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1. Reasons why children miss vaccinations in Western Kenya; A step in a five-point plan to improve routine immunization

Agócs M, Ismail A, Kamande K, Tabu C, Momanyi C, Sale G, et al.

Vaccine. 2021 Mar 17:S0264-410X(21)00262-0.

PubMed ID: 33744047

ABSTRACT

Global childhood vaccination coverage has stagnated over the past decade and raising coverage will require a collection of approaches since no single approach has been suitable for all countries or situations. The American Red Cross has developed a 5-Point Plana to geolocate under-vaccinated children and determine the reasons why they miss vaccination by capitalizing on the Red Cross Movement's large cadres of trusted community volunteers. The Plan was piloted in Bobasi sub-county in Western Kenya, with volunteers seeking to conduct a face-to-face interview in all households, visiting over 60,000 over 7 days. Six pockets of 233 children without a home-based vaccination record or missing an age-appropriate dose of Penta1, Penta3 or measles-containing vaccine were identified. Three activities were carried out to learn why these children were not vaccinated: 1) one-on-one interviews and 2) focus group discussions with the caregivers of the under-vaccinated children and 3) interviews with healthcare workers who vaccinate in Bobasi. Complacency was commonly reported by caregivers during one-on-one interviews while bad staff attitude or practice was most frequently reported in focus group discussions; health staff reported caregiver hesitancy, not knowing vaccination due date and vaccine stock-outs as the most common reasons for caregivers to not have their child vaccinated. As reasons varied across the three different activities, the different perspectives and approaches helped characterize vaccination barriers. Civil society organizations working together with the Ministry of Health can provide valuable information for immunization managers to act on.

WEB: 10.1016/j.vaccine.2021.02.071

IMPACT FACTOR: 3.143

CITED HALF-LIFE: 7.3

START COMMENTARY

In this qualitative study, Agócs *et al.* report reasons why children had missed vaccinations in Bobasi sub-county, Kisii County, Kenya. This data was collected as part of the American Red Cross' 5-Point Plan to quantify missed vaccinations among children, follow up to understand and respond to

reasons for missing vaccination. Point 1 of the plan conducted a household survey with 60,361 households and 7,693 children to geo-locate residences of zero-dose and under-vaccinated children. This paper reports on Point 2 activities, namely to understand why children had missed vaccinations. The authors conducted one-on-one interviews and focus group discussions with caregivers, as well as interviews with healthcare workers. Interviews were structured around published reasons for child missing vaccinations (e.g., caregiver reasons; service delivery), described in *Table 1.*

Among caregivers, the most common reasons for missed vaccination were complacency (defined as not a priority, busy, forgot or careless) (26% of caregivers), vaccine administered but not recorded (15%), and not being aware of the vaccine benefits (13%). In focus group discussions with caregivers, the most reported reasons for missing vaccination were related to health facility staff (e.g., bad attitude or practices). Hesitancy-related reasons included not prioritizing vaccination, preferring herbal interventions over hospital interventions, and concerns about judgement from the community (i.e., for giving birth at home or for having a child without marriage). Among healthcare workers, the primary reasons given for caregivers missing child vaccinations included that the caregiver does not know when the vaccination is due (41% of facilities), vaccine hesitancy (41%), and complacency (17%). In terms of service delivery, practices that could increase missed vaccinations included not opening a multi-dose vial because only a few children were present (34% of facilities), not giving the measles vaccine to 5 year olds even though they are eligible (38%), and not vaccinating children who were mildly ill (48%). These insights from caregivers and healthcare works can inform vaccination service strengthening in Bobasi sub-country, Kenya, and other similar regions.

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2. Findings from the initial Stepwise Approach to Rabies Elimination (SARE) Assessment in China, 2019

Chen Q, Ma X, Rainey JJ, Li Y, Mu D, Tao X, et al.

PLoS Negl Trop Dis. 2021 Mar 29;15(3):e0009274.

PubMed ID: 33780454

ABSTRACT

In 2015, China and other member states of the United Nations adopted the goal of eliminating dog-mediated rabies by 2030. China has made substantial progress in reducing dog-mediated human rabies since peaking with more than 3,300 reported cases in 2007. To further improve coordination and planning, the Chinese Center for Disease Control and Prevention, in collaboration with the United States Centers for Disease Control and Prevention, conducted a Stepwise Approach towards Rabies Elimination (SARE) assessment in March 2019. Assessment goals included outlining progress and identifying activities critical for eliminating dog-mediated rabies. Participants representing national, provincial and local human and animal health sectors in China used the SARE assessment tool to answer 115 questions about the current dog-mediated rabies control and prevention programs in China. The established surveillance system for human rabies cases and availability of post-exposure prophylaxis were identified as strengths. Low dog vaccination coverage and limited laboratory confirmation of rabid dogs were identified gaps, resulting in an overall score of 1.5 on a scale of 0 to 5. Participants outlined steps to increase cross-sectoral information sharing, improve surveillance for dog rabies, increase dog vaccination coverage, and increase laboratory capacity to diagnose rabies at the provincial level. All assessment participants committed to strengthening cross-sector collaboration using a One Health approach to achieve dog-mediated human rabies elimination by 2030.

WEB: 10.1371/journal.pntd.0009274

IMPACT FACTOR: 3.885

CITED HALF-LIFE: 4.8

START COMMENTARY

Chen *et al.* present the Stepwise Approach toward Rabies Elimination (SARE) assessment in China. The SARE assessment collects information on the following seven categories: 1) Rabies information, education, and communication; 2) dog population related issues; 3) prevention and control; 4) data collection and analysis; 5) laboratory diagnosis capacity; 6) cross-cutting issues; 7) and legislation. The SARE assessment relies on publicly available data, routine public health data, and animal surveillance data. For the assessment, 33 representatives from national- and 12

provincial-level human and animal health teams participated. There were 13 teams that collected data and represented each province in the assessment.

According to the national notifiable disease surveillance reporting system (NNDRS), there were 661 rabies cases annually between 2014 to 2018. Most cases occurred in Hunan, Guangdong, Guangxi, Guizhou, and Yunnan. Treatment (post-exposure prophylaxis) is widely available in county-level CDCs and in township-based rabies clinics for an out-of-pocket household cost of 48 USD. The SARE assessment resulted in an overall score of 1.5 out of 5 for China. This score was consistent for 11 of the 12 provinces assessed. Examples of common gaps and barriers identified at the provincial level in the assessment included a weak surveillance system for detecting and reporting rabies cases, infrequent information sharing between human and animal sectors, limited dog registration in rural areas, a lack of census data on home, stray, and free-roaming dogs, a lack of laboratory diagnostics for animal rabies, and no national strategic plan for dog-mediated rabies elimination. Chen *et al.* present short-, medium, and long-term activities and goals based on the assessment, which include improving data collection and sharing, controlling the number of dogs, and establishing cross-sector collaborations. This study is important as it highlights strengthens and gaps in national and provincial level rabies control and prevention in China using a One-Health cross sector approach, an important step in eliminating dog-mediated rabies.

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3. Determinants of full childhood immunization among children aged 12-23 months in sub-Saharan Africa: a multilevel analysis using Demographic and Health Survey Data.

Fenta S, Biresaw H, Fentaw K, Gebremichael S.

Trop Med Health. 2021 Apr 08;49(1):29.

PubMed ID: 33795028

ABSTRACT

BACKGROUND: Sub-Saharan Africa is one of the highest under-five mortality and low childhood immunization region in the world. Children in Sub-Saharan Africa are 15 times more likely to die than children from high-income countries. In sub-Saharan Africa, more than half of under-five deaths are preventable through immunization. Therefore, this study aimed to identify the determinant factors of full childhood immunization among children aged 12-23 months in sub-Saharan Africa.

METHODS: Data for the study was drawn from the Demographic and Health Survey of nine sub-Saharan African countries. A total of 21,448 children were included. The two-level mixed-effects logistic regression model was used to identify the individual and community-level factors associated with full childhood immunization RESULT: The prevalence of full childhood immunization coverage in sub-Saharan Africa countries was 59.40% (95% CI: 58.70, 60.02). The multilevel logistic regression model revealed that secondary and above maternal education (AOR = 1.38; 95% CI: 1.25, 1.53), health facility delivery (AOR = 1.51; 95% CI: 1.41, 1.63), fathers secondary education and above (AOR = 1.28, 95% CI: 1.11, 1.48), four and above ANC visits (AOR = 2.01; 95% CI: 1.17, 2.30), PNC visit(AOR = 1.55; 95% CI: 1.46, 1.65), rich wealth index (AOR = 1.26; 95% CI: 1.18, 1.40), media exposure (AOR = 1.11; 95% CI: 1.04, 1.18), and distance to health facility is not a big problem (AOR = 1.42; 95% CI: 1.28, 1.47) were significantly associated with full childhood immunization.

CONCLUSION: The full childhood immunization coverage in sub-Saharan Africa was poor with high inequalities. There is a significant variation between SSA countries in full childhood immunization. Therefore, public health programs targeting uneducated mothers and fathers, rural mothers, poor households, and those who have not used maternal health care services to promote full childhood immunization to improve child health. By enhancing institutional delivery, antenatal care visits and maternal tetanus immunization, the government and other stakeholders should work properly to increase child immunization coverage. Furthermore, policies and programs aimed at addressing cluster variations in childhood immunization need to be formulated and their implementation must be strongly pursued.

WEB: 10.1186/s41182-021-00319-x
IMPACT FACTOR: N/A
CITED HALF-LIFE: N/A

START COMMENTARY

In this cross-sectional study, Fenta *et al*. assessed individual and community level factors associated with full childhood immunization across nine sub-Saharan African (SSA) countries using Demographic Health Survey (DHS) data. This article fills a gap in the literature of understanding community-level factors associated with full immunization status across several countries (Ethiopia, Ghana, Democrat Republic of Congo, Senegal, Rwanda, Malawi, Tanzania, Namibia, and Zambia). The main outcome variable, full immunization for children 12-23 months, was defined as having received all eight Expanded Program for Immunization (EPI) doses of vaccine; this includes one dose of Bacille Calmette-Guerin (BCG), three doses of diphtheria, pertussis, and tetanus (DPT) and three doses of polio, and one dose of measles. Individual- and community-level factors were based on prior literature, and included individual factors such as parents' education, wealth, and prenatal healthcare access and community level factors such as distance to health facility, exposure to media, and country, among others.

Overall, Fenta *et al*. found the pooled prevalence of full childhood immunization across the nine countries was 59.4% (95% CI: 58.7-60.02) with Rwanda having the lowest proportion (39%) and Tanzania having the highest (74.8%). A multi-level logistic regression demonstrated that individual factors (maternal education, maternal occupation, maternal age, marital status, father education, sex of household head, number of ANC visits, postnatal care, place of delivery, number of living children, wealth index) and community factors (place of residence, media exposure, distance to health facilities, and country) were significantly associated with full childhood immunization. When assessing measures of variation (random-effects) in the model, Fenta *et al*. reported that the intra-class correlation coefficients of the null model showed that 29.4% of the variation in full immunization status was related to community level factors. One substantial limitation of this study is the different years of DHS surveys used. Although authors used the most recent DHS in each country, surveys ranged from 2013-2017, all of which may not accurately reflect the current status of full immunization in each country. Overall, this study contributes to the literature on factors related to full immunization, and underscores the importance of targeting specific populations (i.e., rural populations, uneducated mothers and factors, poor households, and those with limited maternal health access) and improving access to other services (i.e., institutional delivery, antenatal care visits, and maternal tetanus immunization) to increase child immunization coverage.

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4. Safety and immunogenicity of inactivated poliovirus vaccine schedules for the post-eradication era: a randomised open-label, multicentre, phase 3, non-inferiority trial

Bandyopadhyay AS, Gast C, Rivera L, Sáez-Llorens X, Oberste MS

Lancet Infect Dis. 2021 Apr;21(4):559-568.

PubMed ID: 33284114

ABSTRACT

BACKGROUND: Following the global eradication of wild poliovirus, countries using live attenuated oral poliovirus vaccines will transition to exclusive use of inactivated poliovirus vaccine (IPV) or fractional doses of IPV (f-IPV; a f-IPV dose is one-fifth of a normal IPV dose), but IPV supply and cost constraints will necessitate dose-sparing strategies. We compared immunisation schedules of f-IPV and IPV to inform the choice of optimal post-eradication schedule.

METHODS: This randomised open-label, multicentre, phase 3, non-inferiority trial was done at two centres in Panama and one in the Dominican Republic. Eligible participants were healthy 6-week-old infants with no signs of febrile illness or known allergy to vaccine components. Infants were randomly assigned (1:1:1:1, 1:1:1:2, 2:1:1:1), using computer-generated blocks of four or five until the groups were full, to one of four groups and received: two doses of intradermal f-IPV (administered at 14 and 36 weeks; two f-IPV group); or three doses of intradermal f-IPV (administered at 10, 14, and 36 weeks; three f-IPV group); or two doses of intramuscular IPV (administered at 14 and 36 weeks; two IPV group); or three doses of intramuscular IPV (administered at 10, 14, and 36 weeks; three IPV group). The primary outcome was seroconversion rates based on neutralising antibodies for poliovirus type 1 and type 2 at baseline and at 40 weeks (4 weeks after the second or third vaccinations) in the per-protocol population to allow non-inferiority and eventually superiority comparisons between vaccines and regimens. Three co-primary outcomes concerning poliovirus types 1 and 2 were to determine if seroconversion rates at 40 weeks of age after a two-dose regimen (administered at weeks 14 and 36) of intradermally administered f-IPV were non-inferior to a corresponding two-dose regimen of intramuscular IPV; if seroconversion rates at 40 weeks of age after a two-dose IPV regimen (weeks 14 and 36) were non-inferior to those after a three-dose IPV regimen (weeks 10, 14, and 36); and if seroconversion rates after a two-dose f-IPV regimen (weeks 14 and 36) were non-inferior to those after a three-dose f-IPV regimen (weeks 10, 14, and 36). The non-inferiority boundary was set at -10% for the lower bound of the two-sided 95% CI for the seroconversion rate difference. Safety was assessed as serious adverse events and important medical events. This study is registered on ClinicalTrials.gov, NCT03239496.

FINDINGS: From Oct 23, 2017, to Nov 13, 2018, we enrolled 773 infants (372 [48%] girls) in Panama and the Dominican Republic (two f-IPV group n=217, three f-IPV group n=178, two IPV group n=178, and three IPV group n=200). 686 infants received all scheduled vaccine doses and

were included in the per-protocol analysis. We observed non-inferiority for poliovirus type 1 seroconversion rate at 40 weeks for the two f-IPV dose schedule (95·9% [95% CI 92·0-98·2]) versus the two IPV dose schedule (98·7% [95·4-99·8]), and for the three f-IPV dose schedule (98·8% [95·6-99·8]) versus the three IPV dose schedule (100% [97·9-100]). Similarly, poliovirus type 2 seroconversion rate at 40 weeks for the two f-IPV dose schedule (97·9% [94·8-99·4]) versus the two IPV dose schedule (99·4% [96·4-100]), and for the three f-IPV dose schedule (100% [97·7-100]) versus the three IPV dose schedule (100% [97·9-100]) were non-inferior. Seroconversion rate for the two f-IPV regimen was statistically superior 4 weeks after the last vaccine dose in the 14 and 36 week schedule (95·9% [92·0-98·2]) compared with the 10 and 14 week schedule (83·2% [76·5-88·6]; p=0·0062) for poliovirus type 1. Statistical superiority of the 14 and 36 week schedule was also found for poliovirus type 2 (14 and 36 week schedule 97·9% [94·8-99·4] vs 10 and 14 week schedule 83·9% [77·2-89·2]; p=0·0062), and poliovirus type 3 (14 and 36 week schedule 84·5% [78·7-89·3] vs 10 and 14 week schedule 73·3% [65·8-79·9]; p=0·0062). For IPV, a two dose regimen administered at 14 and 36 weeks (99·4% [96·4-100]) was superior a 10 and 14 week schedule (88·9% [83·4-93·1]; p<0·0001) for poliovirus type 2, but not for type 1 (14 and 36 week schedule 98·7% [95·4-99·8] vs 10 and 14 week schedule 95·6% [91·4-98·1]), or type 3 (14 and 36 week schedule 97·4% [93·5-99·3] vs 10 and 14 week schedule 93·9% [89·3-96·9]). There were no related serious adverse events or important medical events reported in any group showing safety was unaffected by administration route or schedule.

INTERPRETATION: Our observations suggest that adequate immunity against poliovirus type 1 and type 2 is provided by two doses of either IPV or f-IPV at 14 and 36 weeks of age, and broad immunity is provided with three doses of f-IPV, enabling substantial savings in cost and supply. These novel clinical data will inform global polio immunisation policy for the post-eradication era.

WEB: 10.1016/S1473-3099(20)30555-7
IMPACT FACTOR: 24.446
CITED HALF-LIFE: 4.7

START COMMENTARY

In this randomized controlled trial, Bandyopadhyay *et al.* present results from a study comparing immunisation schedules of fractional-inactive polio vaccine (f-IPV) and IPV to inform the choice of optimal post-eradication schedule. This study makes a critical contribution to the literature by providing data on doses required for adequate immunity when all wild polioviruses are eradicated globally. Once eradication is achieved, there is a need to continue immunizations for years to combat vaccine-derived polioviruses, which come from oral poliovirus vaccines (OPV). However, IPVs are costly and have limited manufacturing capacity, indicated that policies administering f-IPV or fewer doses of IPV are urgently needed.

Bandyopadhyay *et al.* enrolled 773 six-week-old infants in this randomized, open-label, multicenter, phase 3, non-inferiority trial in two sites in Panama and one site in the Dominican Republic. Infants were randomized to receive two or three doses of f-IPV (one-fifth of the full dose presented in 0.1 mL) to compare to full dose IPV. The two dose groups (both f-IPV and IPV) were administered on weeks 14 and 36. The three dose groups (both f-IPV and IPV) were administered vaccines on weeks 10, 14, and 36. Four blood samples were collected from each participant to measure neutralizing antibodies against polioviruses type 1, 2, and 3. The primary study outcome was the immune response against poliovirus type 1 and type 2 four weeks after completion of the vaccine series. Secondary outcomes included seroconversion rates at 40 weeks, immunogenicity, and safety. Results demonstrated non-inferiority for poliovirus type 1 seroconversion rate at 40 weeks for the two f-IPV dose schedule and for the three f-IPV dose schedules versus the three IPV dose schedule. Finding demonstrate that there is adequate immunity against poliovirus type 1 and type 2 with two doses f-IPV and further, broad immunity is shown with three doses of f-IPV, indicating that these options can be considered for future global polio immunization policies post-eradication.

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5. Zero-dose children and the immunisation cascade: Understanding immunisation pathways in low and middle-income countries

de Oliveira Cata-Preta B, Melo Santos T, Mengistu T, R Hogan D

Vaccine. 2021 Mar 17:S0264-410X(21)00263-2.
PubMed ID: 33744046

ABSTRACT

INTRODUCTION: Zero-dose prevalence refers to children who failed to receive any routine vaccination. Little is known about the "immunisation cascade" in low- and middle-income countries (LMICs), defined as how children move from zero dose to full immunisation.

METHODS: Using data from national surveys carried out in 92 LMICs since 2010 and focusing on the four basic vaccines delivered in infancy (BCG, polio, DPT and MCV), we describe zero-dose prevalence and the immunisation cascade in children aged 12 to 23 months. We also describe the most frequent combinations of vaccines (or co-coverage) among children who are partially immunized. Analyses are stratified by country income groups, household wealth quintiles derived from asset indices, sex of the child and area of residence. Results were pooled across countries using child populations as weights.

RESULTS: In the 92 countries, 7.7% were in the zero-dose group, and 3.3%, 3.4% and 14.6% received one, two or three vaccines, respectively; 70.9% received the four types and 59.9% of the total were fully immunised with all doses of the four vaccines. Three quarters (76.8%) of children who received the first vaccine received all four types. Among children with a single vaccine, polio was the most common in low- and lower-middle income countries, and BCG in upper-middle income countries. There were sharp inequalities according to household wealth, with zero-dose prevalence ranging from 12.5% in the poorest to 3.4% in the wealthiest quintile across all countries. The cascades were similar for boys and girls. In terms of dropout, 4% of children receiving BCG did not receive DPT1, 14% receiving DPT1 did not receive DPT3, and 9% receiving DPT3 did not progress to receive MCV.

INTERPRETATION: Focusing on zero-dose children is particularly important because those who are reached with the first vaccine are highly likely to also receive remaining vaccines.

WEB: 10.1016/j.vaccine.2021.02.072
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

In this descriptive study, Oliveira Cata-Preta *et al.* utilize data from national surveys (DHS and Multiple Indicator Cluster Surveys [MICS]) in 92 low-or middle-income countries since 2010 to describe zero dose prevalence. The primary outcome was the prevalence of zero-dose children, defined as any that did not receive BCG, polio (OPV or IPV), DPT, and measles containing vaccines (MCV) in infancy. Secondary outcomes included the immunization cascade score, vaccine co-coverage with two vaccines, and full immunization coverage. The immunization cascade score was defined as a score ranging from 0 to 4 with each type of vaccine accounting for one point in the cascade, regardless of how many doses were received (e.g., one dose of DPT is equal to one point in the score). Vaccine co-coverage was defined as the conditional probabilities of receiving a vaccine given another vaccine was received and of receiving a vaccine when another vaccine was not received. Full immunization coverage was defined as the proportion of children that received all required doses of each vaccine (i.e., one dose of BCG, three doses of polio, three doses of DPT and one dose of MCV).

Results were stratified by the country income (low-, lower-middle, and upper-middle) and further by poorest and wealthiest quintiles within each country. The authors found that zero-dose prevalence ranged from 5.2% in upper-middle income countries compared to 11.1% in low-income countries. Residence (rural vs. poor) and wealth quintile were significantly associated with zero doses, with poorer children in rural areas more likely to be in the zero-dose category. Co-coverage varied greatly based on the vaccine combination and is presented in *Table 2: Co-coverage with the four vaccines according to cascade level (all countries combined).* Most children were either zero dose or received at least the first dose of 3 or more vaccines (i.e., rather than having one dose of 1 or 2 vaccines). Full immunization coverage was 59.9% for the 92 countries combined. Authors noted the most frequent combinations of vaccines; for children with two different vaccines, BCG and polio were most frequently given whereas for those with three vaccines, the combination of BCG, polio, and DPT was the most common. The authors note a J-shaped pattern in the immunization cascade in low- and lower-middle income countries (i.e., 8% of children receiving no dose; 3% in the first step; 3% in the second step; 15% in the fourth step; and 71% in the fifth step indicating receiving all four vaccines), which indicates that children either receive no immunization, or all immunizations. One notable limitation of this study is that it used DHS and MIC surveys which are only administered every few years in LMICs, indicating this information may not accurately represent current zero dose prevalence, particularly during the COVID-19 pandemic when routine immunization has decreased. Despite this limitation, this article highlights importance of getting children out of the zero-dose category in LMICs.

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6. The potential effects of deploying SARS-CoV-2 vaccines on cold storage capacity and immunization workload in countries of the WHO African Region

Ortiz JR, Robertson J, Hsu JS, Yu SL

Vaccine. 2021 Apr 8;39(15):2165-2176.
PubMed ID: 33744049

ABSTRACT

BACKGROUND: SARS-CoV-2 vaccines will be deployed to countries with limited immunization systems.

METHODS: We assessed the effect of deploying SARS-CoV-2 vaccines on cold storage capacity and immunization workload in a simulated WHO African Region country using region-specific data on immunization, population, healthcare workers (HCWs), cold storage capacity (quartile values for national and subnational levels), and characteristics of an approved SARS-CoV-2 vaccine. We calculated monthly increases in vaccine doses, doses per vaccinator, and cold storage volumes for four-month SARS-CoV-2 vaccination campaigns targeting risk groups compared to routine immunization baselines.

RESULTS: Administering SARS-CoV-2 vaccines to risk groups would increase total monthly doses by 27.0% for ≥ 65 years, 91.7% for chronic diseases patients, and 1.1% for HCWs. Assuming median nurse density estimates adjusted for absenteeism and proportion providing immunization services, SARS-CoV-2 vaccination campaigns would increase total monthly doses per vaccinator by 29.3% for ≥ 65 years, 99.6% for chronic diseases patients, and 1.2% for HCWs. When we applied quartiles of actual African Region country vaccine storage capacity, routine immunization vaccine volumes exceeded national-level storage capacity for at least 75% of countries, but subnational levels had sufficient storage capacity for SARS-CoV-2 vaccines for at least 75% of countries.

CONCLUSIONS: In the WHO African Region, SARS-CoV-2 vaccination campaigns would substantially increase doses per vaccinator and cold storage capacity requirements over routine immunization baselines. Pandemic vaccination campaigns would increase storage requirements of national-level stores already at their limits, but sufficient capacity exists at subnational levels. Immediate attention to strengthening immunization systems is essential to support pandemic responses.

WEB: 10.1016/j.vaccine.2021.02.037
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

In this article, Ortiz *et al.* estimate the effect of deploying SARS-CoV-2 vaccines on cold storage capacity and immunization workload in the African Region. Authors did not focus on a specific country, but rather aimed to describe the potential impact of SARS-CoV-2 vaccines on immunization systems for a simulated country with a population of 20 million with an age distribution similar to the African region. Authors compare vaccine storage volumes and number of doses needed for routine immunization (i.e., non-pandemic immunization programs) alone and with SARS-CoV-2 mass vaccination campaigns. Estimates were then compared to actual vaccine cold storage capacities in countries in Africa. Outcomes included the monthly percentage increases in vaccine doses to be administered, doses administered per vaccinator, and cold storage volume requirements for mass vaccination campaigns compared to routine immunization. Some key assumptions included that SARS-CoV-2 mass vaccination campaigns prioritized at-risk groups identified by the WHO and included people over 65 years of age, those with certain chronic medical conditions, and healthcare workers, that the routine immunization would be based on current WHO policies, and the volume per dose required was the same as the SARS-CoV-2 vaccine developed by AstraZeneca/Oxford University and produced by Serum Institute of India. Vaccine storage volume estimates were determined through WHO tools and guidance, which assumed 3% wastage, 0% reserve stock, and monthly resupply intervals. Estimates for vaccine cold storage capacity were obtained from Gavi, the Vaccine Alliance.

Ortiz *et al.* estimated that 11.8% of the population would need to be vaccinated; 3.1% of the population are 65 or older, 10.4% have chronic conditions, and 0.1% are healthcare workers. In addition to the 1,030,931 doses given monthly, an additional 1,058,536 doses (representing a 103.7% monthly increase) would be needed to target the at-risk group with the SARS-CoV-2 vaccine. The immunization workload would increase 112.7%, from 165.3 to 186.3 doses per month per vaccinator. The total storage capacity would range from 38,403 L to 1,605,826 L, and national-level storage capacity would range from 12,535 L to 524,141 L. Interestingly, at the national level, only the highest value capacity had enough storage for routine immunizations, indicating that they did not have storage space for additional vaccines. However, at subnational levels, there was excess storage space, indicating that there would be capacity for SARS-CoV-2 vaccines in at least 75% of countries. These results are presented in detail in *Table 5. Maximum monthly storage volume for routine and SARS-CoV-2 vaccines by quartile of African Region country storage capacity.* This study is impactful as it focuses on the challenges of vaccine deployment and delivery and takes into account actual immunization, population, healthcare worker density, cold storage capacity data available for the region, and approved SARS-CoV-2 vaccine characteristics. Some limitations are that this study only includes characteristics for one vaccine product, whereas others with different requirements (e.g., different temperature requirements, single dose) are available or in development.

The authors conclude that African countries are likely have adequate subnational-levels storage capacity to accommodate SARS-CoV-2 vaccines for mass vaccination campaigns, but the planning and implementation must be executed carefully to ensure adequate surge capacity.

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7. Epidemiological, clinical, and public health response characteristics of a large outbreak of diphtheria among the Rohingya population in Cox's Bazar, Bangladesh, 2017 to 2019: A retrospective study

Polonsky JA, Ivey M, Mazhar MKA, Rahman Z

PLoS Med. 2021 Apr 1;18(4):e1003587.

PubMed ID: 33793554

ABSTRACT

BACKGROUND: Unrest in Myanmar in August 2017 resulted in the movement of over 700,000 Rohingya refugees to overcrowded camps in Cox's Bazar, Bangladesh. A large outbreak of diphtheria subsequently began in this population.

METHODS AND FINDINGS: Data were collected during mass vaccination campaigns (MVCs), contact tracing activities, and from 9 Diphtheria Treatment Centers (DTCs) operated by national and international organizations. These data were used to describe the epidemiological and clinical features and the control measures to prevent transmission, during the first 2 years of the outbreak. Between November 10, 2017 and November 9, 2019, 7,064 cases were reported: 285 (4.0%) laboratory-confirmed, 3,610 (51.1%) probable, and 3,169 (44.9%) suspected cases. The crude attack rate was 51.5 cases per 10,000 person-years, and epidemic doubling time was 4.4 days (95% confidence interval [CI] 4.2-4.7) during the exponential growth phase. The median age was 10 years (range 0-85), and 3,126 (44.3%) were male. The typical symptoms were sore throat (93.5%), fever (86.0%), pseudomembrane (34.7%), and gross cervical lymphadenopathy (GCL; 30.6%). Diphtheria antitoxin (DAT) was administered to 1,062 (89.0%) out of 1,193 eligible patients, with adverse reactions following among 229 (21.6%). There were 45 deaths (case fatality ratio [CFR] 0.6%). Household contacts for 5,702 (80.7%) of 7,064 cases were successfully traced. A total of 41,452 contacts were identified, of whom 40,364 (97.4%) consented to begin chemoprophylaxis; adherence was 55.0% (N = 22,218) at 3-day follow-up. Unvaccinated household contacts were vaccinated with 3 doses (with 4-week interval), while a booster dose was administered if the primary vaccination schedule had been completed. The proportion of contacts vaccinated was 64.7% overall. Three MVC rounds were conducted, with administrative coverage varying between 88.5% and 110.4%. Pentavalent vaccine was administered to those aged 6 weeks to 6 years, while tetanus and diphtheria (Td) vaccine was administered to those aged 7 years and older. Lack of adequate diagnostic capacity to confirm cases was the main limitation, with a majority of cases unconfirmed and the proportion of true diphtheria cases unknown.

CONCLUSIONS: To our knowledge, this is the largest reported diphtheria outbreak in refugee settings. We observed that high population density, poor living conditions, and fast growth rate were associated with explosive expansion of the outbreak during the initial exponential growth phase.

Three rounds of mass vaccinations targeting those aged 6 weeks to 14 years were associated with only modestly reduced transmission, and additional public health measures were necessary to end the outbreak. This outbreak has a long-lasting tail, with Rt oscillating at around 1 for an extended period. An adequate global DAT stockpile needs to be maintained. All populations must have access to health services and routine vaccination, and this access must be maintained during humanitarian crises.

WEB: 10.1371/journal.pmed.1003587
IMPACT FACTOR: 10.500
CITED HALF-LIFE: 8.4

START COMMENTARY

In this retrospective study, Polonsky *et al.* present the epidemiological, clinical, and public health response characteristics of large outbreaks of diphtheria among a highly vulnerable Rohingya refugee population in Cox's Bazar, Bangladesh. Data were collected from 9 Diphtheria Treatment Centers (DTCs) during the first 2 years of the ongoing outbreak from November 10, 2017 to November 9, 2019. Field investigators used a standardized case investigation form that included detailed sociodemographic characteristics, history of contact with known cases, and vaccination history. Further, clinical and laboratory results were recorded and used to classify cases as suspected, probable, and confirmed.

The authors reported 7,064 cases with diphtheria among the Rohingya population; of these only 4.0% (n=285) were laboratory-confirmed, 51.1% (n=3,610) were probable, and 44.9% (n=3,169) were clinically suspected. Most patients recovered (n=5,850, 82.8%) recovered whereas 45 died from diphtheria yielding a case fatality rate of 0.6%. Sensitivity analyses detected the exponential growth period, when R was estimated to be as high as 3.0 (95% CI 2.8 to 3.3) in the early stage of the epidemic from November 13 to December 7, 2017, which declined over time. The median delay between illness onset to examination was 2 days with an interquartile range (IQR) of 1 to 3 days and a range of 0 to 33 days. About 23.2% (n=1640) of cases reported receiving one dose of diphtheria. However, no fatal cases were vaccinated prior to disease onset. A multi-variable model found that younger age, respiratory distress, presenting with pseudomembrane, and treatment with Diphtheria Antitoxin (DAT) were strongly associated with a higher risk of dying, whereas treatment with an antibiotic was significantly associated with a lower risk of dying. About 80.7% (n=5,702) household contacts were successfully traced leading to a total identification of 41,452 contacts, 97.5% (n=40,364) consented to begin chemoprophylaxis. Nearly 64.7% of household contacts were vaccinated. Limitations of this study include the poor diagnostics which led to few confirmed cases and loss to follow up (i.e., an inability to assess outcomes among 15.2% [n=1,075] of the cases) This study makes an important contribution to the literature as it demonstrates that diphtheria can cause

large, concurrent outbreaks among susceptible populations, such as refugees, and that there is a need for a larger global supply of vaccines and DAT to mitigate future diphtheria threats.

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8. Developing a manufacturing process to deliver a cost effective and stable liquid human rotavirus vaccine

Hamidi A, Hoeksema F, Velthof P, Lemckert A

Vaccine. 2021 Apr 8;39(15):2048-2059.
PubMed ID: 33744044

ABSTRACT

Despite solid evidence of the success of rotavirus vaccines in saving children from fatal gastroenteritis, more than 82 million infants worldwide still lack access to a rotavirus vaccine. The main barriers to global rotavirus vaccine coverage include cost, manufacturing capacity and suboptimal efficacy in low- and lower-middle income countries. One vaccine candidate with the potential to address the latter is based on the novel, naturally attenuated RV3 strain of rotavirus, RV3-BB vaccine administered in a birth dose strategy had a vaccine efficacy against severe rotavirus gastroenteritis of 94% at 12 months of age in infants in Indonesia. To further develop this vaccine candidate, a well-documented and low-cost manufacturing process is required. A target fully loaded cost of goods (COGs) of ≤$3.50 per course of three doses was set based on predicted market requirements. COGs modelling was leveraged to develop a process using Vero cells in cell factories reaching high titers, reducing or replacing expensive reagents and shortening process time to maximise output. Stable candidate liquid formulations were developed allowing two-year storage at 2-8 °C. In addition, the formulation potentially renders needless the pretreatment of vaccinees with antacid to ensure adequate gastric acid neutralization for routine oral vaccination. As a result, the formulation allows small volume dosing and reduction of supply chain costs. A dose ranging study is currently underway in Malawi that will inform the final clinical dose required. At a clinical dose of ≤6.3 log10 FFU, the COGs target of ≤$3.50 per three dose course was met. At a clinical dose of 6.5 log10 FFU, the final manufacturing process resulted in a COGs that is substantially lower than the current average market price, 2.44 USD per dose. The manufacturing and formulation processes were transferred to BioFarma in Indonesia to enable future RV3-BB vaccine production.

WEB: 10.1016/j.vaccine.2021.03.033
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

Hamidi *et al.* describe a low-cost manufacturing process for neonatal rotavirus vaccines. This article is important as it addresses limited manufacturing capacity, one of the main barriers of rotavirus vaccine implementation globally. The authors set up to develop a low-cost, scalable process which could produce a liquid RV3-BB rotavirus vaccine. Three key objectives were

established for the process; firstly, the process should allow for scale-up of the RV3-BB at a cost of goods (COGs) of 3.50 USD per complete vaccination course (i.e., three doses). Secondly, the trypsin should be animal-component free and non-porcine. Lastly, the liquid vaccine formulation should be stable at 2–8°C for two years and during passage through the stomach (i.e., does not require pre-neutralization of gastric acid upon administration).

The authors report a drug substance manufacturing process that could allow for 16 runs on a yearly basis. They report an optimized multiplicity of infection which allowed for a 10-fold more efficient use of master virus seed-stocks. Further, authors report that the process was able to produce consistent harvests with the use of an animal-origin free source of trypsin. Hamidi *et al.* also show results of a virus purification and a novel analytical method for virus particle quantification. Overall, this study shows that it is possible to develop a low-cost manufacturing process for rotavirus vaccines, an important step in increasing access to rotavirus vaccines globally and reducing the burden of fatal gastroenteritis among children globally.

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9. Determining the burden of missed opportunities for vaccination among children admitted in healthcare facilities in India: a cross-sectional study

Albaugh N, Mathew J, Choudhary R, Sitaraman S

BMJ Open. 2021 Mar 19;11(3):e046464.
PubMed ID: 33741673

ABSTRACT

OBJECTIVES: Children accessing healthcare systems represent a vulnerable population with risk factors for poor health outcomes, including vaccine-preventable diseases. We aimed to quantify missed vaccination opportunities among hospitalised children in India, and identify vaccination barriers perceived by caregivers and healthcare providers.

DESIGN: Cross-sectional study.

SETTING: Two public-sector tertiary-care hospitals in northern India, during November 2018 and March 2019.

PARTICIPANTS: We tracked 263 hospitalised children aged 1-59 months through hospital discharge, to assess vaccination status, and document catch-up vaccinations given during the hospital stay. We interviewed caregivers and healthcare providers to assess their perceptions on vaccination.

OUTCOMES: Proportion of hospitalised children considered under-vaccinated for their age; proportion of missed opportunities for vaccination among under-vaccinated children who were eligible for vaccination; and vaccine coverage by antigen.

RESULTS: We found that 65.4% (172/263) of hospitalised children were under-vaccinated for their age when they presented to the hospital. Among under-vaccinated children, 61.0% were less than 4 months old, and 55.6% reported prior contact with a health facility for a sick visit. The proportion of under-vaccinated children in hospitals were higher compared with the general population as indicated by regional vaccination coverage data. Among under-vaccinated children who were tracked till discharge, 98.1% (158/161) remained incompletely vaccinated at discharge and were considered 'missed opportunities for vaccination'. Perceived vaccination contraindications that are not part of established contraindications included in national and international guidelines was the most common reason for healthcare providers not to vaccinate children during hospital stay. Among caregivers of under-vaccinated children, 90.1% reported being comfortable having their children vaccinated while they were sick, if recommended by the healthcare provider.

CONCLUSION: This pilot study confirmed that hospitalised sick children had substantial missed vaccination opportunities. Addressing these opportunities through concerted actions involving caregivers, healthcare providers and healthcare systems can improve overall vaccination coverage.

WEB: 10.1136/bmjopen-2020-046464
IMPACT FACTOR: 2.496
CITED HALF-LIFE: 3.5

START COMMENTARY

In this cross-sectional study, Albaugh *et al.* present the prevalence of under vaccination, missed opportunities for vaccination among under-vaccinated inpatient children, and vaccine coverage by antigen. This article is impactful as it enrolls 263 hospitalized children aged 1-59 months to assess their vaccination status and determine missed opportunities for vaccination during the hospitalization, which provide a critical opportunity to protect susceptible children against vaccine-preventable diseases. Hospitalized children may be particularly at risk of poor health and infectious diseases, underscoring the importance of understanding missed opportunities for vaccinations among this population.

Albaugh *et al.* enrolled children from two tertiary care government hospitalizations in Chandigarh and Jaipur. Vaccination status was assessed using vaccination cards or by recall if unavailable. Additionally, caregivers were interviewed to assess household, demographic, and health seeking factors. Hospital healthcare providers involved in the children's treatment were surveyed anonymously about their professional experiences, vaccination practices, and hospital policies. The primary outcome was the proportion of hospitalized children considered under-vaccinated for their age. Secondary outcomes included the proportion of missed opportunities for vaccination among the under-vaccination children, and vaccine coverage by antigen. Of the 263 children included in the study, 59.7% (n=157) were able to show a vaccination card, whereas 40.3% (n=106) provided vaccination status via recall. About 65.4% (n=172) of children were under vaccinated. The proportion of under vaccinated children was highest in the youngest age group, those under 4 months of age (76.6%, n=59 of 77). In univariate analyses, several factors were significantly associated with under-vaccination, including younger age (i.e., children under 4 months compared to older children), low parental education attainment, mothers not being involved with vaccination decisions, and children who had vaccination status reported through recall rather than a vaccination card. However, in multivariable analysis, these results were no longer significant. The authors found the lowest coverage for OPV3 (53.9%), DPT3 (54.9%) and DPT2 (63.1%). Among the 161 under-vaccinated children that had a chart available at discharge, 98.1% (n=158) represented a missed opportunity for vaccination. Among the 21 healthcare providers that participated in the survey, 95% agreed it was appropriate to vaccinate a hospitalized child. However, 80% also had

concerns about vaccinating a child recovering from an acute illness and 80% did not believe vaccines were available in inpatient units. Although this article shows important findings related to under vaccination in two hospitals in India, there are some important limitations to note. Firstly, the study population is small (n=263 children and n=21 healthcare providers). Secondly, 40% of the vaccination statuses were determined by parental recall, which can be biased. Despite these limitations, this article shows that there are opportunities for under-vaccinated children to receive vaccines when they encounter healthcare facilities, which is relevant for healthcare policies in India.

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10. Incorporating equity in infectious disease modeling: Case study of a distributional impact framework for measles transmission

Menkir TF, Jbaily A, Verguet S.

Vaccine. 2021 Apr 13:S0264-410X(21)00291-7.

PubMed ID: 33863575.

ABSTRACT

INTRODUCTION: Deterministic compartmental models of infectious diseases like measles typically reflect biological heterogeneities in the risk of infection and severity to characterize transmission dynamics. Given the known association of socioeconomic status and increased vulnerability to infection and mortality, it is also critical that such models further incorporate social heterogeneities.

METHODS: Here, we aimed to explore the influence of integrating income-associated differences in parameters of traditional dynamic transmission models. We developed a measles SIR model, in which the Susceptible, Infected and Recovered classes were stratified by income quintile, with income-specific transmission rates, disease-induced mortality rates, and vaccination coverage levels. We further provided a stylized illustration with secondary data from Ethiopia, where we examined various scenarios demonstrating differences in transmission patterns by income and in distributional vaccination coverage, and quantified impacts on disparities in measles mortality.

RESULTS: The income-stratified SIR model exhibited similar dynamics to that of the traditional SIR model, with amplified outbreak peaks and measles mortality among the poorest income group. All vaccination coverage strategies were found to substantially curb the overall number of measles deaths, yet most considerably for the poorest, with select strategies yielding clear reductions in measles mortality disparities.

DISCUSSION: The incorporation of income-specific differences can reveal distinct outbreak patterns across income groups and important differences in the subsequent effects of preventative interventions like vaccination. Our case study highlights the need to extend traditional modeling frameworks (e.g. SIR models) to be stratified by socioeconomic factors like income and to consider ensuing income-associated differences in disease-related morbidity and mortality. In so doing, we build on existing tools and characterize ongoing challenges in achieving health equity.

WEB: 10.1016/j.vaccine.2021.03.023

IMPACT FACTOR: 3.143

CITED HALF-LIFE: 7.3

START COMMENTARY

In this modelling study, Menkir *et al.* integrate income-associated differences in parameters of traditional dynamic transmission models. This study expands the existing body of literature on transmission dynamics by incorporating social heterogeneities related to income, which are known to play an important role in increase vulnerability and progression to disease. Authors describe an income-stratified Susceptible, Infected Recovered (SIR) model which account for income heterogeneity in infection risk and mortality for measles in an Ethiopian setting. The main input parameters for this model include income-specific values for disease transmission rates, measles case-fatality ratios, and vaccination coverage using published modeling parameters and secondary data from Ethiopia. The analysis included five types of income-stratified transmission matrices (scenarios 1-5), which reports the effective contact rate between a susceptible and infected person across any two quintiles. Five distributional vaccine coverage cases were included: 1) Demographic Health Survey (DHS) quintile specific measles containing vaccine (MCV) 1 coverage rates; 2) DHS mean MCV1 coverage; 3) 50% relative increase from the quintile specific MCV1 coverage; 4) quintile coverage set to equal the coverage of the top quintile; 5) full coverage.

Results indicate that the lowest quintile has a higher risk of infection at the epidemic's apex and a higher risk of death. At the onset (in the first twenty days), the lower quintiles reach higher maximum proportions than the upper quintiles. Further, the proportion of deaths due to measles decreases with income. *Figure 2* demonstrates these trends by showing the mean values for the Susceptible, Infected, Recovered, and Deceased for quintile 1 and 5. Unsurprisingly, increasing coverage rates reduces disease mortality, particularly for low-income quintiles. However, there are marked differences in the reduction of measles deaths by quintile in each scenario, which are shown in *Figure 2.* In conclusion, this article shows how SIR models for infectious disease, which are closely related to income and other social determinants, could incorporate income-associated heterogeneities. The inclusion of these considerations allows greater understanding of the distribution of infectious disease burden which can inform future vaccination efforts and promote health equity.

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Appendix

The literature search for the May 2021 Vaccine Delivery Research Digest was conducted on April, 23, 2021. We searched English language articles indexed by the US National Library of Medicine and published between March 15, 2021 and April 14, 2021. The search resulted in 369 items.

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]) (“2021/03/15”[PDAT] : “2021/04/14”[PDAT]))