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1. From cervical cancer elimination to eradication of vaccine-type human papillomavirus: Feasibility, public health strategies and cost-effectiveness.

Jit M, Prem K, Benard E, Brisson M.

Prev Med. 2020 Dec 19:106354.
PubMed ID: 33309871

ABSTRACT

The Director-General of the World Health Organization has called for global action towards elimination of cervical cancer as a public health problem. Cervical cancer is caused by human papillomavirus (HPV), an infectious agent with no non-human reservoir. One way to achieve this is through very high levels of vaccine coverage that could enable global eradication of vaccine-type HPV. Using the case study of India, we show that HPV eradication can meet all the Dahlem and Strüngmann criteria for feasibility of eradication. It can be achieved with 90% gender-neutral HPV vaccine coverage together with 95% coverage in high-risk groups such as female sex workers. Such a strategy would likely be cost-effective compared to no vaccination. Although it would be more costly in the short-term than achieving cervical cancer elimination alone, it would save costs in the long-term by removing or at least sharply reducing the need for preventive measures.

WEB: 10.1016/j.ypmed.2020.106354
IMPACT FACTOR: 3.788
CITED HALF-LIFE: 7.6

START COMMENTARY

Jit *et al.* use mathematical modelling using epidemiologic and economic data from India to explore key criteria and cost-effectiveness of the public health strategies needed to achieve elimination and eradication of cervical cancer. The analysis combined epidemiological outcomes from an individual-based dynamic model (HPV-ADVISE) and economic parameters from a multi-cohort, static, proportional impact model (PRIME) to evaluate outcomes from three vaccination strategies compared to the no HPV vaccination scenario: 1) 80% vaccine coverage of 10-year old females (80% F), 2) 90% vaccine coverage of all 10-year olds (90% F + M), and 3) 90% vaccine coverage of

all 10-year olds together with 95% vaccine coverage of female sex workers (90% F + M, 95% FSW). The authors present average (i.e., vs no vaccination) and incremental cost-effectiveness ratios (i.e., vs the next most costly option) for different vaccine strategies and different discounting of health effects and costs (0% and 3%). The model projected that only the 90% F + M, 95% FSW scenario met an eradication target for vaccine-type HPV (prevalence < 10 cases per 100,000 population, in the year 2100). Both an elimination strategy (80% F) and an eradication strategy (90% F + M, 95% FSW) were likely to be cost-effective compared to India's GDP per capita threshold, with the cost per DALY averted levelled off at approximately US $58 and $151, respectively. When health effects were undiscounted, both strategies were found to be cost-effective with a much lower threshold ($3 and $6 per DALY averted, respectively). While an eradication strategy will initially cost more due to the need to deliver more than twice as many vaccine doses, costs will drop to zero after 2100. The distinction between elimination and eradication will become increasingly important as we approach the disease end game and make the case for international cooperation. *Jit et al.* argue that elimination should be regarded as a milestone towards eradication, as the eradication of vaccine-type HPV is feasible, cost-effective compared to no vaccination, and will eventually bring greater and more equitable benefits than elimination alone.

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2. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK.

Voysey M, Clemens S, Madhi S, Weckx L, Folegatti P, Aley P, et al.

Lancet. 2020 Dec 17.

PubMed ID: 3330698933293710

ABSTRACT

BACKGROUND: A safe and efficacious vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), if deployed with high coverage, could contribute to the control of the COVID-19 pandemic. We evaluated the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in a pooled interim analysis of four trials.

METHODS: This analysis includes data from four ongoing blinded, randomised, controlled trials done across the UK, Brazil, and South Africa. Participants aged 18 years and older were randomly assigned (1:1) to ChAdOx1 nCoV-19 vaccine or control (meningococcal group A, C, W, and Y conjugate vaccine or saline). Participants in the ChAdOx1 nCoV-19 group received two doses containing 5 x 10^{10} viral particles (standard dose; SD/SD cohort); a subset in the UK trial received a half dose as their first dose (low dose) and a standard dose as their second dose (LD/SD cohort). The primary efficacy analysis included symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test-positive swab more than 14 days after a second dose of vaccine. Participants were analysed according to treatment received, with data cutoff on Nov 4, 2020. Vaccine efficacy was calculated as 1 − relative risk derived from a robust Poisson regression model adjusted for age. Studies are registered at ISRCTN89951424 and ClinicalTrials.gov, NCT04324606, NCT04400838, and NCT04444674.

FINDINGS: Between April 23 and Nov 4, 2020, 23 848 participants were enrolled and 11 636 participants (7548 in the UK, 4088 in Brazil) were included in the interim primary efficacy analysis. In participants who received two standard doses, vaccine efficacy was 62.1% (95% CI 41.0–75.7; 27 [0.6%] of 4440 in the ChAdOx1 nCoV-19 group vs 71 [1.6%] of 4455 in the control group) and in participants who received a low dose followed by a standard dose, efficacy was 90.0% (67.4–97.0; three [0.2%] of 1367 vs 30 [2.2%] of 1374; p interaction=0.010). Overall vaccine efficacy across both groups was 70.4% (95.8% CI 54.8–80.6; 30 [0.5%] of 5807 vs 101 [1.7%] of 5829). From 21 days after the first dose, there were ten cases hospitalised for COVID-19, all in the control arm; two were

classified as severe COVID-19, including one death. There were 74 341 person-months of safety follow-up (median 3.4 months, IQR 1.3–4.8): 175 severe adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group. Three events were classified as possibly related to a vaccine: one in the ChAdOx1 nCoV-19 group, one in the control group, and one in a participant who remains masked to group allocation.

INTERPRETATION: ChAdOx1 nCoV-19 has an acceptable safety profile and has been found to be efficacious against symptomatic COVID-19 in this interim analysis of ongoing clinical trials.

WEB: 10.1016/S0140-6736(20)32661-1
IMPACT FACTOR: 60.39
CITED HALF-LIFE: 8.6

START COMMENTARY

Voysey *et al.* report on the clinical efficacy results of ChAdOx1 nCoV-19 in a pooled interim analysis of phase 2/3 trials in Brazil and the United Kingdom (UK), and safety data from more than 20,000 participants enrolled across four randomized clinical trials ongoing in Brazil, South Africa, and the UK. This article is impactful as it is the first peer-reviewed publication on a COVID-19 vaccine candidate. Additionally, as this chimpanzee adenoviral vector vaccine can be stored and distributed at 2–8°C, it is particularly suitable for global distribution and thus could have wider application in combating the COVID-19 pandemic in low- and middle-income countries. The study used a Poisson regression model with robust variance adjusted for age to compute vaccine efficacy = 1 − relative risk. The analysis found that ChAdOx1 nCoV-19 is efficacious against symptomatic COVID-19, with significant vaccine efficacy of 70.4% (95.8% CI: 54.8–80.6) after two doses. Due to differences with quantification of initial ChAdOx1 nCoV-19 vaccine doses, a subset of 1,367 participants in the UK received one low-dose vaccine and a second standard-dose vaccine. This subset showed an intriguingly high vaccine efficacy of 90.0% (95% CI: 67.4–97.0), however the wide CIs indicate that more data are needed to confirm preliminary findings. In the participants who received ChAdOx1 nCoV-19, there were two hospitalizations (vs. 16 in the control arm), one event classified as possibly related to the vaccine (vs. 1 in the control arm and 1 unmasked), and no severe cases of COVID-19 (vs. 2 in control arm). Serious adverse events (SAEs) and adverse events (AEs) were balanced across the study arms, with SAEs in 168 participants (79 ChAdOx1 nCoV-19 arm, 89 control arm) and 175 AEs (84 ChAdOx1 nCoV-19 arm, 91 control arm). As the development of safe, effective, affordable, and deployable vaccines against COVID-19 remains paramount in solving the pandemic crisis, the positive results presented in this study support continued follow-up towards regulatory submissions for conditional or emergency use of ChAdOx1 nCoV-19.

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3. Timeliness of immunisation with the pentavalent vaccine at different levels of the health care system in the Lao People's Democratic Republic: A cross-sectional study.

Hefele L, Syphan S, Xayavong D, Homsana A, Kleine D, Chanthavilay P, et al.

PLoS One. 2020 Dec 17;15(12):e0242502.
PubMed ID: 33290386

ABSTRACT

BACKGROUND: The timely administration of vaccines is considered to be important for both individual and herd immunity. In this study, we investigated the timeliness of the diphtheria-tetanus-whole cell pertussis-hepatitis B-Haemophilus influenzae type b (pentavalent) vaccine, scheduled at 6, 10 and 14 weeks of age in the Lao People's Democratic Republic. We also investigated factors associated with delayed immunization.

METHODS: 1162 children aged 8-28 months who had received the full course of the pentavalent vaccine at different levels of the health care system were enrolled. Vaccination dates documented in hospital records and/or immunisation cards were recorded. Age at vaccination and time intervals between doses were calculated. Predictors for timely completion with the pentavalent vaccine at 24 weeks were assessed by bivariate and multivariable analyses.

RESULTS: Several discrepancies in dates between vaccination documents were observed. In general, vaccination with the pentavalent vaccine was found to be delayed, especially in health care settings below the provincial hospital level. Compared to the central hospital level, less participants who were vaccinated at the district/health center level received the third dose by 16 (48% at the central hospital level vs. 7.1% at the district and 12.4% at the health center level) and 24 weeks of age (94.4% at the central hospital level vs 64.6% at the district-outreach and 57.4% at the health center level) respectively. In logistic regression analyses, lower education level of the mother as well as vaccination by outreach service, were independently associated with delayed completion of vaccination.

CONCLUSION: We observed a general delay of vaccination, especially at lower ranked facilities, which correlated with indicators of poor access to health services. This highlights the need for further improving health equity in rural areas. Age-appropriate vaccination should become a quality indicator

for the national immunization programme. In addition, we recommend further training of the health care staff regarding the importance of reliable documentation of dates.

WEB: 10.1371/journal.pone.0242502
IMPACT FACTOR: 2.74
CITED HALF-LIFE: 5.6

START COMMENTARY

In this cross-sectional study, Hefele *et al.* analyze documentation and timeliness of pentavalent immunization among 1162 children who received the full course of pentavalent vaccination from 2017-2018 in Lao People's Democratic Republic (PDR). Hospital records and immunization cards were collected at various levels of the health care system, including central hospitals (n=319), provincial hospitals (n=197), district hospitals (n=206), and health centers (n=440) (ordered highest to lowest level of care). Serum samples were taken to assess antibody levels, and additional information on socio-economic background, access to health care, history and location of vaccination were obtained through a standardized questionnaire. Vaccination was defined as "timely" when between 6–7 weeks for the first dose, 10–11 weeks for the second dose, and 14–15 weeks for the third dose, with 16 weeks and 24 weeks as cut-offs for "early timely" and "late timely" completion of pentavalent vaccination. Participants vaccinated at health centers had the largest mean discrepancy between recorded vaccination dates (-9.9 days) and highest proportion of mismatches (41.1%). The proportion of children with early timely vaccine completion was 48% at the central hospital level (95% CI: 42.6–53.6), compared to 7.1% at the district level (95% CI: 3.4–10.8) and 12.4% health level (95% CI: 9.2–15.5). Logistic regression showed greater odds of timely vaccine completion among participants who had received the hepatitis B birth dose (OR: 2.14, 95% CI: 1.42–3.24), had higher maternal education (OR: 1.64, 95% CI: 1.09–2.47), and higher maternal age (OR: 1.05, 95% CI: 1.01–1.09), as well as lower odds among those who were vaccinated through outreach services (OR: 0.23, 95% CI: 0.14–0.36) and had fewer number of siblings (OR: 0.81, 95% CI: 0.69–0.94). In total, 22% of the children did not complete the pentavalent immunization by the age of 24 weeks. While the study found no negative impact of delayed vaccination on seroconversion rates, delayed vaccination increases the window of susceptibility and may facilitate disease outbreaks. Limitations of this study include potential recall bias of location of vaccination (outreach vs. facility, collected through the questionnaire), as well as the inability to provide information on children who missed pentavalent doses. The authors demonstrate the need for improvements to vaccine documentation and suggest including timely completion of vaccination as a quality indicator in the Lao PDR national immunization program.

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4. Complete basic childhood vaccination and associated factors among children aged 12-23 months in East Africa: a multilevel analysis of recent demographic and health surveys.

Tesema G, Tessema Z, Tamirat K, Teshale A.

BMC Public Health. 2020 Dec 07;20(1):1837.
PubMed ID: 33256701

ABSTRACT

Background: Complete childhood vaccination remains poor in Sub-Saharan Africa, despite major improvement in childhood vaccination coverage worldwide. Globally, an estimated 2.5 million children die annually from vaccine-preventable diseases. While studies are being conducted in different East African countries, there is limited evidence of complete basic childhood vaccinations and associated factors in East Africa among children aged 12-23 months. Therefore, this study aimed to investigate complete basic childhood vaccinations and associated factors among children aged 12-23 months in East Africa.

Methods: Based on the Demographic and Health Surveys (DHSs) of 12 East African countries (Burundi, Ethiopia, Comoros, Uganda, Rwanda, Tanzania, Mozambique, Madagascar, Zimbabwe, Kenya, Zambia, and Malawi), secondary data analysis was performed. The study included a total weighted sample of 18,811 children aged 12-23 months. The basic childhood vaccination coverage was presented using a bar graph. Multilevel binary logistic regression analysis was fitted for identifying significantly associated factors because the DHS has a hierarchical nature. The Intra-class Correlation Coefficient (ICC), Median Odds Ratio (MOR), Proportional Change in Variance (PCV), and deviance (-2LLR) were used for checking model fitness, and for model comparison. Variable with p-value ≤0.2 in the bi-variable multilevel analysis were considered for the multivariable analysis. In the multivariable multilevel analysis, the Adjusted Odds Ratio (AOR) with 95% Confidence Interval (CI) were reported to declare the significance and strength of association with full vaccination.

Results: Complete basic childhood vaccination in East Africa was 69.21% (95% CI, 69.20, 69.21%). In the multivariable multilevel analysis; Mothers aged 25-34 years (AOR = 1.21, 95% CI: 1.10, 1.32), mothers aged 35 years and above (AOR = 1.50, 95% CI: 1.31, 1.71), maternal primary education (AOR = 1.26, 95% CI: 1.15, 1.38), maternal secondary education and above (AOR = 1.54, 95% CI: 1.36, 1.75), husband primary education (AOR = 1.25, 95% CI: 1.13, 1.39), husband secondary education and above (AOR = 1.24, 95% CI: 1.11, 1.40), media exposure (AOR = 1.23, 95% CI: 1.13,

1.33), birth interval of 24-48 months (AOR = 1.28, 95% CI: 1.15, 1.42), birth interval greater than 48 months (AOR = 1.35, 95% CI: 1.21, 1.50), having 1-3 ANC visit (AOR = 3.24, 95% CI: 2.78, 3.77), four and above ANC visit (AOR = 3.68, 95% CI: 3.17, 4.28), PNC visit (AOR = 1.34, 95% CI: 1.23, 1.47), health facility delivery (AOR = 1.48, 95% CI: 1.35, 1.62), large size at birth 1.09 (AOR = 1.09, 95% CI: 1.01, 1.19), being 4-6 births (AOR = 0.83, 95% CI: 0.75, 0.91), being above the sixth birth (AOR = 0.60, 95% CI: 0.52, 0.70), middle wealth index (AOR = 1.16, 95% CI: 1.06, 1.28), rich wealth index (AOR = 1.20, 95% CI: 1.09, 1.33), community poverty (AOR = 1.21, 95% CI: 1.11, 1.32) and country were significantly associated with complete childhood vaccination.

Conclusions: In East Africa, full basic childhood vaccine coverage remains a major public health concern with substantial differences across countries. Complete basic childhood vaccination was significantly associated with maternal age, maternal education, husband education, media exposure, preceding birth interval, number of ANC visits, PNC visits, place of delivery, child-size at birth, parity, wealth index, country, and community poverty. Public health interventions should therefore target children born to uneducated mothers and fathers, poor families, and those who have not used maternal health services to enhance full childhood vaccination to reduce the incidence of child mortality from vaccine-preventable diseases.

WEB: 10.1186/s12889-020-09965-y
IMPACT FACTOR: 2.521
CITED HALF-LIFE: 6

START COMMENTARY

Tesema *et al.* utilize Demographic Health Survey data from 12 East African countries to explore basic childhood vaccination coverage and associated individual factors (e.g., maternal age, sex of child) and community factors (e.g., community media exposure, community poverty) among children aged 12-23 months. Extracted from mother's verbal records and childhood immunization cards, complete basic childhood vaccination included one dose of BCG vaccine, three doses of pentavalent vaccine, three doses of polio vaccine, and one dose of measles vaccine before the age of 12 months. The multilevel logistic regression analysis included four models to assess and address cluster variability. Among the weighted sample of 18,811 children, the overall complete basic childhood vaccination was achieved in 69.21% (95% CI: 69.20–69.21) with wide variation across countries ranging from 39.5% in Ethiopia to 85% in Burundi. The proportion of partially vaccinated children ranged from 13.4% in Zimbabwe to 56.1% in Rwanda, while the proportion of non-vaccinated children ranged from 0.4% in Burundi to 16% in Ethiopia. The study used cross-sectional data that was subject to recall bias when mother's verbal records was the only available form of immunization data, and thus findings may be under or overestimated and cannot establish a causal relationship between complete vaccination and independent variables. Despite these limitations,

Tesema *et al.* underscore the importance of targeting public health interventions to prioritized groups (i.e., parents with low education levels, mothers who didn't use maternal health care services, and poor households) to improve complete childhood vaccination coverage and enhance child survival.

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5. Cost-Effectiveness Analysis of BCG Vaccination against Tuberculosis in Indonesia: A Model-Based Study.

Machlaurin A, Dolk F, Setiawan D, van der Werf T, Postma M.

Vaccines (Basel). 2020 Dec 07;8(4).
PubMed ID: 33256143

ABSTRACT

Bacillus Calmette-Guerin (BCG), the only available vaccine for tuberculosis (TB), has been applied for decades. The Indonesian government recently introduced a national TB disease control programme that includes several action plans, notably enhanced vaccination coverage, which can be strengthened through underpinning its favourable cost-effectiveness. We designed a Markov model to assess the cost-effectiveness of Indonesia's current BCG vaccination programme. Incremental cost-effectiveness ratios (ICERs) were evaluated from the perspectives of both society and healthcare. The robustness of the analysis was confirmed through univariate and probabilistic sensitivity analysis (PSA). Using epidemiological data compiled for Indonesia, BCG vaccination at a price US$14 was estimated to be a cost-effective strategy in controlling TB disease. From societal and healthcare perspectives, ICERs were US$104 and US$112 per quality-adjusted life years (QALYs), respectively. The results were robust for variations of most variables in the univariate analysis. Notably, the vaccine's effectiveness regarding disease protection, vaccination costs, and case detection rates were key drivers for cost-effectiveness. The PSA results indicated that vaccination was cost-effective even at US$175 threshold in 95% of cases, approximating the monthly GDP per capita. Our findings suggest that this strategy was highly cost-effective and merits prioritization and extension within the national TB programme. Our results may be relevant for other high endemic low- and middle-income countries.

WEB: 10.3390/vaccines8040707
IMPACT FACTOR: 4.086
CITED HALF-LIFE: 3.4

START COMMENTARY

Machlaurin *et al.* modeled a cost-effectiveness analysis of the Bacillus Calmette-Guerin (BCG) vaccination program in Indonesia, where tuberculosis (TB) incidence is high. The authors model 4.9 million infants representing the 2017 birth cohort over a lifetime horizon of 70 years, with costs and outcomes discounted at 3%, and results presented in US dollars. The study found that BCG vaccination could prevent 49,713 TB cases and 7,598 TB deaths and had a 100% probability of

being cost-effective at a price of $14/infant and threshold value of one GDP per capita in Indonesia ($3,847). The largest driver of the incremental cost-effectiveness ratios (ICERs) was vaccine effectiveness to prevent disease, followed by vaccination cost, case detection rate, and mortality of untreated TB. BCG vaccination was very cost-effective compared to no vaccination from both a healthcare payer (ICER: $104/QALY) and societal perspective (ICERs: $112/QALY). Increasing the assumption of linear waning of vaccine effectiveness from 10 to 20 years resulted in an almost twofold increase in the respective ICERs for society and healthcare perspective ($226/QALY, $233/QALY); however ICERs did not differ significantly with exponential waning ($113/QALY societal, $121/QALYs healthcare perspective). Limitations of this study include using a linear model that did not evaluate indirect benefits of BCG vaccination and a lack of Indonesia specific BCG vaccine efficacy estimates. As more individual-level data becomes available in Indonesia, future studies will be needed. These results support the continuation of Indonesia's current BCG vaccination program and may be applicable for decision-makers in other low-resource countries with high TB incidence.

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6. The Magnitude and Determinants of Missed Opportunities for Childhood Vaccination in South Africa.

Ndwandwe D, Nnaji C, Wiysonge C.

Vaccines (Basel). 2020 Dec 07;8(4).
PubMed ID: 33255767

ABSTRACT

Missed opportunities for vaccination (MOV) may be among the factors responsible for suboptimal vaccination coverage in South Africa. However, the magnitude and determinants of MOV in the country are not known. Thus, this study seeks to assess the prevalence and determinants of MOV in the country. South Africa is sub-divided into nine administrative provinces. We used nationally representative data from the 2016 South African Demographic and Health Survey. We considered MOV to have occurred if a child aged 12-23 months old had not taken all scheduled basic vaccine doses despite having any of the following contacts with health services: delivery in a health facility; postnatal clinic visit; receipt of vitamin A; and any child-related treatment at a health facility. Multilevel logistic regression was used to determine factors associated with MOV. The national prevalence of MOV among children aged 12-23 months was 40.1%. Children whose mothers attended facility-based antenatal care were considerably less likely to experience MOV than those whose mothers did not attend antenatal care: odds ratio (OR) 0.41, 95% confidence interval (CI) 0.19 to 0.88. Conversely, the independent predictor of an increased MOV among children was residence in either the Gauteng province (OR 2.97, 95% CI 1.29 to 6.81) or Mpumalanga province (OR 2.32, 95%CI 1.04 to 5.18); compared to residence in the Free State province. Our findings suggest a high burden of MOV among children in South Africa and that MOV may be associated with individual and contextual factors. The findings also underscore the need for further exploration of the contextual factors contributing to MOV in South Africa.

WEB: 10.3390/vaccines8040705
IMPACT FACTOR: 4.086
CITED HALF-LIFE: 3.4

START COMMENTARY

Ndwandwe *et al.* use cross-sectional, population-representative household survey data to assess the prevalence and associated factors of missed opportunities for vaccination (MOV) among children aged 12–23 months in South Africa. Extracted from mother's verbal reports and immunization cards from the 2016 Demographic and Health Survey, the study defined MOV as any child with health

service contact but missing at least one recommended vaccine (i.e., one dose of BCG vaccine, three doses of pentavalent vaccine, four doses of polio vaccine, three doses of DTP vaccine, and one dose of measles vaccines) by the time of the survey. The analysis used multilevel logistic regression to determine factors associated with MOV, and Bayesian information criterion to assess the model's goodness of fit and applied variance inflation factor to test for multicollinearity. The magnitude of MOV was substantial, with a MOV prevalence of 40.1% among 708 children included. Findings illustrate that maternal and geographical factors are important determinants for missed opportunities for vaccination in South Africa. While the adjusted odds of MOV was lower among children of mothers who attended antenatal care vs. not (AOR 0.41, 95% CI: 0.19–0.88), the odds of MOV was nearly three times higher among children residing in the Gauteng (OR 2.97, 95% CI: 1.29–6.81) and Mpumalanga (OR 2.32, 95% CI: 1.04–5.18) provinces compared to children living in the Free State. Limitations include potential vaccine recall bias, as well as inability to account for the temporality of children's contacts with health services. This could lead to overestimated MOV in children who had early neonatal contact before becoming eligible for all doses, although most children included had multiple health contacts. This study highlights disparities and gaps in the childhood vaccination in South Africa and provides decision-makers with insight to inform future research and enable contextually tailored policy and vaccination strategies to address current immunization barriers.

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7. Estimated impact of RTS,S/AS01 malaria vaccine allocation strategies in sub-Saharan Africa: A modelling study.

Hogan A, Winskill P, Ghani A.

PLoS Med. 2020 Dec 07;17(11):e1003377.
PubMed ID: 33253211

ABSTRACT

Background: The RTS,S/AS01 vaccine against Plasmodium falciparum malaria infection completed phase III trials in 2014 and demonstrated efficacy against clinical malaria of approximately 36% over 4 years for a 4-dose schedule in children aged 5-17 months. Pilot vaccine implementation has recently begun in 3 African countries. If the pilots demonstrate both a positive health impact and resolve remaining safety concerns, wider roll-out could be recommended from 2021 onwards. Vaccine demand may, however, outstrip initial supply. We sought to identify where vaccine introduction should be prioritised to maximise public health impact under a range of supply constraints using mathematical modelling.

Methods and findings: Using a mathematical model of P. falciparum malaria transmission and RTS,S vaccine impact, we estimated the clinical cases and deaths averted in children aged 0-5 years in sub-Saharan Africa under 2 scenarios for vaccine coverage (100% and realistic) and 2 scenarios for other interventions (current coverage and World Health Organization [WHO] Global Technical Strategy targets). We used a prioritisation algorithm to identify potential allocative efficiency gains from prioritising vaccine allocation among countries or administrative units to maximise cases or deaths averted. If malaria burden at introduction is similar to current levels-assuming realistic vaccine coverage and country-level prioritisation in areas with parasite prevalence >10%-we estimate that 4.3 million malaria cases (95% credible interval [CrI] 2.8-6.8 million) and 22,000 deaths (95% CrI 11,000-35,000) in children younger than 5 years could be averted annually at a dose constraint of 30 million. This decreases to 3.0 million cases (95% CrI 2.0-4.7 million) and 14,000 deaths (95% CrI 7,000-23,000) at a dose constraint of 20 million, and increases to 6.6 million cases (95% CrI 4.2-10.8 million) and 38,000 deaths (95% CrI 18,000-61,000) at a dose constraint of 60 million. At 100% vaccine coverage, these impact estimates increase to 5.2 million cases (95% CrI 3.5-8.2 million) and 27,000 deaths (95% CrI 14,000-43,000), 3.9 million cases (95% CrI 2.7-6.0 million) and 19,000 deaths (95% CrI 10,000-30,000), and 10.0 million cases (95% CrI 6.7-15.7 million) and 51,000 deaths (95% CrI 25,000-82,000), respectively. Under realistic vaccine coverage, if the vaccine is prioritised sub-nationally, 5.3 million cases (95% CrI 3.5-8.2 million) and 24,000 deaths (95% CrI 12,000-38,000) could be averted at a dose constraint of 30 million. Furthermore,

sub-national prioritisation would allow introduction in almost double the number of countries compared to national prioritisation (21 versus 11). If vaccine introduction is prioritised in the 3 pilot countries (Ghana, Kenya, and Malawi), health impact would be reduced, but this effect becomes less substantial (change of <5%) if 50 million or more doses are available. We did not account for within-country variation in vaccine coverage, and the optimisation was based on a single outcome measure, therefore this study should be used to understand overall trends rather than guide country-specific allocation.

Conclusions: These results suggest that the impact of constraints in vaccine supply on the public health impact of the RTS,S malaria vaccine could be reduced by introducing the vaccine at the sub-national level and prioritising countries with the highest malaria incidence.

WEB: 10.1371/journal.pmed.1003377
IMPACT FACTOR: 10.5
CITED HALF-LIFE: 8.4

START COMMENTARY

Hogan *et al.* use a mathematical model of malaria transmission to estimate the impact of the RTS,S malaria vaccine at varying supply constraints, vaccine coverage levels, and intervention scenarios in malaria-endemic regions sub-Saharan Africa. A ranking algorithm was applied to explore optimal vaccine allocation at the country and sub-national level in the first five years following vaccine introduction in children up to five years old. The study found that if initial malaria vaccine demand is higher than supply, prioritizing the countries with the highest incidence would have the greatest impact in reducing malaria burden. Vaccine allocation modelled at the sub-national level was shown to maximize the overall public health benefit by averting the greatest number of clinical malaria cases and deaths. Additionally, sub-national implementation was more efficient and equitable, allowing RTS,S introduction in almost twice as many countries (21 vs. 11 with country level introduction) and providing earlier access for high risk populations. Spatial estimates of malaria levels differ in quality by country and thus may not fully capture variation at finer spatial scales. Furthermore, suboptimal scenarios can be indistinguishable from the optimal scenarios from a public health perspective because they are based on very small differences and thus, findings from this study should be considered in the context of understanding overall patterns rather than as directly guiding country-specific prioritization. This study can inform vaccine allocation if RTS,S is recommended to be implemented more widely; however, additional research would be needed to define locally appropriate metrics for vaccine prioritization, including in the context of local malaria interventions and challenges.

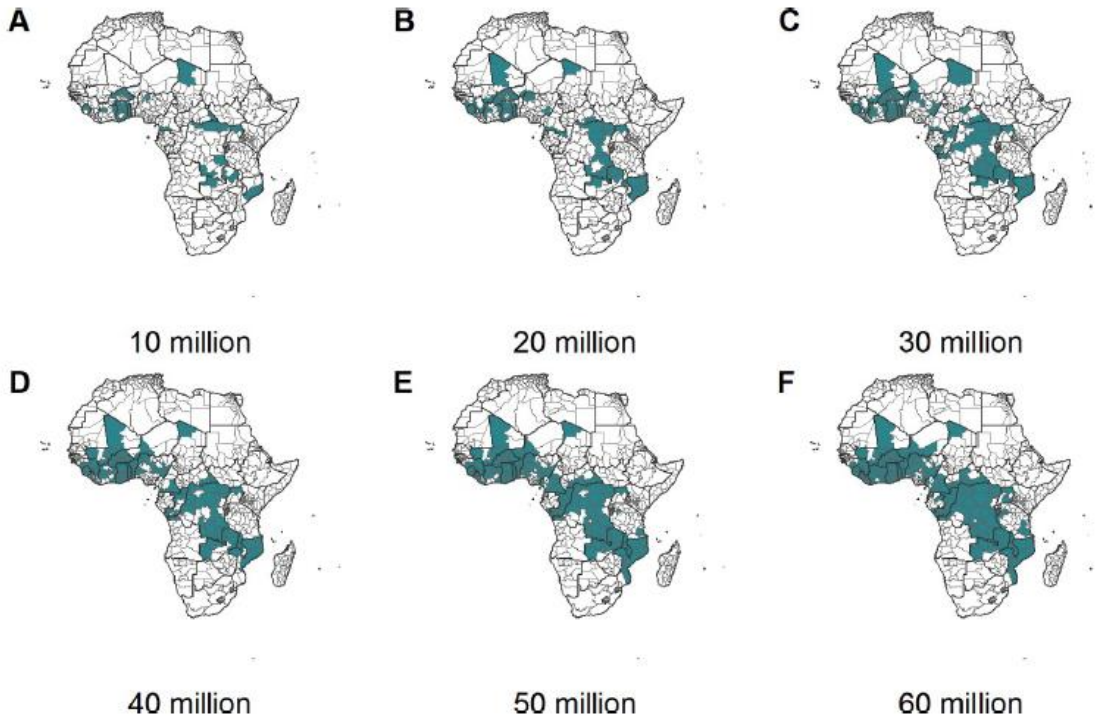

Figure Map of administrative units prioritized for vaccine delivery for a range of dose constraints (i.e., maximum available RTS,S doses/year), for the baseline intervention scenario of maintaining 2016 intervention coverage and realistic vaccine coverage. *Figure 3* in manuscript.

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8. Strategies to Improve Coverage of Typhoid Conjugate Vaccine (TCV) Immunization Campaign in Karachi, Pakistan.

Qamar F, Batool R, Qureshi S, Ali M, Sadaf T, Mehmood J, et al.

Vaccines (Basel). 2020 Dec 07;8(4).
PubMed ID: 33228111

ABSTRACT

The emergence and spread of extensively drug-resistant (XDR) typhoid in Karachi, Pakistan led to an outbreak response in Lyari Town, Karachi utilizing a mass immunization campaign with typhoid conjugate vaccine (TCV), Typbar TCV®. The mass immunization campaign, targeted Lyari Town, Karachi, one of the worst affected towns during the XDR typhoid outbreak. Here we describe the strategies used to improve acceptance and coverage of Typbar TCV in Lyari Town, Karachi. The mass immunization campaign with Typbar TCV was started as a school- and hospital-based vaccination campaign targeting children between the age of 6 months to 15 years old. A dose of 0.5 mL Typbar TCV was administered intramuscularly. A mobile vaccination campaign was added to cope with high absenteeism and non-response from parents in schools and to cover children out of school. Different strategies were found to be effective in increasing the vaccination coverage and in tackling vaccine hesitancy. Community engagement was the most successful strategy to overcome refusals and helped to gain trust in the newly introduced vaccine. Community announcements and playing typhoid jingles helped to increase awareness regarding the ongoing typhoid outbreak. Mop-up activity in schools was helpful in increasing coverage. Networking with locally active groups, clubs and community workers were found to be the key factors in decreasing refusals.

WEB: 10.3390/vaccines8040697
IMPACT FACTOR: 4.086
CITED HALF-LIFE: 3.4

START COMMENTARY

In this evaluation of a mass typhoid conjugate vaccine (TCV) immunization campaign among children 6 months-15 years old, Qamar *et al.* describe and assess strategies used to improve acceptance and coverage of TCV during an outbreak in Lyari Town, Karachi, an urban slum in Pakistan. Vaccination campaigns immunized a total of 87,993 children of which 45.39% occurred in schools (n=39,939), 5.74% in school mop-up activities (n=5,054), 18.23% in hospitals (n=16,042), and 30.64% in the mobile community camps (n=26,958). The acceptance of school-based campaigns was 48.2%. Utilizing a multi-component approach, strategies found to be in effective in

improving vaccination coverage include stakeholder engagement, vaccine education sessions in schools and religious institutions, community engagement and social media campaigns, staff trainings and field supervision, and health care provider education. Table 4 summarizes strategies used and suggested recommendations. Incorporating community feedback and tailoring strategies to the local context were essential components in the campaign's success, with authors highlighting that every interaction with the community at any point serves as an intervention for the successful implementation of strategies to increase vaccination coverage. This study provides key insights that can inform development of future mass immunization campaigns, especially those in similar urban slums in low- and middle-income countries.

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9. Implications of gestational age at antenatal care attendance on the successful implementation of a maternal respiratory syncytial virus (RSV) vaccine program in coastal Kenya.

Nyiro J, Bukusi E, Mwaengo D, Walumbe D, Nyaguara A, Nyawanda B, et al.

BMC Public Health. 2020 Nov 20;20(1):1723.
PubMed ID: 33198696

ABSTRACT

Background: Maternal immunisation to boost respiratory syncytial virus (RSV) specific antibodies in pregnant women is a strategy to enhance infant protection. The timing of maternal vaccination during pregnancy may be critical for its effectiveness. However, Kenya has no documented published data on gestational age distribution of pregnant women attending antenatal care (ANC), or the proportion of women attending ANC during the proposed window period for vaccination, to inform appropriate timing for delivery or estimate potential uptake of this vaccine.

Methods: A cross-sectional survey was conducted within the Kilifi Health and Demographic Surveillance System (KHDSS), coastal Kenya. A simple random sample of 1000 women who had registered pregnant in 2017 to 2018 and with a birth outcome by the time of data collection was taken. The selected women were followed at their homes, and individually written informed consent was obtained. Records of their antenatal attendance during pregnancy were abstracted from their ANC booklet. The proportion of all pregnant women from KHDSS (55%) who attended for one or more ANC in 2018 was used to estimate vaccine coverage.

Results: Of the 1000 women selected, 935 were traced with 607/935 (64.9%) available for interview, among whom 470/607 (77.4%) had antenatal care booklets. The median maternal age during pregnancy was 28.6 years. The median (interquartile range) gestational age in weeks at the first to fifth ANC attendance was 26 (21-28), 29 (26-32), 32 (28-34), 34 (32-36) and 36 (34-38), respectively. The proportion of women attending for ANC during a gestational age window for vaccination of 28-32 weeks (recommended), 26-33 weeks and 24-36 weeks was 76.6% (360/470), 84.5% (397/470) and 96.2% (452/470), respectively. Estimated vaccine coverage was 42.1, 46.5 and 52.9% within the narrow, wide and wider gestational age windows, respectively.

Conclusions: In a random sample of pregnant women from Kilifi HDSS, Coastal Kenya with card-confirmed ANC clinic attendance, 76.6% would be reached for maternal RSV vaccination within the

gestational age window of 28-32 weeks. Widening the vaccination window (26-33 weeks) or (24-36 weeks) would not dramatically increase vaccine coverage and would require consideration of antibody kinetics data that could affect vaccine efficacy.

WEB: 10.1186/s12889-020-09841-9
IMPACT FACTOR: 2.521
CITED HALF-LIFE: 6

START COMMENTARY

In this cross-sectional study, Nyiro *et al.* describe the distribution of gestational age at each antenatal care (ANC) visit among pregnant women in Kilifi, Kenya to estimate potential maternal RSV vaccine coverage. This article is impactful as it is the first to analyze how timing of ANC attendance is likely to affect the success of a maternal RSV vaccine program in sub-Saharan Africa. The study assessed three potential gestational age windows for RSV vaccine delivery: 28–32 weeks (narrow), 26–33 weeks (wide), and 24–36 weeks (wider). Of 1,000 women randomly selected from the census register with a pregnancy and birth outcome between 2017-2019, fieldworkers traced 935 women via three home visit attempts and follow-up with family members, and interviewed 607 women. Chi-square tests assessed the association between gestational age at first ANC attendance and maternal characteristics, while density curves illustrated the distribution of gestational age at ANC attendance (Figures 2 and 3). Among women with ANC booklet confirmed attendance, 76.6%, 84.5%, and 96.2% would be reached for maternal RSV vaccination within the narrow, wide, and wider gestational age windows, respectively. Using these percentages and the local estimate of 55% of women attending at least one ANC visit, the authors calculated maternal RSV vaccine coverage of 42.1%, 46.5% and 52.9% within the narrow, wide and wider gestational age windows, respectively. Limitations include measurement of gestational age through fundal height documented in the ANC booklet, as only 47% of the sample had an ANC book and fundal height may inaccurately estimate gestational age. These findings can guide policy development towards maternal RSV vaccination through the Kenyan ANC platform and may be useful to inform other maternal vaccine implementation (e.g., influenza, pertussis) more broadly in sub-Saharan Africa. Mathematical modeling incorporating antibody kinetics data that could affect vaccine efficacy is ongoing to further inform estimates for the optimal gestational age for maternal RSV.

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10. Engaging traditional barbers to identify and refer newborns for routine immunization services in Sokoto, Nigeria: a mixed methods evaluation.

Dougherty L, Abdulkarim M, Ahmed A, Cherima Y, Ladan A, Abdu S, et al.
Int J Public Health. 2020 Dec 07;65(9):1785-1795.
PubMed ID: 33140237

ABSTRACT

Objectives: This study evaluates the effectiveness of an intervention that engaged traditional barbers to inform parents about the importance of vaccination and then refer newborns for vaccination services.

Methods: We conducted a pre-post quasi-experimental study (n = 2639) to evaluate changes in the coverage of three birth antigens among children aged 0-5 months in response to the intervention. We also conducted in-depth interviews and focus group discussions to assess the enabling factors and challenges associated with implementation.

Results: We found mothers who received a yellow referral card from a traditional barber were two to three times more likely to vaccinate their children with the three birth antigens. Qualitative findings indicated that the intervention influenced parent's decision to vaccinate their newborn because the barbers were considered a trusted community advisor. Challenges stemmed from the low levels of literacy among community leaders and barbers that resulted in the need for continuous training, low-literacy training materials and supervision.

Conclusions: Efforts to increase vaccine coverage rates in northern Nigeria should consider expanding the role of traditional barbers to encourage parents to accept vaccines.

WEB: 10.1007/s00038-020-01518-9
IMPACT FACTOR: 2.419
CITED HALF-LIFE: 5.7

START COMMENTARY

In this quasi-experimental study using mixed-methods, Dougherty *et al.* evaluate change in birth dose vaccine coverage among children aged 0–5 months in response to referral intervention from traditional barbers in Sokoto, Nigeria. In May 2018, 1,210 traditional barbers from five Local

Government Areas (LGAs) were selected and trained to identify and refer newborns to immunization services. Estimated logistic regressions assessed whether the intervention group was more likely to achieve higher coverage of three birth antigens: 1) BCG, 2) OPV0, and 3) HepB. The authors first conducted an intention to treat analysis by computing an interaction variable (study period: pre vs. post * study group), but did not find a significant effect on vaccine coverage in the intervention group (BCG AOR=1.1, 95%CI=0.7–1.6; OPV0 AOR=1.1, 95%CI=0.7–1.7; HepB AOR=1.1, 95%CI=0.6–2.1). In a second adjusted model, the authors used the predictor of receiving a yellow immunization referral card from a barber and found that among mothers who received a referral card (n=2,639), infants were two to three times more likely to have received their birth antigens of BCG (AOR=3.0, 95%CI=1.9–4.9), OPV0 (AOR=2.4, 95%CI=1.6–3.6), and HepB (AOR=2.7, 95%CI=1.6–4.4). In-depth interviews and focus group discussions coded using the Theory of Change model, revealed enabling factors of the intervention including, two-way communication, linkage to support, working within traditional structures. Challenges associated with implementation included biased selection of barbers, lack of financial incentive for barbers, and training gaps causing barber confusion on how to use referral cards. Of mothers of infants interviewed from the intervention group, only 16% indicated that they had received a yellow referral card from a traditional barber, highlighting these implementation challenges. This study offers important lessons on how community resource partners, such as traditional barbers, can be leveraged to increase demand for vaccination services and address vaccine hesitancy to improve coverage.

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Appendix

The literature search for the January 2021 Vaccine Delivery Research Digest was conducted on December 16, 2020. We searched English language articles indexed by the US National Library of Medicine and published between November 15, 2020 and December 14, 2020. The search resulted in 344 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]) (“2020/11/15”[PDAT] : “2020/12/14”[PDAT]))