment area radii, additional increases in catchment area radius raise population coverage with diminishing returns.

**CONCLUSIONS:** Much of the population in Mozambique is unable to reach any existing immunization location, thereby reducing the potential impact of HPV vaccine. The geospatial information system analysis can assist in planning vaccine introduction strategies to maximize access and help the population reap the maximum benefits from an immunization program.

**WEB:** https://dx.doi.org/ 10.1097/OLQ.0000000000000574

**IMPACT FACTOR:** 2.97

**CITED HALF-LIFE:** 7.30

**START SCIENTIFIC COMMENT:** Investigators developed a GIS model— SIGMA for immunization, to determine the number of individuals residing in the catchment area of existing immunization locations in Mozambique. Investigators used 2000-2015 estimates of population density from the Global Rural-Urban Mapping Project scaled to project the density of the target population of 10 year old girls per square km. Investigators then plotted the location of 1377 geo-referenced health centers serving as routine immunization locations from the WHO EPI program in Mozambique to determine the proportion of 10 year old girls living within the catchment area of any health center delivering immunization services. Cost associated care for HPV are reported in USD and are adjusted for severity and World Bank inflation estimates for Mozambique in 2015. DALYs averted due to HPV immunization and HPV vaccine efficacy are borrowed from Goldie et al (2008) estimates health and economic outcomes of HPV 16,18 vaccination in LMIC settings. Investigators estimate a 20km radial catchment area would reach 91% of the target population and would result in 114 (95% CI [102, 127]) fewer cases, 411 DALYs 95% CI[365, 456]) saved, $204,847 in health care costs and $262,442 in productivity losses. Increasing radial distance beyond 20km yielded diminished returns. Figure 2 displays SIGMA visualizations illustrating the relationship between population density and catchment area radii.

**8. Cost Description and Comparative Cost Efficiency of Post-Exposure Prophylaxis and Canine Mass Vaccination against Rabies in N'Djamena, Chad.** Mindekem R, Léchenne MS, Naissengar KS, Oussiguéré A, Kebkiba B, Moto DD, Alfaroukh IO, Ouedraogo LT, Salifou S, Zinsstag J.
Frontiers in Veterinary Science. 2017;4.
PMID: 28421186


**ABSTRACT**

Rabies claims approximately 59,000 human lives annually and is a potential risk to 3.3 billion people in over 100 countries worldwide. Despite being fatal in almost 100% of cases, human rabies can be prevented by vaccinating dogs, the most common vector, and the timely administration of post-exposure prophylaxis (PEP) to exposed victims. For the control and prevention of human rabies in N'Djamena, the capital city of Chad, a free mass vaccination campaign for dogs was organized in 2012 and 2013. The campaigns were monitored by parallel studies on the incidence of canine rabies based on diagnostic testing of suspect animals and the incidence of human bite exposure recorded at selected health facilities. Based on the cost description of the campaign and the need for PEP registered in health centers, three cost scenarios were compared: cumulative cost-efficiency of (1) PEP alone, (2) dog mass vaccination and PEP, (3) dog mass vaccination, PEP, and maximal communication between human health and veterinary workers (One Health communication). Assuming ideal One Health communication, the cumulative prospective cost of dog vaccination and PEP break even with the cumulative prospective cost of PEP alone in the 10th year from the start of the calculation (2012). The cost efficiency expressed in cost per human exposure averted is much higher with canine vaccination and One Health communication than with PEP alone. As shown in other studies, our cost-effectiveness analysis highlights that canine vaccination is financially the best option for animal rabies control and rabies prevention in humans. This study also provides evidence of the beneficial effect of One Health communication. Only with close communication between the human and animal health sectors will the decrease in animal rabies incidence be translated into a decline for PEP. An efficiently applied One Health concept would largely reduce the cost of PEP in resource poor countries and should be implemented for zoonosis control in general.



**WEB:** https://dx.doi.org/10.3389/fvets.2017.00038

**IMPACT FACTOR:** NA

**CITED HALF-LIFE:** NA


**START SCIENTIFIC COMMENT:** The overall cost efficiency is based on the assumption that after two rounds of vaccination to interrupt rabies transmission, the only costs incurred for prevention would stem from the reintroduction canine rabies cases outside of N'Djamena. Figure 4 summarizes the cost trend of the three different scenarios. Including maximum One Health communication to mass canine vaccination is projected to reduce the time to cost-effectiveness by a third. Authors suggest this may be due to a reduction in inappropriate use of PEP by individuals uncertain of the canine immunization status. Scenarios 2 and 3 each estimated 9,055 total DALYS averted after 20 years. The cost per DALY averted over 20 years were estimated to be greater in scenario 2, but it is worth noting estimates for scenario 3 do not include cost required to facilitate the One Health communication component; these were omitted due to absence of reliable data regarding meeting fees, transport costs, telephone credit and other potential costs.

## 9. Cost-effectiveness of dengue vaccination in Yucatán, Mexico using a dynamic dengue transmission model.

Shim E.
PloS one. 2017 Apr 5;12(4).
PMID: 28380060

**ABSTRACT**

**BACKGROUND:** The incidence of dengue fever (DF) is steadily increasing in Mexico, burdening health systems with consequent morbidities and mortalities. On December 9th, 2015, Mexico became the first country for which the dengue vaccine was approved for use. In anticipation of a vaccine rollout, analysis of the cost-effectiveness of the dengue vaccination program that quantifies the dynamics of disease transmission is essential.

**METHODS:** We developed a dynamic transmission model of dengue in Yucatán, Mexico and its proposed vaccination program to incorporate herd immunity into our analysis of cost-effectiveness analysis. Our model also incorporates important characteristics of dengue epidemiology, such as clinical cross-immunity and susceptibility enhancement upon secondary infection. Using our model, we evaluated the cost-effectiveness and economic impact of an imperfect dengue vaccine in Yucatán, Mexico.

**CONCLUSIONS:** Our study indicates that a dengue vaccination program would prevent 90% of cases of symptomatic DF incidence as well as 90% of dengue hemorrhagic fever (DHF) incidence and dengue-related deaths annually. We conclude that a dengue vaccine program in Yucatán, Mexico would be very cost-effective as long as the vaccination cost per individual is less than $140 and $214 from health care and societal perspectives, respectively. Furthermore, at an exemplary vaccination cost of $250 USD per individual on average, dengue vaccination is likely to be cost-effective 43% and 88% of the time from health care and societal perspectives, respectively.

**WEB:** https://dx.doi.org/10.1371/journal.pone.0175020

**IMPACT FACTOR:** 3.06

**CITED HALF-LIFE:** 3.10

**START SCIENTIFIC COMMENT:** Dengvaxia is tetravalent chimeric yellow-fever dengue (CYD) vaccine demonstrating varying degrees of vaccine efficacy in the four-targeted serovars. WHO Strategic Advisory Group of Experts recommend vaccination in endemic settings where the seroprevalence ≥70% in the targeted age group. The overall seroprevalence of dengue in Yucatán is 81.5%, and the seroprevalence between ages 9 and 45 is estimated to be 82.3%.
DHF and dengue shock syndrome (DSS) are of particular concern to individuals residing in high endemic areas with multiple concurrent circulating serovars. The authors developed an age-structured model of transmission which considers how clinical cross-immunity and vaccine-induced antibody-dependent enhancement (ADE) influence the probability of developing severe disease upon primary and secondary infection. The authors assert that because 3rd and 4th infections from dengue are very rare, individuals recovering from secondary infection in the model are assumed to gain immunity from all serovars. However, all 4 serotypes of dengue have been observed in Mexico, which may make the assumption of cross-immunity post-secondary infection untenable should the genetic diversity or prevalence of serotypes change over time. Still, authors assert that despite increased infectivity due to ADE, the vaccine is cost saving if priced below $89 and cost effective if priced below $140.

## 10. Effectiveness of UNAIDS targets and HIV vaccination across 127 countries.

Medlock J, Pandey A, Parpia AS, Tang A, Skrip LA, Galvani AP.
Proceedings of the National Academy of Sciences. 2017 Apr 11;114(15):4017-22.
PMID: 28320938

**ABSTRACT**

The HIV pandemic continues to impose enormous morbidity, mortality, and economic burdens across the globe. Simultaneously, innovations in antiretroviral therapy, diagnostic approaches, and vaccine development are providing novel tools for treatment-as-prevention and prophylaxis. We developed a mathematical model to evaluate the added benefit of an HIV vaccine in the context of goals to increase rates of diagnosis, treatment, and viral suppression in 127 countries. Under status quo interventions, we predict a median of 49 million [first and third quartiles 44M, 58M] incident cases globally from 2015 to 2035. Achieving the Joint United Nations Program on HIV/AIDS 95–95–95 target was estimated to avert 25 million [20M, 33M] of these new infections, and an additional 6.3 million [4.8M, 8.7M] reduction was projected with the 2020 introduction of a 50%-efficacy vaccine gradually scaled up to 70% coverage. This added benefit of prevention through vaccination motivates imminent and ongoing clinical trials of viable candidates to realize the goal of HIV control.

**WEB:** https://dx.doi.org/10.1073/pnas.1620788114

**IMPACT FACTOR:** 9.42
**CITED HALF-LIFE:** 8.70

**START SCIENTIFIC COMMENT:** The Thai RV144 trial of ALVAC-HIV demonstrated vaccine efficacies of 60.5% after one year and 31.2% after 3.5 years among Thai adults aged 18-30. In recent years subsequent vaccine trials of ALVAC have gained considerable attention. Results published from phase 1 and 2 of the HYTVN 100 trial in 2016 demonstrated safety and immunogenicity of the ALVAC-HIV vaccine in combination with a Bivalent Subtype C gp120/MF59 adjuvant. Phase 3 of HTVN 702 trial began in November 2016 and will evaluate the preventive vaccine efficacy, safety, and tolerability of ALVAC-HIV (vCP2438) and Bivalent Subtype C gp120/MF59 in HIV-seronegative South African adults over 24. Recent advancements in the HIV vaccine research and development pipeline have spurred interest in modeling how the vaccine may perform in different settings. The authors designed a model illustrating HIV progression, transmission, and the impacts of a vaccine with 127 countries that that make up 90% of the HIV global burden. In their model the authors stratify HIV infection into acute, chronic undiagnosed, chronic diagnosed, chronic treated, chronic virally suppressed, and AIDS. Viral suppression with respect to survival and transmission are both included in the model, in addition to country-specific transmission rates. In the absence of data authors state simplifying assumptions were made but do not detail the nature of their assumptions. The authors do not address the potential for waning immunity over time, as was observed in the RV144 trial, nor do they include risk strata accounting for variation in transmission among high-risk populations. Findings from sensitivity analysis suggested vaccine effectiveness was more heavily influenced by the transmission rate, acute transmission rate, and transmissibility during and after the acute phase, than to viral suppression mediated reductions in transmissibility. Whereas likelihood of achieving the UNAIDS 90-90-90 and 95-95-95 targets were more influenced by the transmission rate, acute progression rate, and relative transmissibility during viral suppression.

## 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]) ("2017/3/15"[PDAT] : "2017/4/14"[PDAT]))

* On April 25, 2017, this search of English language articles published between March 15th, 2017 and April 14th, 2017 and indexed by the US National Library of Medicine resulted in 173 unique manuscripts.