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REPORT TO THE BILL & MELINDA GATES FOUNDATION

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PRODUCED BY: KIDANE L.; SLYKER, J.



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- Investigators conduct population-based surveillance and case-control studies in children aged 2–59 months (minimum age 3 months in the case-control study) to measure the impact of the vaccines on pneumonia incidence.

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1. Vaccines are different: A systematic review of budget impact analyses of vaccines

Loze PM, Nasciben LB, Sartori AMC, Itria A, Novaes HMD, de Soárez PC.

Vaccine 2017 May 15;35 (21):2781-2793.. Epub 2017 Apr 17.

PMID: 28427846

ABSTRACT

INTRODUCTION: Several countries require manufacturers to present a budget impact analysis (BIA), together with a cost-effectiveness analysis, to support national funding requests. However, guidelines for conducting BIA of vaccines are scarce.

OBJECTIVES: To analyze the methodological approaches used in published budget impact analysis (BIA) of vaccines, discussing specific methodological issues related to vaccines.

MATERIAL AND METHODS: This systematic review of the literature on BIA of vaccines was carried out in accordance with the Centre for Reviews and Dissemination – CRD guidelines. We searched multiple databases: MedLine, Embase, Biblioteca Virtual de Saúde (BVS), Cochrane Library, DARE Database, NHS Economic Evaluation Database (NHS EED), HTA Database (via Centre for Reviews and Dissemination - CRD), and grey literature. Two researchers, working independently, selected the studies and extracted the data. The methodology quality of individual studies was assessed using the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. A qualitative narrative synthesis was conducted.

RESULTS: Twenty-two studies were reviewed. The most frequently evaluated vaccines were pneumococcal (41%), influenza (23%) and rotavirus (18%). The target population was stated in 21 studies (95%) and the perspective was clear in 20 (91%). Only 36% reported the calculations used to complete the BIA, 27% informed the total and disaggregated costs for each time period, and 9% showed the change in resource use for each time period. More than half of the studies (55%, n = 12) reported less than 50% of the items recommended in the checklist.

CONCLUSION: The production of BIA of vaccines has increased from 2009. The report of the methodological steps was unsatisfactory, making it difficult to assess the validity of the RESULTS presented. Vaccines specific issues should be discussed in international guidelines for BIA of vaccines, to improve the quality of the studies.

WEB: <https://dx.doi.org/10.1016/j.vaccine.2017.03.088>

IMPACT FACTOR: 3.62

CITED HALF-LIFE: 5.50

START Scientific Comment: The review does not include any studies conducted in low-income countries. South Africa (Hontelez 2011), Thailand (Muangchana 2012) and the Philippines (Haasis 2015) are the only middle-income countries represented in the sample. Studies conducted in the Philippines and Thailand received funding from public research agencies to assess the cost of pneumococcal and rotavirus vaccination in infants, respectively. The funding source of the South African study estimating the costs of an RV144-like vaccine in adults aged 15-49 is not reported. The remaining 19 studies were conducted in high-income countries in Europe, North America, Japan, and New Zealand and all but one were funded by industry manufactures. Six of the 19 studies conducted in high income countries targeted infants, these included two pneumococcal vaccine studies targeting infants, three rotavirus vaccine studies—two targeting infants and one children <5, and a combined TDaP, hepatitis B, polio and Hib vaccine study targeting infants. The remaining studies examined costs for a range of pneumococcal, influenza, TDaP, or HPV vaccines targeting at risk adults and the elderly.

Tables 2, 3, 4 included epidemiologic and vaccine related data, methodological characteristics, and types of costs and their data sources. While all of the studies used local data to estimate vaccine costs, less than half report the data sources used to estimate available resources. Pre-intervention disease incidence was extracted from local data (n = 13), epidemiological studies (n = 10) and economic evaluation studies (n = 6). The authors do not draw distinctions between studies measuring vaccine efficacy or vaccine effectiveness. The majority of vaccine efficacy/effectiveness estimates were drawn from randomized clinical trials (n=12), followed by meta-analyses (n=8), and observational studies (n=7). Vaccine coverage estimates were drawn from local data (n=14), author's assumptions (n=4), and manufacture reports (n=2). Authors assert the design of BIA should take into consideration the resource constraints and disease burden to develop budgets specific to the context where vaccines will be deployed instead of a generally applicable crude reference case.



2. Inactivated polio vaccines from three different manufacturers have equivalent safety and immunogenicity when given as 1 or 2 additional doses after bivalent OPV: Results from a randomized controlled trial in Latin America.

Lopez-Medina E, Melgar M, Gaensbauer JT, Bandyopadhyay AS, Borate BR, Weldon WC, Rüttimann R, Ward J, Clemens R, Asturias EJ

Vaccine 2017 Jun 16;35(28):3591-3597 Epub 2017 Apr 25.

PMID: 28455172

ABSTRACT

BACKGROUND: Since April 2016 inactivated poliovirus vaccine (IPV) has been the only routine source of polio type 2 protection worldwide. With IPV supply constraints, data on comparability of immunogenicity and safety will be important to optimally utilize available supplies from different manufacturers.

METHODS: In this multicenter phase IV study, 900 Latin American infants randomly assigned to six study groups received three doses of bOPV at 6, 10 and 14 weeks and either one IPV dose at 14 weeks (groups SP-1, GSK-1 and BBio-1) or two IPV doses at 14 and 36 weeks (groups SP-2, GSK-2 and BBio-2) from three different manufacturers. Children were challenged with mOPV2 at either 18 (one IPV dose) or 40 weeks (two IPV doses) and stools were collected weekly for 4 weeks to assess viral shedding. Serum neutralizing antibodies were measured at various time points pre and post vaccination. Serious adverse events and important medical events (SAE and IME) were monitored for 6 months after last study vaccine.

RESULTS: At week 18, 4 weeks after one dose of IPV, overall type 2 seroconversion rates were 80.4%, 80.4% and 73.3% for SP-1, GSK-1 and BBio-1 groups, respectively; and 92.6%, 96.8% and 88.0% in those who were seronegative before IPV administration. At 40 weeks, 4 weeks after a second IPV dose, type 2 seroconversion rates were ≥99% for any of the three manufacturers. There were no significant differences in fecal shedding index endpoint (SIE) after one or two IPV doses (SP: 2.3 [95% CI: 2.1-2.6]); GSK: 2.2 [1.7-2.5]; BBio 1.8 [1.5-2.3].

All vaccines appeared safe, with no vaccine-related SAE or IME.

CONCLUSION: Current WHO prequalified IPV vaccines are safe and induce similar humoral and intestinal immunity after one or two doses. The parent study was registered with ClinicalTrials.gov, number [NCT01831050](https://clinicaltrials.gov/ct2/show/study/NCT01831050).

WEB: <https://dx.doi.org/10.1016/j.vaccine.2017.04.041>

IMPACT FACTOR: 3.62

CITED HALF-LIFE: 5.50

START Scientific Comment: Challenges to scaling up GMP for bulk production of wild type IPV have resulted in a global shortage of vaccines. Previous investigation evaluated the safety and immunogenicity of OPV-IPV sequential schedules. Study participants were randomly allocated to nine groups using randomly allocated using a computer generated block randomization design. This phase IV open-label, observer-blind, multicenter study was conducted in six sites across Colombia, the Dominican Republic, Guatemala and Panama. Investigators aimed to evaluate the safety and ability of three IPV vaccines to illicit a humoral or humoral and local (intestinal) immune reaction for type 2 poliovirus in six of the nine block randomized groups. The study population consisted of healthy 6 week-old, full-term infants, attending well baby clinics for their first polio vaccinations and primary inclusion criteria were no prior polio vaccination and no household members or siblings with recent or scheduled oral polio vaccination. Sample sizes for GSK-2 and BBio-2 were created to facilitate the comparison of IPV+bOPV to bOPV alone, assuming ≤50% rate of seroconversion for type 2 in bOPV group and 90% seroconversion for serotypes 1 and 3 in IPV +bOPV treatment groups. Investigators enrolled 190 infants per treatment group, accounting for 20% participant attrition, to determine joint non-inferiority for all serotypes with a power of 80%-86% and a 90% confidence interval. Secondary analyses, for which this study is not powered, compares the equivalence of bOPV + 1 dose of IPV and bOPV + 2 doses of IPV assuming 90% and 98% seroconversion rates of the respective treatments for all manufactures. Group sizes for these comparisons were much smaller (n=50) and statistical power for comparison between manufactures varied considerably with GSK-1 vs BBio-1 powered at 12%, SP-1 vs GSK-1/BBio-1 powered at 41% and SP-2 vs GSK-2 vs BBio-2 powered at >99%. Overall seroconversion was determined using a binary indicator of seroconversion, the difference in mean neutralization titers, and difference in mean SIE as endpoints. Though authors report equivalence was observed between IPV in many instances this was not consistent across all endpoints (tables 2-4) it is important to note that the study is underpowered to determine manufacture equivalence for all endpoints. Investigators also did not account for multiple testing. A total of 73 SAE were reported in 50 subjects but none were reportedly related to treatment.



3. Coverage and determinants of childhood immunization in Nigeria: A systematic review and meta-analysis.

Adeloye D, Jacobs W, Amuta AO, Ogundipe O, Mosaku O, Gadanya MA, Oni G
Vaccine. 2017 May 19;35(22):2871-2881. Epub 2017 Apr 21
PMID: 28438406

ABSTRACT

INTRODUCTION: The proportion of fully immunized children in Nigeria is reportedly low. There are concerns over national immunization data quality, with this possibly limiting country-wide response. We reviewed publicly available evidence on routine immunization across Nigeria to estimate national and zonal coverage of childhood immunization and associated determinants.

METHODS: A systematic search of Medline, EMBASE, Global Health and African Journals Online (AJOL) was conducted. We included population-based studies on childhood immunization in Nigeria. A random effects meta-analysis was conducted on extracted crude rates to arrive at national and zonal pooled estimates for the country.

RESULTS: Our search returned 646 hits. 21 studies covering 25 sites and 26,960 children were selected. The estimated proportion of fully immunized children in Nigeria was 34.4% (95% confidence interval [CI]: 27.0-41.9), with South-south zone having the highest at 51.5% (95% CI: 20.5-82.6), and North-west the lowest at 9.5% (95% CI: 4.6-14.4). Mother's social engagements (OR=4.0, 95% CI: 1.9-8.1) and vaccines unavailability (OR=3.9, 95% CI: 1.2-12.3) were mostly reported for low coverage. Other leading determinants were vaccine safety concerns (OR=3.0, 95% CI: 0.9-9.4), mother's low education (OR=2.5, 95% CI: 1.8-3.6) and poor information (OR=2.0, 95% CI: 0.8-4.7).

CONCLUSION: Our study suggests a low coverage of childhood immunization in Nigeria. Due to the paucity of data in the Northern states, we are still uncertain of the quality of evidence presented. It is hoped that this study will prompt the needed research, public health and policy changes toward increased evenly-spread coverage of childhood immunization in the country.

WEB: <https://dx.doi.org/10.1016/j.vaccine.2017.04.034>

IMPACT FACTOR: 3.62

CITED HALF-LIFE: 5.50

START Scientific Comment: Investigators included population and community based studies or reports with numerical data or estimates of vaccine coverage rates and its drivers in different settings across Nigeria. Immunization coverage was defined as a children aged <1yr that received one dose of BCG, three doses each of OPV, DPT, HBV, and one dose of measles vaccine. Studies with children receiving the aforementioned EPI schedule in addition to an RV, pneumococcal, or other vaccines were also included into the sample. Cases where a child did not receive the complete EPI schedule were categorized as partially immunized and completely unvaccinated children were categorized as "non-immunized". Vaccination status was validated using vaccination cards and/or maternal report. To ensure adequate representation of the target population, composition of the sample population was assessed against the local population within the geopolitical zone. Studies were then graded according to the aforementioned quality criteria, with a grade of 5 indicating high quality studies, 3-4 moderate quality studies, and studies receiving a grade of <3 were excluded. Investigators report that despite these efforts variation in the design and conduct of immunization surveys reflected high heterogeneity across studies ($I^2 = 99.3\%$, $p = 0.000$). Determinants of vaccine coverage was reported with odds ratios (OR) and when OR was not available investigators estimated a standardized OR using the proportion of immunization determinants in the sample as a function of those fully immunized in the study. Coverage rates and crude ORs were pooled across studies to produce national or zonal pooled estimates using a random effects meta-analysis. Data was collected from studies conducted between 1995 and 2016. Greater coverage was seen in rural sites though this may be due to the fact that 60% of studies were conducted in rural communities. The mean age of all children included in the review was 15.5 months and ranged from 11 to 19.7 months. See figure 2 for the pooled full immunization coverage in Nigeria, regional subgroup analysis and sensitivity analysis for the pooled full immunization after excluding moderate quality studies.

4. Global Impact of Rotavirus Vaccination on Childhood Hospitalizations and Mortality from Diarrhea.

Burnett E, Jonesteller CL, Tate JE, Yen C, Parashar UD

J Infect Dis. 2017 Jun 1;215(11):1666-1672. Epub 2017 Apr 18.

PMID: 28430997

ABSTRACT

In 2006, 2 rotavirus vaccines were licensed. We summarize the impact of rotavirus vaccination on hospitalizations and deaths from rotavirus and all-cause acute gastroenteritis (AGE) during the first 10 years since vaccine licensure, including recent evidence from countries with high child mortality. We used standardized guidelines (PRISMA) to identify observational evaluations of rotavirus vaccine impact among children <5 years of age that presented at least 12 months of pre- and post-vaccine introduction surveillance data. We identified 57 articles from 27 countries. Among children <5 years of age, the median percentage reduction in AGE hospitalizations was 38% overall and 41%, 30%, and 46% in countries with low, medium, and high child mortality, respectively. Hospitalizations and emergency department visits due to rotavirus AGE were reduced by a median of 67% overall and 71%, 59%, and 60% in countries with low, medium, and high child mortality, respectively. Implementation of rotavirus vaccines has substantially decreased hospitalizations from rotavirus and all-cause AGE.

WEB: <https://dx.doi.org/10.1016/10.1093/infdis/jix186>

IMPACT FACTOR: 6.34

CITED HALF-LIFE: 8.60

START Scientific Comment: To capture the overall impact of rotavirus vaccines authors excluded studies comparing subnational populations and studies focusing on the impact of a particular strain of rotavirus. As a result, the study makes no distinction between the relative impact of RV1 and RV5 vaccines. Countries included in the study were categorized into 3 mortality strata based on 2014 UNICEF <5 mortality rates quintiles. Low mortality countries were defined as those in the lowest quintile and ranged from 1.9-7 deaths/1000 live births. Those countries in the second lowest quintile were categorized as medium mortality and ranged from 8-17 deaths/1000 live births. Lastly, high mortality countries are those in the highest two quintiles and ranged from 18-157 deaths/1000 live births. The considerably wide range of deaths in the high mortality stratum may have been motivated by the geographic diversity of data in low income countries where the burden of rotavirus and overall child mortality is greater than middle and high income countries. The absence of data from studies representing rotavirus mortality and hospitalization in Asian countries is a significant limitation of the study. The supplementary table reveals that low mortality appears to be related to high-income countries and the least amount of geographic variation. There are 29 studies representing 5 high income countries in the low mortality category, 20 studies representing 7 middle income countries are included in the moderate category and 15 studies representing 13 countries low income countries are included in the high mortality category. The distribution of vaccine coverage rates in Low and middle income countries appear normal where data from low mortality countries show either minimal (e.g UK) or skewed variation (e.g. US) of coverage data, moreover this is the only category where countries have no or incomplete data regarding coverage during the final year of surveillance.

In their findings the authors suggest the minimal differences in the impact of rotavirus vaccines between <1 year and <5 year age groups may be due to a large proportion of older children missing vaccination opportunities due to the narrow age range for immunization eligibility. Symptoms associated with AGE are featured in a number of systemic infections and serious bacterial infections so studies documenting confirmed cases of rotavirus infections provide the best source of evidence to avoid misclassification of the primary outcome. The review includes just six countries with laboratory confirmed rotavirus gastroenteritis hospitalizations (figure 7A) and authors report comparable reductions for children aged <1 year years, 1 to <2 years, and the 2 to <5 years in the US and Moldova, moderate reductions for children in the 2 to <5 year category in Armenia, Belgium, and Ghana and an increase in rotavirus hospitalizations in the 2 to <5 year age group in Austria and 1 to <2 year age groups in Tanzania.



5. A trivalent, inactivated influenza vaccine (Vaxigrip®): summary of almost 50 years of experience and more than 1.8 billion doses distributed in over 120 countries.

Haugh M, Gresset-Bourgeois V, Macabeo B, Woods A, Samson SI
Expert Rev Vaccines. 2017 Jun;16(6):545-564. Epub 2017 May 10.
PMID: 28460594

ABSTRACT

INTRODUCTION: Vaxigrip, a trivalent split-virion, inactivated vaccine available since 1968 has been in use longer than any other influenza vaccine. It is the most widely-used influenza vaccine, with more than 1.8 billion doses distributed in more than 120 countries. Areas covered: The significant body of evidence that confirms the efficacy, effectiveness, immunogenicity, and safety of Vaxigrip in healthy individuals of all ages and at-risk populations is summarized. The RESULTS from at least 15 randomized efficacy trials and 15 other studies have demonstrated that vaccination with Vaxigrip is efficacious against various clinical endpoints. It was estimated that more than 37 million laboratory-confirmed influenza episodes, 476,000 influenza-related hospitalizations, and 67,000 influenza-related deaths have been avoided by the more than 1.8 billion doses of Vaxigrip that have been distributed, emphasizing its important public health impact. Expert commentary: This strong evidence base in favor of Vaxigrip provides a robust foundation to support the implementation of the quadrivalent formulation. This quadrivalent formulation of Vaxigrip contains two A and two B influenza strains (VaxigripTetra), and has a similar immunogenicity and safety profile to the trivalent formulation while offering broader protection due to the addition of the second influenza B strain.

WEB: <https://dx.doi.org/10.1080/14760584.2017.1324302>

IMPACT FACTOR: 3.55

CITED HALF-LIFE: 5.50

START Scientific Comment: Vaxigrip is formulated twice a year to coincide with influenza seasons in the northern and southern hemisphere. The manufacturing process has been adjusted to meet regulation and guarantee high quality and reliable “ready-to use” vaccine formulations. The primary formulation of Vaxigrip contains 15 µg of hemagglutinin for each strain in 0.5 mL buffer solution and a pediatric formulation contains 7.5 µg of hemagglutinin for each strain in a 0.25 mL buffer solution. In response to the 2009 influenza pandemic a similar vaccine—Panenza, was developed to address the (H1N1)v-like A/California/7/2009 strain. In 2009 the (H1N1)v-like A/California/7/2009 strain of influenza resulted in a pandemic that triggered the development of another split virion inactivated influenza vaccine called Panenza. Vaxigrip is indicated in adults, children over 6 months, and is safe during all stages of pregnancy. Overall, the RESULTS from nine RCTs, two non-randomized comparative studies and 2 cohort studies conducted in healthy children demonstrated Vaxigrip induced between 8- and 13-fold geometric mean titer (GMT) increases against the seasonal influenza A and B strains. In children aged 6-11 months a full dose of Vaxigrip was more immunogenic than the half dose traditionally administered to children for H3N2 and B strains but not the H1N1 strain. These effects did not extend to children aged 12-23 months. The full dose and half dose of Vaxigrip for children in all age groups have proven to be effective against clinical outcomes associated with influenza. Other vulnerable populations of interest include pregnant women and individuals with underlying conditions that place them at increased risk of acquiring influenza. Maternal antibodies may confer passive protection to infants <6 months. Vaxigrip trials in pregnant women have assessed both immunogenicity and clinical outcomes in mothers and their infants and clinical trials in South Africa (n=2), Nepal (n=1), and Mali (n=1) have found Vaxigrip confirmed generally consistent, albeit modest, vaccine efficacy against laboratory-confirmed end points (see table 4). The RESULTS of studies in children and adults with HIV-infection, Vaxigrip demonstrated a vaccine efficacy of 17.7% (95% CI: <0; 62.4) in children and 75.5% (95% CI: 9.2; 95.6) in adults. See table 5 for published RESULTS of clinical efficacy/effectiveness, immunogenicity, and safety of Vaxigrip in immunocompromised populations). In healthy adults Vaxigrip has been evaluated in 3 RCTs, one non-randomized comparative study and five cohort studies. In two RCTs, Vaxigrip was compared to a quadrivalent inactivated influenza vaccine and in the third RCT compared Vaxigrip with a virosomal influenza vaccine. GMT ratios in all three randomized clinical trials indicated adequate immunogenicity of Vaxigrip (See table 2 for nonrandomized studies). Vaxigrip has been evaluated in randomized controlled trials, randomized clinical trials, and prospective cohort studies in adults aged >64. Immunosenescence in older adults places them at an increased risk of influenza morbidity and mortality but vaccination performance has demonstrated mixed RESULTS (see table 3). Only one retrospective cohort study has been conducted in Health Care Workers.



6. Poliovirus vaccination during the endgame: insights from integrated modeling.

Duintjer Tebbens RJ, Thompson KM

Expert Rev Vaccines. 2017 Jun;16(6):577-586. Epub 2017 May 9.

PMID: 28437234

ABSTRACT

INTRODUCTION: Managing the polio endgame requires access to sufficient quantities of poliovirus vaccines. After oral poliovirus vaccine (OPV) cessation, outbreaks may occur that require outbreak response using monovalent OPV (mOPV) and/or inactivated poliovirus vaccine.

AREAS COVERED: We review the experience and challenges with managing vaccine supplies in the context of the polio endgame. Building on models that explored polio endgame risks and the potential mOPV needs to stop outbreaks from live poliovirus reintroductions, we conceptually explore the potential demands for finished and bulk mOPV doses from a stockpile in the context of limited shelf-life of finished vaccine and time delays to convert bulk to finished vaccine. Our analysis suggests that the required size of the mOPV stockpile varies by serotype, with the highest expected needs for serotype 1 mOPV. Based on realizations of poliovirus risks after OPV cessation, the stockpile required to eliminate the chance of a stock-out appears considerably larger than the currently planned mOPV stockpiles.

EXPERT COMMENTARY: The total required stockpile size depends on the acceptable probability of a stock-out, and increases with longer times to finish bulk doses and shorter shelf-lives of finished doses. Successful polio endgame management will require careful attention to poliovirus vaccine supplies.

WEB: <https://dx.doi.org/10.1080/14760584.2017.1322514>

IMPACT FACTOR: 3.55

CITED HALF-LIFE: 5.0

START Scientific Comment: Delays and capacity constraints in vaccine production thwart the successful introduction and cessation of OPV programs. Current limitations of IPV, the only available vaccine following globally coordinated OPV cessation, suggest IPV will not be introduced globally until 2018. Previous work suggested continued use of OPV following the eradication of wild type polioviruses (WPVs) would not sufficiently curb high costs and high case counts, however, including one round of IPV to OPV cessation programs until 2024 would result in an estimated \$16 billion in net benefits during the 2013-2052 period when compared with continued OPV use. Circulating vaccine-derived poliovirus (cVDPV) may be prevented provided countries ensure widespread adherence to homotypic OPV administration prior to globally coordinated OPV cessation. There is still a high probability non-cVDPV outbreaks may occur but may be mitigated/controlled by aggressive mOPV vaccination campaigns, but this relies on the availability of and access to OPV. Time delays required to convert bulk to finished products limit the shelf life of finished products. One manufacturer developed the option of stockpiling mOPV2 as semi-finished vaccine products ((i.e. filled but not labeled or packaged)) to extend the shelf life of vaccines and the time to convert semi-finished products may take as little as 5 months.. Authors estimate mPOV needs using a model combining a deterministic poliovirus transmission and oral polio vaccine evolution model with randomly varied introductions of immunodeficiency-associated vaccine-derived poliovirus (iVDPV) and other polio strains following OPV cessation. The model also addresses variability between populations in addition to economic factors that influence transmission dynamics. Following 1,000 realizations the authors demonstrate how optimal stockpile ordering strategies and stockout probabilities are determined by the expected demand for each polio serotype, the shelf life of mOPV, and the time required to convert bulk and/or semi-finished mOPV to fully finished mOPV. mOPV requirements for serotype 1 exceed that of serotypes 2 and 3. Planned stockpile sizes for all serotypes of mOPV are not enough to achieve a less than 1% chance of stockout. Authors recommend the Global Polio Eradication Initiative should adopt a strategy of maintaining a sufficient stockpile of mOPV for outbreak response should the need to restart OPV occur in addition to an IPV stockpile for future risk management.



7. Community engagement and integrated health and polio immunisation campaigns in conflict-affected areas of Pakistan: a cluster randomised controlled trial.

Habib MA, Soofi S, Cousens S, Anwar S, Haque NU, Ahmed I, Ali N, Tahir R, Bhutta ZA.

Lancet Glob Health. 2017 Jun;5(6):e593-e603.

PMID: 28495264

ABSTRACT

BACKGROUND: Pakistan faces huge challenges in eradicating polio due to widespread poliovirus transmission and security challenges. Innovative interventions are urgently needed to strengthen community buy-in, to increase the coverage of oral polio vaccine (OPV) and other routine immunisations, and to enhance immunity through the introduction of inactivated polio vaccine (IPV) in combination with OPV. We aimed to evaluate the acceptability and effect on immunisation coverage of an integrated strategy for community engagement and maternal and child health immunisation campaigns in insecure and conflict-affected polio-endemic districts of Pakistan.

METHODS: We did a community-based three-arm cluster randomised trial in healthy children aged 1 month to 5 years that resided within the study sites in three districts of Pakistan at high risk of polio. Clusters were randomly assigned by a computer algorithm using restricted randomisation in blocks of 20 by an external statistician (1:1:1) to receive routine polio programme activities (control, arm A), additional interventions with community outreach and mobilisation using an enhanced communication package and provision of short-term preventive maternal and child health services and routine immunisation (health camps), including OPV (arm B), or all interventions of arm B with additional provision of IPV delivered at the maternal and child health camps (arm C). An independent team conducted surveys at baseline, endline, and after each round of supplementary immunisation activity for acceptability and effect. The primary outcome measures for the study were coverage of OPV, IPV, and routine extended programme on immunisation vaccines and changes in the proportion of unvaccinated and fully vaccinated children. This trial is registered with ClinicalTrials.gov, number [NCT01908114](https://clinicaltrials.gov/ct2/show/study/NCT01908114).

FINDINGS: Between June 4, 2013, and May 31, 2014, 387 clusters were randomised (131 to arm A, 127 to arm B, and 129 to arm C). At baseline, 28 760 children younger than 5 years were recorded in arm A, 30 098 in arm B, and 29 126 in arm C. 359 clusters remained in the trial until the end (116 in arm A, 120 in arm B, and 123 in arm C; with 23 334 children younger than 5 years in arm A, 26 110 in arm B, and 25 745 in arm C). The estimated OPV coverage was 75% in arm A compared with 82% in arm B (difference vs arm A 6.6%; 95% CI 4.8-8.3) and 84% in arm C (8.5%, 6.8-10.1; overall $p < 0.0001$). The mean proportion of routine vaccine doses received by children younger than 24 months of age was 43% in arm A, 52% in arm B (9%, 7-11) and 54% in arm C (11%, 9-13; overall $p < 0.0001$). No serious adverse events requiring hospitalisation were reported after immunisation.

INTERPRETATION: Despite the challenges associated with the polio end-game in high-risk, conflict-affected areas of Pakistan, a strategy of community mobilisation and targeted community based health and immunisation campus during polio immunization campaigns was successful in increasing vaccine coverage, including polio vaccine coverage.

WEB: [https://dx.doi.org/10.1016/S2214-109X\(17\)30184-5](https://dx.doi.org/10.1016/S2214-109X(17)30184-5)

IMPACT FACTOR: 17.68

CITED HALF-LIFE: 2.10

START Scientific Comment: Interventions were launched in Bajaur, Karachi and Kashmore, three regions identified by WHO for their ongoing insurgency, general insecurity and high-risk for polio transmission (Fig. 1). Prior to the initiation of the intervention a baseline census collecting demographic, socioeconomic, routine immunization and health-seeking data was performed by locally recruited and trained teams. Investigators also conducted a series of consultative meetings at provincial, national, and international levels to ensure buy-in from stakeholders and the successful integration of IPV through existing immunization program channels for OPV delivery. Survey data were collected at baseline, following each round of vaccination, and end-line. Vaccination coverage was calculated at each time point in each intervention arm for all three sites using a per-protocol analysis (Fig. 3). Vaccination coverage was analyzed using a general linear model with binomial probability distribution and identity link function to compare the difference in coverage between intervention arms. To account for clustering, investigators treated randomized clusters as primary sampling units stratified by study area and then applied Taylor series linearization methods to estimate stratum specific and pooled overall variance. Findings show community mobilisation combined with delivery of maternal and child health and immunisation interventions may increase vaccine coverage, and investigators noted securing local political support is critical for success.



8. An update of the global burden of pertussis in children younger than 5 years: a modelling study.

Yeung KHT, Duclos P, Nelson EAS, Hutubessy RCW.

Lancet Infect Dis. 2017 Jun 13. [Epub ahead of print]

PMID: 28623146

ABSTRACT

BACKGROUND: Since the publication in 2003 of a model to estimate the disease burden of pertussis, new evidence of the protective effect of incomplete pertussis vaccination against severe pertussis has been reported. We revised the model to provide new estimates of regional and global pertussis cases and deaths for children younger than 5 years.

METHODS: We developed a revised model with data from 2014 to estimate pertussis cases and deaths. Pertussis cases were defined according to the WHO clinical case definition, as a coughing illness lasting at least 2 weeks with paroxysms of coughing, inspiratory whooping, or post-tussive vomiting. We used UN population estimates and WHO and UNICEF data on national pertussis immunisation coverage. Estimates were made for vaccine effectiveness against pertussis cases and deaths for one, two, and three doses of vaccination, probability of infection in low and high coverage countries, and case fatality ratios in low and high mortality countries in two age groups: infants younger than 1 year and children aged 1-4 years. We did sensitivity analyses with a range of input parameters to assess the effect of uncertainty of the input parameters on the model outputs.

FINDINGS: We estimated that there were 24.1 million pertussis cases and 160 700 deaths from pertussis in children younger than 5 years in 2014, with the African region contributing the largest proportions (7.8 million [33%] cases and 92 500 [58%] deaths). 5.1 million (21%) estimated pertussis cases and 85 900 (53%) estimated deaths were in infants younger than 1 year. In the sensitivity analyses, the estimated number of cases ranged from 7 million to 40 million and deaths from 38 000 to 670 000.

INTERPRETATION: Our estimates suggest that, compared with the 1999 estimates published in 2003 (30.6 million pertussis cases and 390 000 deaths from pertussis in children younger than 5 years), the numbers of cases and deaths of pertussis have fallen substantially. Model sensitivity emphasised the importance of better surveillance to improve country-level decision-making and pertussis control.

WEB: [https://dx.doi.org/10.1016/S1473-3099\(17\)30390-0](https://dx.doi.org/10.1016/S1473-3099(17)30390-0)

IMPACT FACTOR: 19.86

CITED HALF-LIFE: 4.40

START Scientific Comment: The paucity of surveillance data in low-income countries impedes estimating the global burden of pertussis and limits the ability of stakeholders to compare the relative potential impact of vaccines when setting national priorities for vaccination programs. This work builds on a model developed by Crowcroft et al. in 2003 to estimate the burden of pertussis in children aged <15 years using pertussis mortality data from 1999. A search of published literature identified recent estimates of pertussis deaths from 2013 WHO vital registration data, Global Burden of Disease Study in 2013 and 2015. The model was also updated to address the differential waning rates observed among acellular and whole-cell pertussis vaccines recipients and the protective effects of partial pertussis vaccination. The current model estimates pertussis disease burden cases and mortality in children aged <5 years. A lack of data regarding protection conferred to children after 5 years prevents the estimation of pertussis cases and deaths in children aged 5-14 years. The previous model relied on WHO mortality strata, which have since fallen out of use, as these data are more likely to reflect administrative rather than epidemiological data. The current study uses country-level under-5 mortality rates from the UN Inter-agency Group for Child Mortality Estimation. Authors use the global average <5-mortality rate (.033) as a cutpoint delineating countries into low and high mortality groups. Estimated case fatality ratios were 0.2% for infants <1 year and 0.04% for children aged 1-4 years in low mortality countries and 3.7% for infants <1 year and 1% for children aged 1-4 years in high mortality countries. Estimates of pertussis cases and deaths in 2014 by WHO region illustrate high proportions in Africa and Asia (Table 3) and authors assert this may largely reflect the large populations of these regions and the proportions of high mortality countries (Table 4).

9. Neighborhood-targeted and case-triggered use of a single dose of oral cholera vaccine in an urban setting: Feasibility and vaccine coverage.

Parker LA, Rumunu J, Jamet C, Kenyi Y, Lino RL, Wamala JF, Mpairwe AM, Muller V, Llosa AE, Uzzeni F, Luquero FJ, Ciglenecki I, Azman AS.
PLoS Negl Trop Dis. 2017 Jun 8;11(6):e0005652.
PMID: 28594891

ABSTRACT

INTRODUCTION: In June 2015, a cholera outbreak was declared in Juba, South Sudan. In addition to standard outbreak control measures, oral cholera vaccine (OCV) was proposed. As sufficient doses to cover the at-risk population were unavailable, a campaign using half the standard dosing regimen (one-dose) targeted high-risk neighborhoods and groups including neighbors of suspected cases. Here we report the operational details of this first public health use of a single-dose regimen of OCV and illustrate the feasibility of conducting highly targeted vaccination campaigns in an urban area.

METHODOLOGY/PRINCIPAL FINDINGS: Neighborhoods of the city were prioritized for vaccination based on cumulative attack rates, active transmission and local knowledge of known cholera risk factors. OCV was offered to all persons older than 12 months at 20 fixed sites and to select groups, including neighbors of cholera cases after the main campaign ('case-triggered' interventions), through mobile teams. Vaccination coverage was estimated by multi-stage surveys using spatial sampling techniques. 162,377 individuals received a single-dose of OCV in the targeted neighborhoods. In these neighborhoods vaccine coverage was 68.8% (95% Confidence Interval (CI), 64.0-73.7) and was highest among children ages 5-14 years (90.0%, 95% CI 85.7-94.3), with adult men being less likely to be vaccinated than adult women (Relative Risk 0.81, 95% CI: 0.68-0.96). In the case-triggered interventions, each lasting 1-2 days, coverage varied (range: 30-87%) with an average of 51.0% (95% CI 41.7-60.3).

CONCLUSION/SIGNIFICANCE: Vaccine supply constraints and the complex realities where cholera outbreaks occur may warrant the use of flexible alternative vaccination strategies, including highly-targeted vaccination campaigns and single-dose regimens. We showed that such campaigns are feasible. Additional work is needed to understand how and when to use different strategies to best protect populations against epidemic cholera.

WEB: <https://dx.doi.org/10.1371/journal.pntd.0005652>

IMPACT FACTOR: 3.83

CITED HALF-LIFE: 3.70

START Scientific Comment: In May 2015 the first cases of cholera outbreak occurred in a South Sudanese United Nations Protection of Civilians Camp, where approximately 28,000 internally displaced people resided. By June of 2015 the Republic of South Sudan Ministry of Health (MoH) declared a cholera outbreak in Juba. The National Cholera Taskforce was developed to launch a multi-pronged outbreak response featuring case management, water and sanitation interventions, and health education and hygiene promotion. Despite estimates that the number of individuals at risk ranged between 500,000–1,000,000 people, supply limitations resulted in only 270,000 doses released from the global stockpile. Evidence from modeling studies suggested that in the face of limited OCV supplies one-dose campaigns might save more lives than the traditional two-dose campaign. Moreover, preliminary RESULTS from immunogenicity tests in a large Bangladeshi RCT found a single dose of OCV was still protective in preventing cholera infection. Vaccine campaigns targeted neighborhoods where significant transmission had taken place and vulnerable groups at higher risk of cholera (i.e IDPs, prisoners and health care workers). To limit transmission among individuals living near cholera cases the remaining doses were delivered to neighbors and case-triggered water sanitation and hygiene interventions were deployed in areas where sporadic case reports occurred. MoH in partnership with MSF operated 20 fixed vaccination sites with 3–4 vaccinators, 3–4 individuals preparing the vaccine, 8–10 registrars documenting name, age, vaccination location, date of vaccination and vaccine lot number, 1 security guard, 2 health promoters and 1 team supervisor. All Individuals presenting at vaccination sites aged >1 year were offered OCV regardless of their area of residence. When the number of individuals seeking OCV at vaccination sites dwindled, vaccination teams formed smaller semi-mobile units to set up mini vaccination in communities unreachable by previous efforts. Health promoters disseminated information to targeted communities, as investigators feared that, given limited supplies of OCVs, national media campaigns publicizing the availability of OCV in certain parts of the capital could spur discontent and civil unrest. Coverage was measured using a stratified spatial sampling approach with households serving as the primary sampling unit.



10. Impact of the introduction of pneumococcal conjugate vaccination on pneumonia in The Gambia: population-based surveillance and case-control studies.

Mackenzie GA, Hill PC, Sahito SM, Jeffries DJ, Hossain I, Bottomley C, Uchendu U, Ameh D, Ndiaye M, Osuorah CD, Adeyemi O, Pathirana J, Olatunji Y, Abatan B, Ahameefula E, Muhammad BS et al.

Lancet Infect Dis. 2017 Jun 7[Epub ahead of print]

PMID: 28601421

ABSTRACT

BACKGROUND: Pneumococcal conjugate vaccines (PCVs) are used in many low-income countries but their impact on the incidence of pneumonia is unclear. The Gambia introduced PCV7 in August, 2009, and PCV13 in May, 2011. We aimed to measure the impact of the introduction of these vaccines on pneumonia incidence.

METHODS: We did population-based surveillance and case-control studies. The primary endpoint was WHO-defined radiological pneumonia with pulmonary consolidation. Population-based surveillance was for suspected pneumonia in children aged 2-59 months (minimum age 3 months in the case-control study) between May 12, 2008, and Dec 31, 2015. Surveillance for the impact study was limited to the Basse Health and Demographic Surveillance System (BHDSS), whereas surveillance for the case-control study included both the BHDSS and Fuladu West Health and Demographic Surveillance System. Nurses screened all outpatients and inpatients at all health facilities in the surveillance area using standardised criteria for referral to clinicians in Basse and Bansang. These clinicians recorded clinical findings and applied standardised criteria to identify patients with suspected pneumonia. We compared the incidence of pneumonia during the baseline period (May 12, 2008, to May 11, 2010) and the PCV13 period (Jan 1, 2014, to Dec 31, 2015). We also investigated the effectiveness of PCV13 using case-control methods between Sept 12, 2011, and Sept 31, 2014. Controls were aged 90 days or older, and were eligible to have received at least one dose of PCV13; cases had the same eligibility criteria with the addition of having WHO-defined radiological pneumonia.

FINDINGS: We investigated 18 833 children with clinical pneumonia and identified 2156 cases of radiological pneumonia. Among children aged 2-11 months, the incidence of radiological pneumonia fell from 21.0 cases per 1000 person-years in the baseline period to 16.2 cases per 1000 person-years (23% decline, 95% CI 7-36) in 2014-15. In the 12-23 month age group, radiological pneumonia decreased from 15.3 to 10.9 cases per 1000 person-years (29% decline, 12-42). In children aged 2-4 years, incidence fell from 5.2 to 4.1 cases per 1000 person-years (22% decline, 1-39). Incidence of all clinical pneumonia increased by 4% (-1 to 8), but hospitalised cases declined by 8% (3-13). Pneumococcal pneumonia declined from 2.9 to 1.2 cases per 1000 person-years (58% decline, 22-77) in children aged 2-11 months and from 2.6 to 0.7 cases per 1000 person-years (75% decline, 47-88) in children aged 12-23 months. Hypoxic pneumonia fell from 13.1 to 5.7 cases per 1000 person-years (57% decline, 42-67) in children aged 2-11 months and from 6.8 to 1.9 cases per 1000 person-years (72% decline, 58-82) in children aged 12-23 months. In the case-control study, the best estimate of the effectiveness of three doses of PCV13 against radiological pneumonia was an adjusted odds ratio of 0.57 (0.30-1.08) in children aged 3-11 months and vaccine effectiveness increased with greater numbers of doses ($p=0.026$). The analysis in children aged 12 months and older was underpowered because there were few unvaccinated cases and controls.

INTERPRETATION: The introduction of PCV in The Gambia was associated with a moderate impact on the incidence of radiological pneumonia, a small reduction in cases of hospitalised pneumonia, and substantial reductions of pneumococcal and hypoxic pneumonia in young children. Low-income countries that introduce PCV13 with reasonable coverage can expect modest reductions in hospitalised cases of pneumonia and a marked impact on the incidence of severe childhood pneumonia.

WEB: [https://dx.doi.org/10.1016/S1473-3099\(17\)30321-3](https://dx.doi.org/10.1016/S1473-3099(17)30321-3)

IMPACT FACTOR: 19.86

CITED HALF-LIFE: 4.40

START Scientific Comment: Investigators adjusted for increases in the number of children referred to clinicians over time by applying a correction factor to annual event counts. The correction factor assumed the rate of patient referrals remained constant overtime. Authors suggest the difference in adjusted and crude case counts may indicate crude analyses were influenced by the increased referrals to clinicians during the observation period; however this adjustment may have influenced the precision estimates of vaccine impact. The case definition used by investigators included nonspecific clinical indicators that mimic clinical symptoms of malaria infection, which is endemic across The Gambia. Consequently, estimates of the impact of PCV to reduce clinical pneumonia may have been underestimated due to the over-reporting of misclassified pneumonia cases.

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]) ("2016/5/15"[PDAT] : "2017/6/14"[PDAT]))

* On June 27, 2017, this search of English language articles published between May 15, 2016 and June 14, 2017 and indexed by the US National Library of Medicine resulted in 236 unique manuscripts.

