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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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1. Rotavirus infection and disease in a multi-site birth cohort: Results from the MAL-ED study.

Mohan VR, Ramanujam K, Babji S, McGrath M, Shrestha S, Shrestha J, Mdumah E, Amour C, Samie A, Nyathi E, Haque R, Qureshi S, Yori PP, Lima AAM, Bodhidatta L, Svensen E, Bessong P, Ahmed T, Seidman JC, Zaidi AK, Kosek MN, Guerrant RL, Gratz J, Platts-Mills JA, Lang DR, Gottlieb M, Houpt ER, Kang G; MAL-ED Network Investigators.
J Infect Dis. 2017 May 3.
PMID: 28472348

ABSTRACT

BACKGROUND: In a multi-country birth cohort study, we describe rotavirus infection in the first two years of life in sites with and without rotavirus vaccination programs.
METHODS: Children were recruited by 17 days of age and followed to 24 months with collection of monthly surveillance and diarrheal stools. Data on socio-demographics, feeding and illness were collected at defined intervals. Stools were tested for rotavirus and sera for anti-rotavirus immunoglobulins by enzyme immunoassays.
RESULTS: A total of 1,737 children contributed 22,646 surveillance and 7,440 diarrheal specimens. Overall, rotavirus was detected in 5.5% (408/7440) of diarrheal stools, and 344 (19.8%) children ever had rotavirus gastroenteritis. Household overcrowding and a high pathogen load were consistent risk factors for infection and disease. Three prior infections conferred 74% (P<0.001) protection against subsequent infection in sites not using vaccine. In Peru, incidence of rotavirus disease was relatively higher during second year of life despite high vaccination coverage.
CONCLUSIONS: Rotavirus infection and disease was common, but with significant heterogeneity by site. Protection by vaccination may not be sustained in the second year of life in settings with high burdens of transmission and poor response to oral vaccines.

WEB: https://dx.doi.org/10.1093/infdis/jix199. [Epub ahead of print]
IMPACT FACTOR: 6.34
CITED HALF-LIFE: 8.60
START SCIENTIFIC COMMENT: Investigators define diarrheal episodes as having ≥3 loose stools in a 24-hour period with at least 48 hours between episodes. Severity was assessed using a modified 17-point Vesikari score with participants divided into mild (1-4); moderate (5-8); severe (9-13); and very severe (14-17) categories. The investigators also used the 15-point CODA scoring system designed for community-based studies. The CODA system includes fever, anorexia; vomiting, frequency and duration of loose stools episodes are categorized as mild (0); moderate (1-6); or severe (7+). Stool was collected monthly during the first 12-months of life, then quarterly thereafter with additional collection during any diarrheal episode over 24-months. Rotavirus testing was preformed using ProSpecT EIA. If diarrheal specimens tested positive for rotavirus a child was recorded as having had an infection, positive results were void if stools were collected within 28 days of receiving the vaccine. Serum was collected at months 7 and 15 and prior rotavirus exposure was defined by the presence of IgA or IgG antibodies >20 U/ml. In their analysis investigators used multi-level, site- and age-adjusted Poisson regression models with random effects to account for within-site and within-child correlations. Investigators also used generalized estimating equations to obtain age adjusted incident rate ratios for associations between rotavirus infections, diarrhea, and other exposures. The investigators also performed survival analysis to estimate the time to first rotavirus infection at each site using Kaplan-Meier and Cox proportional hazards models to determine the hazard of rotavirus infection and diarrhea with subsequent rotavirus infection. Investigators note that across all sites the severity of rotavirus diarrhea (median, IQR, 4, 3-6) was higher than non-rotavirus diarrhea (median, IQR, 3, 2-5) ($p < 0.001$). Six percent of rotavirus episodes required hospitalization and the median severity score for hospitalized patients was 6 (IQR 5-8). Median duration of rotavirus was 4 days (IQR 1-35). Vomiting was observed in 54% of all episodes, fever occurred in 5.4%, and bloody stools were recorded in 1.9% of episodes. Serological analysis demonstrates over 80% of children at all sites were exposed to rotavirus, however rotavirus infection and disease were detected at lower rates than previously documented in the literature. Investigators suggest the exclusion of children with positive results collected within 28 days of vaccination may have underestimated the true incidence of rotavirus infections detected in stool.

2. Vaccine vial stopper performance for fractional dose delivery of vaccines.

Jarrahian C, Myers D, Creelman B, Saxon E, Zehrung D.
Hum Vaccin Immunother. 2017 May 2:1-3.
PMID: 28463054

ABSTRACT

Shortages of vaccines such as inactivated poliovirus and yellow fever vaccines have been addressed by administering reduced-or fractional-doses, as recommended by the World Health Organization Strategic Advisory Group of Experts on Immunization, to expand population coverage in countries at risk. We evaluated 3 kinds of vaccine vial stoppers to assess their performance after increased piercing from repeated withdrawal of doses needed when using fractional doses (0.1 mL) from presentations intended for full-dose (0.5 mL) delivery. Self-sealing capacity and fragmentation of the stopper were assessed via modified versions of international standard protocols. All stoppers maintained self-sealing capacity after 100 punctures. The damage to stoppers measured as the fragmentation rate was within the target of ≤ 10% of punctures resulting in a fragment after as many as 50 punctures. We concluded that stopper failure is not likely to be a concern if existing vaccine vials containing up to 10 regular doses are used up to 50 times for fractional dose delivery.

WEB: https://dx.doi.org/10.1080/21645515.2017.1301336. [Epub ahead of print]
IMPACT FACTOR: 2.15
CITED HALF-LIFE: 2.30
START SCIENTIFIC COMMENT: Stopper performance varies by materials and needle gauge. To date, radioopharmaceuticals have demonstrated exceptional efficacy and can withstand upwards of 100 punctures before being compromised, however USP, ISO, and European Pharmacopoeia standards require testing of only up to 10 puntures per stopper for vaccines. The study assesses the performance of three WHO-Prequalified stoppers under high-frequency piercing conditions using 27 gauge half-inch needles to simulate IPV and YFV fractional dose delivery. Stoppers include: 1) 3 mm bromobutyl stopper 2) 20 mm chlorobutyl stopper and 3) 20 mm bromobutyl stopper. Each stopper was pierced 10 times before being checked for self-sealing, removing failed stoppers at each interval. The process was repeated until each stopper had been punctured 100 times though authors note they are unable to avoid repeated punctures to the same site. To assess stopper fragmentation upon piercing, vials were modified to allow their contents to be flushed, filtered and reused without removing the stopper. Vials for 12 stoppers were pierced at 10 puncture intervals and the rinsate evaluated for particulates; this was repeated until the stopper was pierced a total of 80 times or until the fragmentation rate exceeded the USP benchmark of 10%. If any particles were detected these fragments were placed under a microscope to verify if they were stopper fragments or some other particle according to their size shape and color. Authors note that the clinical significance of stopper fragmentation is unknown. Authors do not distinguish between the presences of vial stopper cores, typically long and narrow in shape, and fragments, which are irregular. They also do not account for how other piercing techniques, namely speed and angle, may impact fragmentation rates.

3. Economic impact of thermostable vaccines.

Lee BY, Wedlock PT, Haidari LA, Elder K, Potet J, Manring R, Connor DL, Spiker ML, Bonner K, Rangarajan A, Hunyh D, Brown ST.
Vaccine. 2017 May 25;35(23):3135-3142.
PMID: 28455169

ABSTRACT

BACKGROUND: While our previous work has shown that replacing existing vaccines with thermostable vaccines can relieve bottlenecks in vaccine supply chains and thus increase vaccine availability, the question remains whether this benefit would outweigh the additional cost of thermostable formulations.
METHODS: Using HERMES simulation models of the vaccine supply chains for the Republic of Benin, the state of Bihar (India), and Niger, we simulated replacing different existing vaccines with thermostable formulations and determined the resulting clinical and economic impact. Costs measured included the costs of vaccines, logistics, and disease outcomes averted.
RESULTS: Replacing a particular vaccine with a thermostable version yielded cost savings in many cases even when charging a price premium (two or three times the current vaccine price). For example, replacing the current pentavalent vaccine with a thermostable version without increasing the vaccine price saved from $366 to $10,945 per 100 members of the vaccine's target population. Doubling the vaccine price still resulted in cost savings that ranged from $300 to $10,706, and tripling the vaccine price resulted in cost savings from $234 to $10,468. As another example, a thermostable rotavirus vaccine (RV) at its current (year) price saved between $131 and $1065. Doubling and tripling the thermostable rotavirus price resulted in cost savings ranging from $102 to $936 and $73 to $808, respectively. Switching to thermostable formulations was highly cost-effective or cost-effective in most scenarios explored.
CONCLUSION: Medical cost and productivity savings could outweigh even significant price premiums charged for thermostable formulations of vaccines, providing support for their use.

WEB: https://dx.doi.org/10.1016/j.vaccine.2017.03.081. Epub 2017 Apr 25.
IMPACT FACTOR: 3.41
CITED HALF-LIFE: 5.90
START SCIENTIFIC COMMENT: Investigators use the previously developed Highly Extensible Resource for Modeling Event-Driven Supply Chains (HERMES) software to build and process discrete-event simulation models of the EPI and UIP supply chains for a year in three different country settings. The baseline formula for all vaccines utilized current dose per vial, package volume, and temperature requirements to preserve efficacy for each vaccine. The included thermostable vaccines were all given the same self-life, dose per vial and package volume and the temperature sensitive alternative. Logistics costs of labor, storage, transport, and buildings were allowed to accrue over time and total procurement costs remained fixed. Thermostable vaccines were bounded at 300% the cost of current temperature sensitive alternative. When a vaccine was made thermostable the model determined the number of vaccine-preventable infections (VPI) averted. The direct medical cost saved per infection, DALYS averted per infection, and productivity losses per capita were each multiplied by the VIP averted to calculate their respective national total in each setting. The model illustrates decreases in medical costs and productivity losses improve vaccine coverage resulting in a greater reduction in disease burden. Thermostable vaccines may help to reduce wastage and avert logistic costs associated with ensuring proper transport and storage. However, critics have argued the advantages of thermostable vaccines cannot be generalized to the supply chain *writ large* because the majority of vaccines still require uninterrupted cold chains to preserve their efficacy. While thermostable vaccines cannot eliminate cold chain maintenance costs they would afford a space for the inclusion of additional temperature stable vaccines or supplies. The authors argue the resulting cost savings or improvements to population health by such an opportunity could be indirectly attributed to the thermostable vaccine. Moreover, even if bottlenecks were reduced, the costs associated with attempting to meet the increase in demand would temporarily drive costs up. The authors argue that overtime a long-term reduction in disease burden coupled with supply chain savings counteract initial costs and the net effect is a reduction in overall costs.

4. Exploring new packaging and delivery options for the immunization supply chain.

Zehrung D, Jarrahian C, Giersing B, Kristensen D.
Vaccine. 2017 Apr 19;35(17):2265-2271.
PMID: 28364941

ABSTRACT

A variety of vaccine packaging and delivery technologies may benefit the immunization supply chain. These include alternative primary packaging, such as blow-fill-seal polymer containers, and novel delivery technologies, such intradermal delivery devices, microarray patches, and sublingual formulations of vaccines, and others in development. The potential timeline to availability of these technologies varies and depends on their stage of development and the type of data necessary to achieve licensure. Some new delivery devices are anticipated to be introduced in 2017, such as intradermal devices for delivery of inactivated poliovirus vaccine to stretch vaccine supplies due to a supply limitation. Other new technologies requiring vaccine reformulation, such as microarray patches and sublingual vaccines, may become available in the long term (2021 and beyond). Development of many new technologies requires partnership between vaccine and technology manufacturers and identification of the applicable regulatory pathway. Interaction with public-sector stakeholders early on (through engagement with forums such as the World Health Organization's Immunization Practices Advisory Committee Delivery Technologies Working Group) is important to ensure suitability for immunization program use. Key considerations for programmatic suitability of a new vaccine, packaging, and delivery device include cold chain volume, costs, and health impact.

WEB: https://dx.doi.org/10.1016/j.vaccine.2016.11.095
IMPACT FACTOR: 3.41
CITED HALF-LIFE: 5.90
START SCIENTIFIC COMMENT: Blow-fill-seal (BFS) technology consolidates each manufacturing step in vaccine vial/ampoule assembly into a single continuous automated process. The process reduces the potential for contamination and product loss, and customizable polymer resin models facilitate efficient packaging for a variety of vaccine products, doses, and delivery routes (e.g BFS squeeze tubes containing orally or intranasal delivered vaccine). Intradermal (ID) delivery devices target antigen-processing cells abundant in the dermis. Enhanced immunogenicity makes ID vaccination attractive for dose-sparing delivery techniques. However, ID vaccines must be delivered at a 5-15 degree angle, and several novel devices have been developed to simplify and standardize injection. These include adaptors for conventional needles, hollow microneedle hubs for syringes, mini-needle syringes and needle-free disposable syringe jet injectors. Adapting to these novel delivery devices requires no reformulation and provides substantial cost-savings, and has hence been integrated into routine immunization schedules in India and Sri Lanka. Microarray patches (MAP) are an adaptation of ID delivery that requires vaccine reformulation. Dry formulations of vaccine antigen are coated on an array of solid micro-projections or molded into a dissolving array and applied to the skin. MAP are in early stage of preclinical development (IPV, measles, rotavirus, HPV, PCV) or clinical testing (influenza), and clinical efficacy and large scale cost of production has not been established. Not all MAP formulations are thermostable and application devices present challenges for cold storage. Sublingual vaccines (SV) enhance mucosal immunity against gastrointestinal pathogens by eliciting high levels of both IgA and IgG antibodies, and additionally avert degradation by gastric acid. SV can be delivered in liquid drops and sprays, and fast-dissolving thin films or tablet form. SV are in use for polio, typhoid and cholera. Preclinical studies have demonstrated immunogenicity for prophylactic treatment/therapies in HPV, IPV, HIV, and influenza. The flow of saliva can determine the duration of exposure for some forms and may require reformulations in some settings. SV require administration with an adjuvant since subunit and inactivated vaccines are poorly immunogenic. Timelines are projected for several of these products: BFS containers for oral rotavirus and intradermal delivery devices were made available or are scheduled to be available for use in immunization programs in 2016-2017. BFS containers for parenteral vaccines are estimated to be available in 2018-2020. MAP and sublingual gel, film, or fast-dissolving formulations are projected to become available in 2021-2025+.

5. Innovations in cold chain equipment for immunization supply chains.

Robertson J, Franzel L, Maire D.
Vaccine. 2017 Apr 19;35(17):2252-2259.
PMID: 28364939

ABSTRACT

BACKGROUND: Since 2010, numerous new technologies have entered the immunization cold chain equipment market. The World Health Organization (WHO) Immunization Devices Programme-Performance, Quality and Safety (PQS)-has played a key role in bringing these to market. In this article, the authors explore the emergence of new cold chain equipment technologies from 2004 to 2016 and the role of PQS in this evolution.
METHODS: This review focuses on three major vaccine cold chain technology innovations-solar direct-drive refrigerators, long-term passive cold boxes, and equipment with user-independent freeze prevention. For the review, we used online data from WHO PQS, a literature search, and unpublished research reports.
RESULTS: Timelines with key milestones in the emergence of the three focus technologies show delays of between one and three years between earliest field trials and publication of WHO specifications; procurement builds after the WHO prequalification of initial devices.
DISCUSSION: The timelines show the role of PQS as both gatekeeper and enabler for cold chain equipment technologies. The use of target product profiles by PQS has increased its ability to signal preferred attributes and to engage with manufacturers during the product-development stage. Procurement data show how demand for solar direct-drive refrigerators increased over time. Gavi, the Vaccine Alliance, is employing demand-generation strategies to try to drive procurement of technologies with favorable technical attributes.
CONCLUSIONS:

- PQS plays an important role in early product development.
- Target product profiles have proven to be a successful way to communicate desired attributes and focus developer research.
- Field evaluations provide PQS with invaluable data to help refine specifications in line with actual performance in immunization settings.
- Establishing more systematic post-market surveillance systems for cold chain equipment after large-scale deployment could have positive effects.
- Efforts to communicate to countries and other immunization stakeholders about new technologies is needed to accelerate their uptake.

WEB: https://dx.doi.org/10.1016/j.vaccine.2016.11.094
IMPACT FACTOR: 3.41
CITED HALF-LIFE: 5.90
START SCIENTIFIC COMMENT: Active refrigeration systems use electric, battery, or fuel powered temperature controls and passive refrigeration systems use coolant packs and low thermal conductive materials. Active systems include main and off-grid refrigerators. Off-grid refrigerators can be further subdivided into absorption refrigerators (powered by propane, butane, or kerosene or petroleum) or solar powered refrigerators, which use electric compressors powered directly from solar panels (solar direct drive (SDD)) or solar powered batteries. Long-holdover cold boxes extend the cold life of vaccine product from 6-7 to 30 days, which makes them candidates for long term stationary storage provided coolants are able to be recycled without significant logistical barriers. Finally, equipment with user-independent freeze prevention (UIFP) addresses inadvertent exposure to freezing air temperatures. In 2015 PQS published draft specifications for passive systems with freeze-prevention features and a grading system for UIFP. Grade A devices provide protection without any intervention from the user, mitigating the risk of freezing due to noncompliance. Figures 1-3 illustrate a market emergence timeline for SDD, long-term passive cold boxes, and UIFP technologies, key milestones, and UNICEF procurement dates ending in 2016. Building demand requires time, communication, and a more responsive market. International partners collecting feedback on device performance from in-country partners can guide manufactures in developing technologies that address current demands. Fig. 4 illustrates the gradual supplantation of absorption and battery

powered systems by SDDs may have been triggered by UNICEF procurement in 2010, until reaching an inflection point in 2013 and where procurement rates grew exponentially thereafter.

6. Assessing stability and performance of a digitally enabled supply chain: Retrospective of a pilot in Uttar Pradesh, India.

Gilbert SS, Thakare N, Ramanujapuram A, Akkihal A.
Vaccine. 2017 Apr 19;35(17):2203-2208.
PMID: 28364932

ABSTRACT

BACKGROUND: Immunization supply chains in low resource settings do not always reach children with necessary vaccines. Digital information systems can enable real time visibility of inventory and improve vaccine availability. In 2014, a digital, mobile/web-based information system was implemented in two districts of Uttar Pradesh, India. This retrospective investigates improvements and stabilization of supply chain performance following introduction of the digital information system.
METHODS: All data were collected via the digital information system between March 2014 and September 2015. Data included metadata and transaction logs providing information about users, facilities, and vaccines. Metrics evaluated include adoption (system access, timeliness and completeness), data quality (error rates), and performance (stock availability on immunization session days, replenishment response duration, rate of zero stock events). Stability was defined as the phase in which quality and performance metrics achieved equilibrium rates with minimal volatility. The analysis compared performance across different facilities and vaccines.
RESULTS: Adoption appeared sufficiently high from the onset to commence stability measures of data quality and supply chain performance. Data quality stabilized from month 3 onwards, and supply chain performance stabilized from month 13 onwards. For data quality, error rates reduced by two thirds post stabilization. Although vaccine availability remained high throughout the pilot, the three lowest-performing facilities improved from 91.05% pre-stability to 98.70% post-stability ($p<0.01$; t-test). Average replenishment duration (as a corrective response to stock-out events) decreased 52.3% from 4.93days to 2.35days ($p<0.01$; t-test). Diphtheria-tetanus-pertussis vaccine was significantly less likely to be stocked out than any other material.
CONCLUSION: The results suggest that given sufficient adoption, stability is sequentially achieved, beginning with data quality, and then performance. Identifying when a pilot stabilizes can enable more predictable, reliable cost estimates, and outcome forecasts in the scale-up phase.

WEB: https://dx.doi.org/10.1016/j.vaccine.2016.11.101
IMPACT FACTOR: 3.41
CITED HALF-LIFE: 5.90
START SCIENTIFIC COMMENT: Digitization of the logistics management information system (LMIS) affords standardized data collection, system-wide transmission, quality control, and automated reporting. However user uptake may be mired by low technical literacy and a perception that increased connectivity may increase workloads and accountability. Prior to the pilot, vaccine replenishment in Uttar Pradesh and across India was fractured and disorganized and formalized operating procedures were rarely enforced. Non-uniform paper based registries developed by users tracked inventory balance, consumption and wastage. The cumulative impact of these factors resulted in a reactionary supply chain system. To standardize data collection investigators streamlined paper forms to allow users to tabulate stock utilization for a given session and generate outputs, which could be recorded in the new system. The second intervention enabled up-to-date inventory tracking using the digital LMIS. The third intervention instituted Vaccine Logistics & Cold Chain Managers (VCCMs), individuals who would be accountable for managing stock across facilitates and overseeing cold chain process. Health workers at cold chain-equipped facilities received a one-day training to familiarize Cold Chain Handlers (CHH) with the new standard paper forms, basic features of the mobile phone they would use to report aggregate data into the LMIS, in addition to reviewing standard operating procedures for future reference. Due to the lack of any control districts and unreliable baseline data in two districts, investigators were unable to compare the relative effectiveness of the program compared to districts that did not receive the interventions. The study design prevents investigators for being able to assess the impact of the people, product and process interventions, as all were implemented together. Quality metrics only reflect known errors since the system could not identify incorrect entries if they were input correctly. Authors also note lower performing districts may underestimate the potential impact of a scaled intervention.

7. Vaccine stockouts around the world: Are essential vaccines always available when needed?

Lydon P, Schreiber B, Gasca A, Dumolard L, Urfer D, Senouci K.
Vaccine. 2017 Apr 19;35(17):2121-2126.
PMID: 28364919

ABSTRACT

INTRODUCTION: As countries rise to the challenge of implementing the priorities of this "Decade of Vaccine" and their commitments delineated in the Global Vaccine Action Plan (GVAP), many continue to face important challenges of securing a continuous supply of essential vaccine for their national immunization programme. This study provides evidence on the incidence of vaccine stockouts in countries, their root causes and their potential impact on service delivery.
METHODS: Vaccine stockout indicators collected from the WHO-UNICEF Joint Reporting Form (JRF) and UNICEF's Vaccine Forecasting Tool were analysed for the years covering the first half of the GVAP (2011 to 2015) and using 2010 as the baseline year. While the JRF collects annual information on national and subnational stockouts by vaccine, the UNICEF Vaccine Forecasting Tool has the advantage of requesting UNICEF procuring countries to report on the reasons underpinning any stockouts.
RESULTS: Every year on average, one in every three WHO Member States experiences at least one stockout of at least one vaccine for at least one month. The incidence is most pronounced in Sub-Saharan Africa where 38% of countries in this area of the world report national-level stockouts. The vaccines most affected are DTP containing vaccines (often combined with HepB and Hib) and BCG. They account for respectively 43% and 31% of stockout events reported. While national level vaccine stockouts occur in countries of all income groups, middle-income countries are the most affected. In 80% of cases, national level stockouts were due to reasons internal to countries. More specifically, 39% of stockouts were attributable to government funding delays, 23% were caused by delays in the procurement processes, and poor forecasting and stock management at country level accounted for an additional 18%. When a national level stockout of vaccines occurs, there is an 89% chance that a subnational stockout will occur at district level. More concerning is that if a district level stockout occurs, this will lead to an interruption of vaccination services in 96% of cases.
DISCUSSION: There continues to be important challenges of ensuring a continuous availability of essential vaccines. The global community, together with countries, urgently need to design effective interventions aimed at reducing the frequency and mitigating the impact of stockouts.

WEB: https://dx.doi.org/10.1016/j.vaccine.2016.12.071
IMPACT FACTOR: 3.41
CITED HALF-LIFE: 5.90
START SCIENTIFIC COMMENT: Incidence and duration of vaccine stock-outs serve as proxy indicators of the stability of vaccine supply chains and can identify systems at risk of falling short of national immunization targets. Stockouts are defined as the total number of stockout events so repeated stockouts of the same vaccine and one-time stockouts of multiple vaccines are counted in the same manner. WHO recommends countries maintain a 3 month buffer stock of vaccines in case of interruptions to the supply chain. Full vaccine stockouts are considered to occur after a minimum of 30 days, suggesting the buffer stock were likely exhausted. Stockouts occurring for less than 30 days are excluded from the analysis. To facilitate cross-country comparisons only stockouts for BCG, DTP, polio and measles vaccines were included in the analysis as these vaccines are provided in all 194 member states. The authors then compared aggregate data across WHO regional groups and income. To improve reporting completeness, investigators performed validation checks for all indicators in each country screening for inconsistent response patterns and response agreement across the JRF and Vaccine Forecasting Tool. Investigators also retrofitted data to correct for countries reporting a single antigen for multivalent vaccines. Approximately 25-30 countries with missing data were contacted to verify if and why stockouts occurred. Each country responding to WHO requests reported no stockouts had occurred and investigators assumed this was true for the remaining non-responsive countries with missing data. Root causes identified by investigators included delays resulting from: 1)

Inadequate financing, 2) Inaccurate forecasting and poor stock management, 3) Procurement delays, 4) Insufficient product availability on the global market, 5) Vaccines removed due to quality concerns, 6) All other causes.

8. Vaccine vial monitor availability and use in low- and middle-income countries: A systematic review.

Eriksson P, Gessner BD, Jaillard P, Morgan C, Le Gargasson JB.
Vaccine. 2017 Apr 19;35(17):2155-2161.
PMID: 28364924

ABSTRACT

INTRODUCTION: The vaccine vial monitor (VVM) registers cumulative heat exposure on vaccines over time. As low- and lower-middle-income countries transition beyond support from the Global Alliance for Vaccines and Immunization (Gavi), they will assume full responsibility for vaccine financing and procurement. It is unclear to what extent countries transitioning out of Gavi support will continue to include VVMs on their vaccines. This paper aims to systematically review evidence on VVM availability and use in low- and middle-income countries to document factors behind global access to and country demand for VVMs. Such results could help identify actions needed to ensure continued use of VVMs in countries that transition out of Gavi support.
METHODS: We performed a systematic review of electronic databases, reference lists, and grey literature in English and French languages with publication dates from 2005 onwards. The studies included were analyzed for the following outcomes: (1) availability and deployment of VVM-labeled vaccines; (2) VVM practices and perceptions in the immunization system; (3) vaccine introduction and decision-making processes; (4) Gavi graduation and vaccine program sustainability.
RESULTS: The study found that VVM availability and use was affected by multiple sourcing of vaccines and the extent to which VVM was included in the vaccine specification in the tendering documents when procuring vaccines. Knowledge about VVM and its impact on the EPI program was found to be high among health workers as well as decision-makers. However, the study also found that weak capacity in key national institutions such as NRA and NPA might impact on demand for VVM. As countries take decisions regarding the adoption of new vaccines, factors such as disease burden and vaccine price may assume greater importance than vaccine characteristics and presentation. Finally, the study found that countries rely largely on the advice and recommendations from technical partners such as WHO and PAHO.

WEB: https://dx.doi.org/10.1016/j.vaccine.2016.11.102
IMPACT FACTOR: 3.41
CITED HALF-LIFE: 5.90
START SCIENTIFIC COMMENT: The rapid expansion of EPI programs in some Gavi supported LMICs has outpaced the growth of some national health systems and the impact of this stress comes to bear most prominently on supply chain systems. VVMs provide cold chain monitoring and are critical to ensuring the integrity of the product once vaccines are delivered from the final distribution point to communities. Authors note that each of the small number of studies to date that have examined the challenges and performance of countries transitioning out of GAVI cite institutional weaknesses related to procurement, financing, and management of EPI programs. Studies collecting data at the global, national and sub-national level and implemented methodologies included analyses of program records, key informant interviews, focus group discussions, and literature reviews. The majority of studies were geographically focused on Gavi –eligible and low-income countries, though no studies were conducted on countries in the WHO AMRO region. Studies assessing VVM availability and deployment noted accessing vaccines through UN procurement channels did not preclude the acquisition of vaccines missing VMM. Several studies reported VVM utilization practices and misconceptions were impacted by adequacy of training and tended to decline at lower levels of service delivery. Studies reported that decisions to introduce new vaccines were driven by price and disease burden but a study conducted by Burchett et al. (2012) noted considerations regarding the feasibility and compatibility with current cold-chain capacity did arise if vaccines were previously introduced. This may suggest that as countries become acquainted with new vaccines those challenges provide insights into programmatic limitations that may then be applied to future procurement decisions. Authors note that as countries transition out of Gavi support financial constraints prevent the addition of new vaccines to the existing vaccine schedule. Moreover, a lack of knowledge regarding availability of different vaccine formulations may limit the ability of procurers to select the products that are most suitable for their supply chain system.

9. Cost-Effectiveness of Dengue Vaccination Programs in Brazil.

Shim E.
Am J Trop Med Hyg. 2017 May;96(5):1227-1234.
PMID: 28500811

ABSTRACT

The first approved dengue vaccine, CYD-TDV, a chimeric, live-attenuated, tetravalent dengue virus vaccine, was recently licensed in 13 countries, including Brazil. In light of recent vaccine approval, we modeled the cost-effectiveness of potential vaccination policies mathematically based on data from recent vaccine efficacy trials that indicated that vaccine efficacy was lower in seronegative individuals than in seropositive individuals. In our analysis, we investigated several vaccination programs, including routine vaccination, with various vaccine coverage levels and those with and without large catch-up campaigns. As it is unclear whether the vaccine protects against infection or just against disease, our model incorporated both direct and indirect effects of vaccination. We found that in the presence of vaccine-induced indirect protection, the cost-effectiveness of dengue vaccination decreased with increasing vaccine coverage levels because the marginal returns of herd immunity decreases with vaccine coverage. All routine dengue vaccination programs that we considered were cost-effective, reducing dengue incidence significantly. Specifically, a routine dengue vaccination of 9-year-olds would be cost-effective when the cost of vaccination per individual is less than $262. Furthermore, the combination of routine vaccination and large catch-up campaigns resulted in a greater reduction of dengue burden (by up to 93%) than routine vaccination alone, making it a cost-effective intervention as long as the cost per course of vaccination is $255 or less. Our results show that dengue vaccination would be cost-effective in Brazil even with a relatively low vaccine efficacy in seronegative individuals.

WEB: https://dx.doi.org/10.4269/ajtmh.16-0810
IMPACT FACTOR: 2.45
CITED HALF-LIFE: 9.90
START SCIENTIFIC COMMENT: Dengvaxia is a live-attenuated tetravalent chimeric yellow-fever dengue virus vaccine (CYD-TDV) recently licensed for use in 13 countries across the Americas and Southeast Asia. In 2014 a large phase III trial conducted in Latin America cited the overall vaccine efficacy against virologically confirmed dengue cases was 64.7% (95% CI: 58.7%, 69.8%). Vaccine efficacy was shown to vary according to dengue serostatus, with higher efficacy in seronegatives (52%; 95% CI = 5.9%, 76.1%) compared to seropostives (81.9%; 95% CI: 67.2%, 90.0%). Previous research predicted dengue vaccination in Brazil would be cost-effective at $200. An age-structured model of transmission and vaccination was fitted to dengue incidence data. The authors estimated the economic and epidemiological impact of dengue in Brazil, varying vaccine costs with and without catch-up vaccination to examine the cost effectiveness of vaccination. Findings from the phase III trial indicated prior dengue infection increased vaccine efficacy and this effect was incorporated into the model. CYD-TDV is approved for use in individuals aged 9-45 yrs, and the authors modeled routine vaccination of children aged 9, with 1 year catch-up campaigns targeting ages 10-18, 10-25, 10-35, and 10-45. Authors assumed 70% coverage in children aged 9 and 50% coverage among age groups in the catch-up campaigns.

Brazilian guidelines do not specify a threshold for a cost effect intervention so authors elected to use a threshold derived from the WHO Commission on Macroeconomics and Health. Willingness to pay (WTP) for one DALY saved was assumed to be equivalent to the WTP for one QALY. Interventions that gained one additional QALY for less than $25,620 were deemed cost effective, and less than $8,540 for two additional QALYs were deemed very cost effective. Vaccine efficacy was lower in younger individuals since they were more likely to be seronegative. Despite lower efficacy in younger ages authors reported routine vaccination of 70% of 9-year-olds would reduce the incidence of dengue infection by 79% and would be cost-effective across a age of values (See Fig. 5 and 6). Country- and serotype-specific trial data are not available which prevented the authors from creating serotype-specific efficacy parameters. Other limitations cited by the authors include the inability to distinguish whether vaccination protects against infection or disease since only cases with clinical manifestations were recorded.

10. Cost-effectiveness of human papillomavirus vaccination for adolescent girls in Punjab state: Implications for India's universal immunization program

Prinja S, Bahuguna P, Faujdar DS, Jyani G, Srinivasan R, Ghoshal S, Suri V, Singh MP, Kumar R.
Cancer. 2017 May 4.
PMID: 28472550

ABSTRACT

BACKGROUND: Introduction of human papillomavirus (HPV) vaccination for adolescent girls is being considered in the Punjab state of India. However, evidence regarding cost-effectiveness is sought by policy makers when making this decision. The current study was undertaken to evaluate the incremental cost per quality-adjusted life-years (QALYs) gained with introduction of the HPV vaccine compared with a no-vaccination scenario.
METHODS: A static progression model, using a combination of decision tree and Markov models, was populated using epidemiological, cost, coverage, and effectiveness data to determine the cost-effectiveness of HPV vaccination. Using a societal perspective, lifetime costs and consequences (in terms of QALYs) among a cohort of 11-year-old adolescent girls in Punjab state were modeled in 2 alternate scenarios with and without vaccination. All costs and consequences were discounted at a rate of 3%.
RESULTS: Although immunizing 1 year's cohort of 11-year-old girls in Punjab state costs Indian National Rupees (INR) 135 million (US dollars [USD] 2.08 million and International dollars [Int$] 6.25 million) on an absolute basis, its net cost after accounting for treatment savings is INR 38 million (USD 0.58 million and Int$ 1.76 million). Incremental cost per QALY gained for HPV vaccination was found to be INR 73 (USD 1.12 and Int$ 3.38). Given all the data uncertainties, there is a 90% probability for the vaccination strategy to be cost-effective in Punjab state at a willingness-to-pay threshold of INR 10,000, which is less than one-tenth of the per capita gross domestic product.
CONCLUSIONS: HPV vaccination appears to be a very cost-effective strategy for Punjab state, and is likely to be cost-effective for other Indian states.

WEB: https://dx.doi.org/10.1002/cncr.30734. [Epub ahead of print]
IMPACT FACTOR: 5.65
CITED HALF-LIFE: >10
START SCIENTIFIC COMMENT: The authors chose to use a static progression model to determine the cost effectiveness of HPV immunization in adolescent girls. The decision model was used to estimate the number of cervical cancer cases due to HPV-16 and HPV 18. Authors developed a Markov model to model the life course of individuals who developed cervical cancer. Data from previous research reporting stage-wise progression-free survival and the probability of dying of cervical cancer informed the computation of transition between stages. In choosing to use a static progression model the authors implicitly assume a constant probability of disease exposure. The authors assert that because they are modeling the direct effect of HPV vaccination in girls, it is not necessary to consider dynamic models that would address indirect effects such as herd immunity.
The model estimates that without intervention, 1140 cases of cervical cancer due to HPV-16 and HPV 18 occur in Punjab among a cohort of girls over the course of their lifetime. Overall the lifetime risk of developing cervical cancer in this cohort is 0.54%. Table 2 highlights outcomes and cost-effectiveness of HPV vaccination assuming a lifetime study horizon. HPV Vaccination resulted in a total reduction in morbidity and mortality of 18,477 life-years and 20,999 QALYs. A probabilistic sensitivity analysis estimated HPV vaccination has a 90% probability of cost-effectiveness at a willingness to pay threshold of less than one-tenth of India's per capita GDP.

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]) ("2016/12/15"[PDAT] : "2017/1/14"[PDAT]))

* On May 17, 2017, this search of English language articles published between March 15, 2016 and April 14, 2017 and indexed by the US National Library of Medicine resulted in 237 unique manuscripts.