VACCINE DELIVERY RESEARCH DIGEST

UNIVERSITY OF WASHINGTON GLOBAL HEALTH START PROGRAM
REPORT TO THE BILL AND MELINDA GATES FOUNDATION

AUGUST 1, 2014

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1. PERFORMANCE OF 21 HPV VACCINATION PROGRAMS IMPLEMENTED IN LOW AND MIDDLE-INCOME COUNTRIES, 2009-2013

Ladner J, Besson MH, Rodrigues M, Audureau E, Saba J.

BMC Public Health. 2014 Jun 30;14:670.

PMID: 24981818

ABSTRACT

BACKGROUND: Cervical cancer is the third most common cancer in women worldwide, with high incidence in lowest income countries. Vaccination against Human Papilloma Virus (HPV) may help to reduce the incidence of cervical cancer. The aim of the study was to analyze HPV vaccination programs performance implemented in low and middle-income countries.

METHODS: The Gardasil Access Program provides HPV vaccine at no cost to help national institutions gain experience implementing HPV vaccination. Data on vaccine delivery model, number of girls vaccinated, number of girls completing the three-dose campaign, duration of vaccination program, community involvement and sensitization strategies were collected from each program upon completion. Vaccine Uptake Rate (VUR) and Vaccine Adherence between the first and third doses (VA) rate were calculated. Multivariate linear regressions analyses were fitted.

RESULTS: Twenty-one programs were included in 14 low and middle-income countries. Managing institutions were non-governmental organizations (NGOs) (n = 8) or Ministries of Health (n = 13). Twelve programs were school-based, five were health clinic-based and four utilized a mixed model. A total of 217,786 girls received a full course of vaccination. Mean VUR was 88.7% (SD = 10.5) and VA was 90.8% (SD = 7.3). The mean total number of girls vaccinated per program-month was 2,426.8 (SD = 2,826.6) in school model, 335.1 (SD = 202.5) in the health clinic and 544.7 (SD = 369.2) in the mixed models (p = 0.15). Community involvement in the follow-up of girls participating in the vaccination campaign was significantly associated with VUR. Multivariate analyses identified school-based (β = 13.35, p = 0.001) and health clinic (β = 13.51, p = 0.03) models, NGO management (β = 14.58, p < 10(-3)) and duration of program vaccination (β = -1.37, p = 0.03) as significant factors associated with VUR.

CONCLUSIONS: School and health clinic-based models appeared as predictive factors for vaccination coverage, as was management by an NGO; program duration could play a role in the program's effectiveness. Results suggest that HPV vaccine campaigns tailored to meet the needs of communities can be effective. These results may be useful in the development of national HPV vaccination policies in low and middle-income countries.

WEB: http://dx.doi.org/10.1186/1471-2458-14-670

IMPACT FACTOR: 2.08

CITED HALF-LIFE: 3.60

UW EDITORIAL COMMENT: Data from 21 programs across 14 countries were used to identify significant predictors of vaccine uptake in the target population, as shown in Table 3. Some programs reported over 100% uptake, possibly indicating misclassification of the target population in these programs.

2. COMPARATIVE PERFORMANCE OF PUBLIC AND PRIVATE SECTOR DELIVERY OF BCG VACCINATION: EVIDENCE FROM SUB-SAHARAN AFRICA.

Wagner Z, Szilagyi PG, Sood N.

Vaccine. 2014 Jul 31;32(35):4522-8. Epub 2014 Jun 18.

PMID: 24951863

ABSTRACT

BACKGROUND: The private sector is an important source of health care in the developing world. However, there is limited evidence on how private providers compare to public providers, particularly for preventive services such as immunizations. We used data from Sub-Saharan Africa (SSA) to assess public–private differences in Bacillus Calmette–Guérin (BCG) vaccine delivery.

METHODS AND FINDINGS: We used demographic and health surveys from 102,629 children aged 0–59 months from 29 countries across SSA to measure differences in BCG status for children born at private versus public health facilities (BCG is recommended at birth). We used a probit model to estimate public–private differences in BCG delivery, while controlling for key confounders. Next, we estimated how differences in BCG status evolved over time for children born at private versus public facilities. Finally, we estimated heterogeneity in public–private differences based on wealth and rural–urban residency. We found that children born at a private facility were 7.1 percentage points less likely to receive BCG vaccine in the same month as birth than children born at a public facility (95% CI 6.3–8.0; $p < 0.001$). Most of this difference was driven by for-profit private providers (as opposed to NGOs) where the BCG provision rate was 10.0 percentage points less than public providers (95% CI 9.0–11.2; $p < 0.001$) compared to only 2.4 percentage points for NGOs (95% CI 1.0–3. 8; $p < 0.01$). Moreover, children born at private for-profit facilities remained less likely to be vaccinated up to 59 months after birth. Finally, public–private differences were more pronounced for poorer children and children in rural areas.

CONCLUSIONS: The for-profit private sector performed substantially worse than the public sector in providing BCG vaccine to newborns, resulting in a longer duration of vulnerability to tuberculosis. This disparity was greater for poorer children and children in rural areas.

WEB: http://dx.doi.org/10.1016/j.vaccine.2014.06.020

IMPACT FACTOR: 3.49

CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: Table 2 shows discrepancies in BCG provision by public and private providers, with private divided into for-profit and NGO categories. Figure 2 demonstrates how removing the highest wealth categories leads to a much more pronounced disparity in BCG provision, with private sector providers performing significantly worse.

3. ACHIEVING HIGH UPTAKE OF HUMAN PAPILLOMAVIRUS VACCINE IN CAMEROON: LESSONS LEARNED IN OVERCOMING CHALLENGES.

Ogembo JG, Manga S, Nulah K, Foglabenchi LH, Perlman S, Wamai RG, et al.

Vaccine. 2014 Jul 31;32(35):4399-403. Epub 2014 Jun 24.

PMID: 24968154

ABSTRACT

BACKGROUND: Cameroon has the highest age-standardized incidence rate of cervical cancer (30/100,000 women) in Central Africa. In 2010-2011, the Cameroon Baptist Convention Health Services (CBCHS) received donated human papillomavirus (HPV) vaccine, Gardasil, from Merck & Co. Inc. through Axios Healthcare Development to immunize 6400 girls aged 9-13 years. The aim was to inform the Cameroon Ministry of Health (MOH) of the acceptability, feasibility, and optimal delivery strategies for HPV vaccine.

METHODS AND FINDINGS: Following approval by the MOH, CBCHS nurses educated girls, parents, and communities about HPV, cervical cancer, and HPV vaccine through multimedia coverage, brochures, posters, and presentations. Because educators were initially reluctant to allow immunization in schools, due to fear of adverse events, the nurses performed 40.7% of vaccinations in the clinics, 34.5% in community venues, and only 24.7% in schools. When no adverse events were reported, more schools and communities permitted HPV vaccine immunization on their premises. To recover administrative costs, CBCHS charged a fee of US$8 per 3-dose series only to those who were able to pay. Despite the fee, 84.6% of the 6,851 girls who received the first dose received all three doses.

CONCLUSIONS AND LESSONS LEARNED: With adequate education of all stakeholders, HPV vaccination is acceptable and feasible in Cameroon. Following this demonstration project, in 2014 the Global Access to Vaccines and Immunization (GAVI) Alliance awarded the Cameroon MOH HPV vaccine at a price of US$4.50 per dose to immunize sixth grade girls and girls aged 10 years who are not in school in two districts of Cameroon.

WEB: http://dx.doi.org/10.1016/j.vaccine.2014.06.064

IMPACT FACTOR: 3.49

CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: A review of the challenges related to the acceptability and feasibility of a demonstration HPV vaccination program in Cameroon. Table 1 nicely summarizes the approaches used to reach the target population, addresses barriers to vaccine acceptance, and provides recommendations for implementation of future programs.

4. THE ROLE OF OLDER CHILDREN AND ADULTS IN WILD POLIOVIRUS TRANSMISSION

Blake IM, Martin R, Goel A, Khetsuriani N, Everts J, Wolff C, et al.

Proc Natl Acad Sci U S A. 2014 Jul 22;111(29):10604-9. Epub 2014 Jul 7.

PMID: 25002465

ABSTRACT

As polio eradication inches closer, the absence of poliovirus circulation in most of the world and imperfect vaccination coverage are resulting in immunity gaps and polio outbreaks affecting adults. Furthermore, imperfect, waning intestinal immunity among older children and adults permits reinfection and poliovirus shedding, prompting calls to extend the age range of vaccination campaigns even in the absence of cases in these age groups. The success of such a strategy depends on the contribution to poliovirus transmission by older ages, which has not previously been estimated. We fit a mathematical model of poliovirus transmission to time series data from two large outbreaks that affected adults (Tajikistan 2010, Republic of Congo 2010) using maximum-likelihood estimation based on iterated particle-filtering methods. In Tajikistan, the contribution of unvaccinated older children and adults to transmission was minimal despite a significant number of cases in these age groups [reproduction number, R = 0.46 (95% confidence interval, 0.42-0.52) for >5-y-olds compared to 2.18 (2.06-2.45) for 0- to 5-y-olds]. In contrast, in the Republic of Congo, the contribution of older children and adults was significant [R = 1.85 (1.83-4.00)], perhaps reflecting sanitary and socioeconomic variables favoring efficient virus transmission. In neither setting was there evidence for a significant role of imperfect intestinal immunity in the transmission of poliovirus. Bringing the immunization response to the Tajikistan outbreak forward by 2 wk would have prevented an additional 130 cases (21%), highlighting the importance of early outbreak detection and response.

WEB: http://dx.doi.org/10.1073/pnas.1323688111

IMPACT FACTOR: 9.74

CITED HALF-LIFE: 8.00

UW EDITORIAL COMMENT: Mathematical models were used to determine if unvaccinated older children contributed significantly to polio outbreaks in Tajikistan and the Republic of Congo. Figures 1 and 2 illustrate a vast difference in age of cases between these two outbreaks, suggesting a greater contribution of older children in the Republic of Congo, while delayed immunization response in Tajikistan made a greater contribution to case load based on model simulations.

5. COSTS OF INTRODUCING AND DELIVERING HPV VACCINES IN LOW AND LOWER MIDDLE INCOME COUNTRIES: INPUTS FOR GAVI POLICY ON INTRODUCTION GRANT SUPPORT TO COUNTRIES.

Levin A, Wang SA, Levin C, Tsu V, Hutubessy R.

PLoS One. 2014 Jun 26;9(6):e101114. eCollection 2014.

PMID: 24968002

ABSTRACT

BACKGROUND: In November 2011, the GAVI Alliance made the decision to add HPV vaccine as one of the new vaccines for which countries eligible for its funding (less than $1520 per capita income) could apply to receive support for national HPV vaccination, provided they could demonstrate the ability to deliver HPV vaccines. This paper describes the data and analysis shared with GAVI policymakers for this decision regarding GAVI HPV vaccine support. The paper reviews why strategies and costs for HPV vaccine delivery are different from other vaccines and what is known about the cost components from available data that originated primarily from HPV vaccine delivery costing studies in low and middle income-countries.

METHODS: Financial costs of HPV vaccine delivery were compared across three sources of data: 1) vaccine delivery costing of pilot projects in five low and lower-middle income countries; 2) cost estimates of national HPV vaccination in two low income countries; and 3) actual expenditure data from national HPV vaccine introduction in a low income country. Both costs of resources required to introduce the vaccine (or initial one-time investment, such as cold chain equipment purchases) and recurrent (ongoing costs that repeat every year) costs, such as transport and health personnel time, were analyzed. The cost per dose, cost per fully immunized girl (FIG) and cost per eligible girl were compared across studies.

RESULTS: Costs varied among pilot projects and estimates of national programs due to differences in scale and service delivery strategy. The average introduction costs per fully immunized girl ranged from $1.49 to $18.94 while recurrent costs per girl ranged from $1.00 to $15.69, with both types of costs varying by delivery strategy and country. Evaluating delivery costs along programme characteristics as well as country characteristics (population density, income/cost level, existing service delivery infrastructure) are likely the most informative and useful for anticipating costs for HPV vaccine delivery.

CONCLUSIONS: This paper demonstrates the importance of country level cost data to inform global donor policies for vaccine introduction support. Such data are also valuable for informing national decisions on HPV vaccine introduction.

WEB: http://dx.doi.org/10.1371/journal.pone.0101114

IMPACT FACTOR: 3.73

CITED HALF-LIFE: 2.40

UW EDITORIAL COMMENT: Table 4 offers a summary of average costs of existing pilot studies by country characteristic, with categories based on population density and resource infrastructure. These data are used to determine projected national scale up costs (Table 5).

6. EVIDENCE-TO-POLICY GAP ON HEPATITIS A VACCINE ADOPTION IN 6 COUNTRIES: LITERATURE VS. POLICYMAKERS' BELIEFS.

Ozawa S, Privor-Dumm LA, Nanni A, Durden E, Maiese BA, et al.

Vaccine. 2014 Jul 7;32(32):4089-96. Epub 2014 May 15.

PMID: 24837537

ABSTRACT

BACKGROUND: National vaccine adoption decisions may be better understood by linking multiple data sources. When examining countries' decisions to adopt the hepatitis A vaccine, applying multiple research methods can facilitate assessments of gaps between evidence and policy. We conducted a literature review on hepatitis A and stakeholder interviews about decisions to adopt the vaccine in six countries (Chile, India, South Korea, Mexico, Russia, and Taiwan).

METHODS: A systematic literature review was conducted across five literature databases. The review identified and abstracted 340 articles, supplemented by internet search. In addition, we interviewed 62 experts and opinion leaders on hepatitis A and/or vaccines. Data from the two sources were analyzed to identify gaps around epidemiologic data, economic data, and barriers/facilitators of hepatitis A vaccine adoption.

RESULTS: Epidemiologic data gaps were found in Chile and Russia, where stakeholders believed data to be more solid than the literature documented. Economic data on hepatitis A was found to be weak across all countries despite stakeholders' agreement on its importance. Barriers and facilitators of vaccine adoption such as political will, prioritization among vaccines, and global or local recommendations were discussed more by stakeholders than the literature. Stakeholders in India and Mexico were not concerned with the lack of data, despite growing recognition in the literature of the epidemiological transition and threat of outbreaks.

CONCLUSIONS: Triangulation of results from two methods captured a richer story behind vaccine adoption decisions for hepatitis A. The discrepancy between policymakers' beliefs and existing data suggest a decline in priority of hepatitis A or weak investment in data collection. Filling the confirmed data gaps in seroprevalence or economic data is important to help guide policy decisions. Greater communication of the risk of hepatitis A and the benefits of the vaccine may help countries undergoing the epidemiologic transition.

WEB: http://dx.doi.org/10.1016/j.vaccine.2014.05.026

IMPACT FACTOR: 3.49

CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: This qualitative comparison of information collected from literature reviews and key stakeholder interviews found discrepancies between perceived need of vaccination programs and epidemiologic evidence of hepatitis A prevalence. The results were limited by a relatively small sample size of key stakeholder interviews (63 completed of 143 contacted).

7. PERFORMANCE-BASED FINANCING WITH GAVI HEALTH SYSTEM STRENGTHENING FUNDING IN RURAL CAMBODIA: A BRIEF ASSESSMENT OF THE IMPACT.

Matsuoka S, Obara H, Nagai M, Murakami H, Chan Lon R.

Health Policy Plan. 2014 Jul;29(4):456-65. Epub 2013 Jun 3

PMID: 23735736

ABSTRACT

INTRODUCTION: Though Cambodia made impressive gains in immunization coverage between the years 2000 and 2005, it recognized several health system challenges to greater coverage of immunization and sustainability. The Global Alliance for Vaccines and Immunization (GAVI) opened a Health System Strengthening (HSS) funding window in 2006. To address the health system challenges, Cambodia has been receiving the GAVI HSS fund since October 2007. The major component of the support is performance-based financing (PBF) for maternal, neonatal and child health (MNCH) services.

OBJECTIVE: To examine the impact of the PBF scheme on MNCH services and administrative management in rural Cambodia.

METHODS: Quantitative and qualitative studies were conducted in Kroch Chhmar Operational District (OD), Cambodia. Quantitative analyses were conducted on the trends of the numbers of MNCH services. A brief analysis was conducted using qualitative data.

RESULTS: After the commencement of the PBF support, the volume of MNCH services was significantly boosted. In addition, strengthened financial and operational management was observed in the study area. However, the quality of the MNCH services was not ensured. Technical assistance, rather than the PBF scheme, was perceived by stakeholders to play a vital role in increasing the quality of the services.

DISCUSSION: To improve the quality of the health services provided, it is better to include indicators on the quality of care in the PBF scheme. Mutual co-operation between PBF models and technical assistance may ensure better service quality while boosting the quantity. A robust but feasible data validation mechanism should be in place, as a PBF could incentivize inaccurate reporting. The capacity for financial management should be strengthened in PBF recipient ODs. To address the broader aspects of MNCH, a balanced input of resources and strengthening of all six building blocks of a health system are necessary.

WEB: http://dx.doi.org/10.1093/heapol/czt030

IMPACT FACTOR: 3.06

CITED HALF-LIFE: 7.20

UW EDITORIAL COMMENT: While implementation of this program appeared to increase immunization rates for several vaccines (Table 1 and Figure 1) and boost ANC visits, concerns arose about the quality of MNCH care. Limitations of this study include lack of control site to compare against the reported increase in rates of immunization from the scheme.

8. THE ROLE OF MICRONEEDLES FOR DRUG AND VACCINE DELIVERY.

Quinn HL, Kearney MC, Courtenay AJ, McCrudden MT, Donnelly RF.

Expert Opin Drug Deliv. 2014 Jul 14:1-12. [Epub ahead of print]

PMID: 25020088

ABSTRACT

INTRODUCTION: Transdermal drug delivery offers a number of advantages for the patient, not only due to its non-invasive and convenient nature, but also due to factors such as avoidance of first-pass metabolism and prevention of gastrointestinal degradation. It has been demonstrated that microneedles (MNs) can increase the number of compounds amenable to transdermal delivery by penetrating the skin's protective barrier, the stratum corneum, and creating a pathway for drug permeation to the dermal tissue below.

AREAS COVERED: MNs have been extensively investigated for drug and vaccine delivery. The different types of MN arrays and their delivery capabilities are discussed in terms of drugs, including biopharmaceutics and vaccines. Patient usage and effects on the skin are also considered.

EXPERT OPINION: MN research and development is now at the stage where commercialisation is a viable possibility. There are a number of long-term safety questions relating to patient usage which will need to be addressed moving forward. Regulatory guidance is awaited to direct the scale-up of the manufacturing process alongside provision of clearer patient instruction for safe and effective use of MN devices.

WEB: http://dx.doi.org/10.1517/17425247.2014.938635

IMPACT FACTOR: 4.87

CITED HALF-LIFE: 3.70

UW EDITORIAL COMMENT: This review highlights many potential positive aspects of using miconeedles for vaccines, including the possibility of a more stable vaccine that does not require cold storage, and a reduced need for trained personnel and sharps storage. Phase II and III clinical trials are currently underway to test microneedles with some vaccines.

9. INTRANASAL FORMULATIONS: PROMISING STRATEGY TO DELIVER VACCINES.

Riese P, Sakthivel P, Trittel S, Guzmán CA.

Expert Opin Drug Deliv. 2014 Jun 25:1-16. [Epub ahead of print]

PMID: 24962722

ABSTRACT

INTRODUCTION: The emergence of new diseases and the lack of efficient vaccines against numerous nontreatable pathogens require the development of novel vaccination strategies. To date, only a few mucosal vaccines have been approved for humans. This was in part due to i) the use of live attenuated vaccines, which are not suitable for certain groups of individuals, ii) safety concerns derived from implementation in humans of some mucosal vaccines, iii) the poor stability, absorption and immunogenicity of antigens delivered by the mucosal route and iv) the limited number of available technologies to overcome the bottlenecks associated with mucosal antigen delivery. Recent advances make feasible the development of efficacious mucosal vaccines with adequate safety profile. Thus, currently intranasal vaccines represent an attractive and valid alternative to conventional vaccines.

AREAS COVERED: The present review is focused on the potentials and limitations of market-approved intranasal vaccines and promising candidates undergoing clinical investigations. Furthermore, emerging strategies to overcome main bottlenecks including efficient breaching of the mucosal barrier and safety concerns by implementation of new adjuvants and delivery systems are discussed.

EXPERT OPINION: The rational design of intranasal vaccines requires an in-depth understanding of the anatomic, physicochemical and barrier properties of the nasal mucosa, as well as the molecular mechanisms governing the activation of the local innate and adaptive immune system. This would provide the critical knowledge to establish effective approaches to deliver vaccine antigens across the mucosal barrier, supporting the stimulation of a long-lasting protective response at both mucosal and systemic levels. Current developments in the area of adjuvants, nanotechnologies and mucosal immunology, together with the identification of surface receptors that can be exploited for cell targeting and manipulating their physiological properties, will become instrumental for developing a new generation of more effective intranasal vaccines.

WEB: http://dx.doi.org/10.1517/17425247.2014.931936

IMPACT FACTOR: 4.87

CITED HALF-LIFE: 3.70

UW EDITORIAL COMMENT: Table 1 highlights advantages of intranasal compared to traditional vaccine delivery. Table 2 shows ongoing clinical trials using intranasal delivery.

10. TOOLS AND APPROACHES TO ENSURE QUALITY OF VACCINES THROUGHOUT THE COLD CHAIN.

Kartoglu U, Milstien J.

Expert Rev Vaccines. 2014 Jul;13(7):843-54. Epub 2014 May 28.

PMID: 24865112

ABSTRACT

The Expanded Program on Immunization was designed 40 years ago for two types of vaccines: those that are heat stable but freeze sensitive and those that are stable to freezing but heat labile. A cold chain was developed for transport and storage of such vaccines and established in all countries, despite limited access to resources and electricity in the poorest areas. However, cold chain problems occur in all countries. Recent changes to vaccines and vaccine handling include development and introduction of new vaccines with a wide range of characteristics, improvement of heat stability of several basic vaccines, observation of vaccine freezing as a real threat, development of regulatory pathways for both vaccine development and the supply chain, and emergence of new temperature monitoring devices that can pinpoint and avoid problems. With such tools, public health groups have now encouraged development of vaccines labeled for use in flexible cold chains and these tools should be considered for future systems.

WEB: http://dx.doi.org/10.1586/14760584.2014.923761

IMPACT FACTOR: 4.22

CITED HALF-LIFE: 3.60

UW EDITORIAL COMMENT: This article summarizes current technologies that can be utilized to control vaccine temperature to ensure safe storage and transportation of vaccines. Table 1 summarizes the devices currently recommended by the WHO to monitor temperature.

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 ("2014/06/15"[PDAT] : "2014/07/14"[PDAT])

*On July 24, 2014, this search of English language articles published between June 15, 2014 and July 14, 2014 and indexed by the US National Library of Medicine resulted in 168 unique manuscripts.