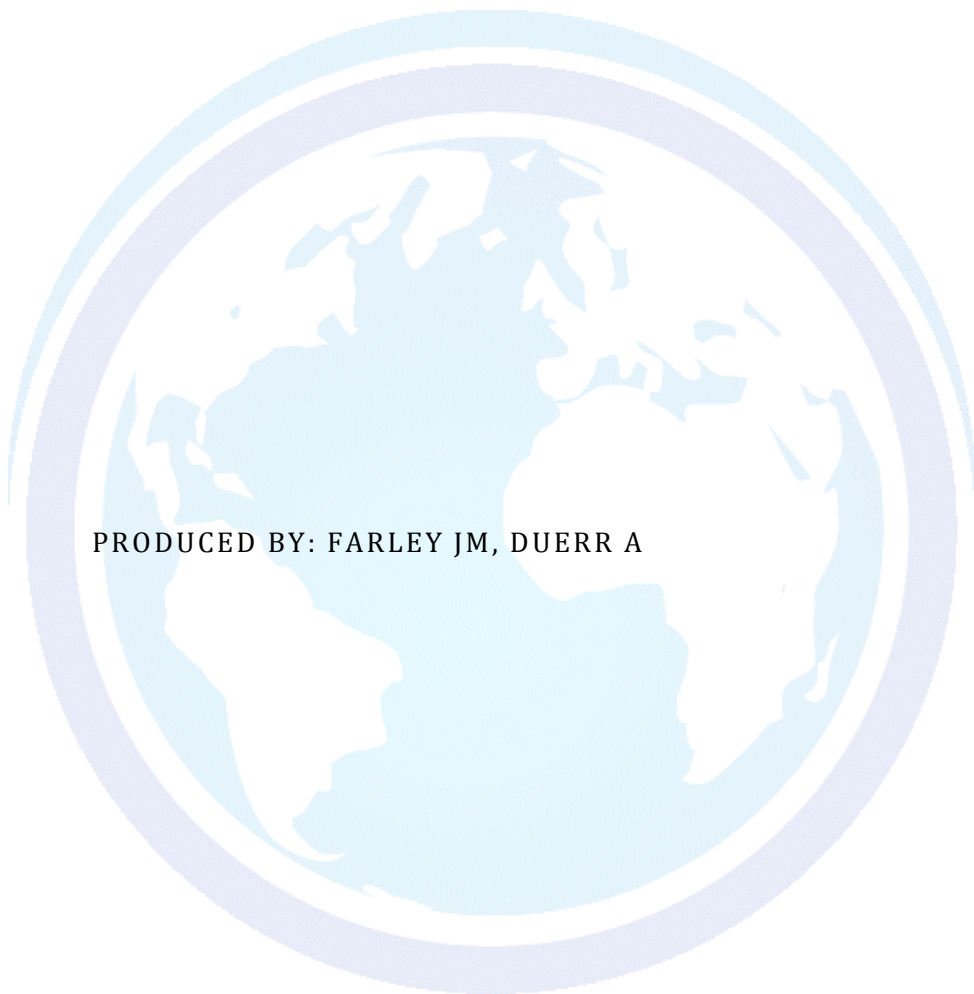# VACCINE DELIVERY RESEARCH DIGEST

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

OCTOBER 15, 2015

PRODUCED BY: FARLEY JM, DUERR A

TABLE OF CONTENTS

1. A RANDOMIZED, NON-INFERIORITY TRIAL COMPARING TWO BIVALENT KILLED, WHOLE CELL, ORAL CHOLERA VACCINES (EUVICHOL VS SHANCHOL) IN THE PHILIPPINES.

Baik YO, Choi SK, Olveda RM, Espos RA, Ligsay AD, Montellano MB et al.

ABSTRACT

BACKGROUND: Currently, there are two oral cholera vaccines (OCV) that are prequalified by the World Health Organization. Both (Dukoral and Shanchol) have been proven to be safe, immunogenic, and effective. As the global supply of OCV remains limited, we assessed the safety and immunogenicity of a new low cost, killed, bivalent OCV (Euvichol) in the Philippines.

METHODS: The randomized controlled trial was carried out in healthy Filipino adults and children. Two doses of either the current WHO prequalified OCV (Shanchol) or the same composition OCV being considered for WHO prequalification (Euvichol) were administered to participants.

RESULTS: The pivotal study was conducted in total of 1263 healthy participants (777 adults and 486 children). No serious adverse reactions were elicited in either vaccine groups. Vibriocidal antibody responses to V. cholerae O1 Inaba following administration of two doses of Euvichol were non-inferior to those of Shanchol in adults (82% vs 76%) and children (87% vs 89%). Similar findings were observed for O1 Ogawa in adults (80% vs 74%) and children (91% vs 88%).

CONCLUSION: A two dose schedule with Euvichol induces a strong vibriocidal response comparable to those elicited by the currently WHO prequalified OCV, Shanchol. Euvichol will be an oral cholera vaccine suitable for use in lower income countries, where cholera still has a significant economic and public health impact.

UW EDITORIAL COMMENT: Table 3 shows vibriocidal antibody titers and proportion of ≥4-fold rise from baseline GMT to *V. cholera* for Shanchol and Euvichol; although some statistically significant differences were seen, they did not consistently favor one vaccine or the other. With the investment that Gavi has to stockpile 20 million doses of OCV by 2018, the possibility of a second OCV (although Euvichol is not yet WHO pre-qualified) will have important public health and economic implications.

2. AFRICAN VACCINATION WEEK AS A VEHICLE FOR INTEGRATED HEALTH SERVICE DELIVERY.

Mihigo R, Anya B, Okeibunor J, Ajibola S, Boakye-Agyemang C, Muzenda L et al.

ABSTRACT

BACKGROUND: African Vaccination Week (AVW) is an initiative of the Member States of the African Region aimed at promoting vaccination and ensuring equity and access to its benefits. The initiative has proven to be particularly effective in reaching populations with limited access to regular health services as well as providing an opportunity to integrate other interventions with immunization services.

METHODS: Using data available from the countries within the African Region, the effectiveness of AVW in creating awareness on vaccination as well as providing platform for integrated delivery of other interventions with immunization in the African Region were explored during the 2013 and 2014 campaigns of the AVW.

RESULTS: Countries that participated in the two campaigns of AVW have integrated other interventions with immunization during the AVW. The most common integrated intervention is vitamin A supplementation, followed by deworming. However, other interventions integrated, include public health educational activities, supplementation with vitamins and minerals, provision of other health services as well as introduction of new interventions. In 2013, more than 7,500,000 doses of different vaccine antigens were delivered in17 countries. Vitamin A administered to children under 5 years and women in post-partum in 13 countries with 31,500,000 tablets distributed. Polio eradication campaigns reaching young children in ten countries with 36,711,984 doses of oral polio vaccines (OPV) was the third most common intervention added onto the AVW activities. Over 21,190,000 deworming tablets were distributed to children <5 years and pregnant women in 9 countries. With respect to nutritional interventions, 6,377,222 children were screened for malnutrition in 3 countries while 3,814,680 water, sanitation and hygiene kits were distributed in 3 countries. In 2014, these results were even higher as many more countries integrated multiple interventions in the AVW.

CONCLUSION: Integration of other interventions with immunization during AVW, in the African Region is common and has shown potentials for improving immunization coverage, as this dedicated period is used both for catch-up campaigns and periodic intensified routine immunization. While its impact may call for further examination, it is a potential platform for integrated delivery of health interventions to people with limited access to regular health service.

WEB: http://dx.doi.org/10.1186/s12913-015-0989-7

IMPACT FACTOR: 1.71

CITED HALF-LIFE: 4.50

UW EDITORIAL COMMENT: Table 1 details interventions planned and conducted during African Vaccination Week by country in 2013 and 2014.

3. SEASONAL INFLUENZA VACCINE DOSE DISTRIBUTION IN 195 COUNTRIES (2004-2013): LITTLE PROGRESS IN ESTIMATED GLOBAL VACCINATION COVERAGE.

Palache A, Oriol-Mathieu V, Fino M, Xydia-Charmanta M; Influenza Vaccine Supply task force (IFPMA IVS).

ABSTRACT

Seasonal influenza is an important disease which results in 250,000-500,000 annual deaths worldwide. Global targets for vaccination coverage rates (VCRs) in high-risk groups are at least 75% in adults ≥65 years and increased coverage in other risk groups. The International Federation of Pharmaceutical Manufacturers and Associations Influenza Vaccine Supply (IFPMA IVS) International Task Force developed a survey methodology in 2008, to assess the global distribution of influenza vaccine doses as a proxy for VCRs. This paper updates the previous survey results on absolute numbers of influenza vaccine doses distributed between 2004 and 2013 inclusive, and dose distribution rates per 1000 population, and provides a qualitative assessment of the principal enablers and barriers to seasonal influenza vaccination. The two main findings from the quantitative portion of the survey are the continued negative trend for dose distribution in the EURO region and the perpetuation of appreciable differences in scale of dose distribution between WHO regions, with no observed convergence in the rates of doses distributed per 1000 population over time. The main findings from the qualitative portion of the survey were that actively managing the vaccination program in real-time and ensuring political commitment to vaccination are important enablers of vaccination, whereas insufficient access to vaccination and lack of political commitment to seasonal influenza vaccination programs are likely contributing to vaccination target failures. In all regions of the world, seasonal influenza vaccination is underutilized as a public health tool. The survey provides evidence of lost opportunity to protect populations against potentially serious influenza-associated disease. We call on the national and international public health communities to re-evaluate their political commitment to the prevention of the annual influenza disease burden and to develop a systematic approach to improve vaccine distribution equitably.

WEB: http://dx.doi.org/10.1016/j.vaccine.2015.08.082

IMPACT FACTOR: 3.62

CITED HALF-LIFE: 5.50

UW EDITORIAL COMMENT: Figure 1 shows seasonal influenza vaccine dose distribution by region, while Figure 2 shows seasonal influenza vaccine doses distributed per 1,000 persons in each region. This article points to large gaps in achievement of recommended vaccination coverage rates: "in 2013, 89% of countries had not achieved the hurdle rate of 159 doses distributed per 1000 population." The authors suggest greater commitment from professional agencies and national health departments, as well as the WHO, to remedy this situation.

4. DATA QUALITY ASSESSMENT IN THE ROUTINE HEALTH INFORMATION SYSTEM: AN APPLICATION OF THE LOT QUALITY ASSURANCE SAMPLING IN BENIN.

Glèlè Ahanhanzo Y, Ouendo EM, Kpozèhouen A, Levêque A, Makoutodé M, Dramaix-Wilmet M.

ABSTRACT

Health information systems in developing countries are often faulted for the poor quality of the data generated and for the insufficient means implemented to improve system performance. This study examined data quality in the Routine Health Information System in Benin in 2012 and carried out a cross-sectional evaluation of the quality of the data using the Lot Quality Assurance Sampling method. The results confirm the insufficient quality of the data based on three criteria: completeness, reliability and accuracy. However, differences can be seen as the shortcomings are less significant for financial data and for immunization data. The method is simple, fast and can be proposed for current use at operational level as a data quality control tool during the production stage.

WEB: http://dx.doi.org/10.1093/heapol/czu067

IMPACT FACTOR: 3.47

CITED HALF-LIFE: 7.20

UW EDITORIAL COMMENT: This study assesses Lot Quality Assurance Sampling (LQAS), a statistical method of quality control that is useful in health assessments. For this study, a lot was defined as "the set of data generated by a single person during the 12 months preceding the survey," and quality was assessed by data completeness, reliability, and accuracy. Table 1 shows the relative frequency of different reporting form types in lots, while Table 3 shows the distribution of rejected data according to type of report, by percentage.

5. IMMUNISATION COVERAGE IN RURAL-URBAN MIGRANT CHILDREN IN LOW AND MIDDLE-INCOME COUNTRIES (LMICS): A SYSTEMATIC REVIEW AND META-ANALYSIS.

Awoh AB, Plugge E.

ABSTRACT

BACKGROUND: The majority of children who die from vaccine-preventable diseases (VPDs) live in low-income and-middle-income countries (LMICs). With the rapid urbanisation and rural-urban migration ongoing in LMICs, available research suggests that migration status might be a determinant of immunisation coverage in LMICs, with rural-urban migrant (RUM) children being less likely to be immunised.

OBJECTIVES: To examine and synthesise the data on immunisation coverage in RUM children in LMICs and to compare coverage in these children with non-migrant children.

METHODS: A multiple database search of published and unpublished literature on immunisation coverage for the routine Expanded Programme on Immunisation (EPI) vaccines in RUM children aged 5 years and below was conducted. Following a staged exclusion process, studies that met the inclusion criteria were assessed for quality and data extracted for meta-analysis.

RESULTS: Eleven studies from three countries (China, India and Nigeria) were included in the review. There was substantial statistical heterogeneity between the studies, thus no summary estimate was reported for the meta-analysis. Data synthesis from the studies showed that the proportion of fully immunised RUM children was lower than the WHO bench-mark of 90% at the national level. RUMs were also less likely to be fully immunised than the urban-non-migrants and general population. For the individual EPI vaccines, all but two studies showed lower immunisation coverage in RUMs compared with the general population using national coverage estimates.

CONCLUSIONS: This review indicates that there is an association between rural-urban migration and immunisation coverage in LMICs with RUMs being less likely to be fully immunised than the urban non-migrants and the general population. Specific efforts to improve immunisation coverage in this subpopulation of urban residents will not only reduce morbidity and mortality from VPDs in migrants but will also reduce health inequity and the risk of infectious disease outbreaks in wider society.

UW EDITORIAL COMMENT: Findings suggest that lower immunization rates among rural-urban migrants have particular implications for vaccine-preventable diseases such as polio and measles, as these diseases have occasionally been driven by RUMs in study areas. Table 4 outlines individual vaccine coverage in RUM populations versus national coverage estimates, among studies that included this information. No summary measures were reported for the meta-analysis due to heterogeneity between studies reviewed.

6. USING MHEALTH TO IMPROVE USAGE OF ANTENATAL CARE, POSTNATAL CARE, AND IMMUNIZATION: A SYSTEMATIC REVIEW OF THE LITERATURE.

Watterson JL, Walsh J, Madeka I.

ABSTRACT

Mobile health (mHealth) technologies have been implemented in many low- and middle-income countries to address challenges in maternal and child health. Many of these technologies attempt to influence patients', caretakers', or health workers' behavior. The purpose of this study was to conduct a systematic review of the literature to determine what evidence exists for the effectiveness of mHealth tools to increase the coverage and use of antenatal care (ANC), postnatal care (PNC), and childhood immunizations through behavior change in low- and middle-income countries. The full text of 53 articles was reviewed and 10 articles were identified that met all inclusion criteria. The majority of studies used text or voice message reminders to influence patient behavior change (80%, n = 8) and most were conducted in African countries (80%, n = 8). All studies showed at least some evidence of effectiveness at changing behavior to improve antenatal care attendance, postnatal care attendance, or childhood immunization rates. However, many of the studies were observational and further rigorous evaluation of mHealth programs is needed in a broader variety of settings.

WEB: http://dx.doi.org/10.1155/2015/153402

IMPACT FACTOR: 2.71

CITED HALF-LIFE: 2.50

UW EDITORIAL COMMENT: Table 1 is a summary of included articles on mHealth interventions to increase use of antenatal care, postnatal care, and childhood immunizations, classified by methods used. Four of the ten included studies specifically pertained to childhood immunization. Among these, one found an increase from 34.5% to 44.2% in childhood immunizations in the Thai-Myanmar border area with mHealth interventions for patient record management and appointment reminders. A second study in South Africa found that mothers positively reported on the influence of text message reminders for immunization. In another study with a similar intervention in Malawi, mothers reported intended or actual behavior change related to vaccinating their children. Finally, using mHealth applications in a mass vaccination campaign in Kenya was associated with a 92% measles vaccination coverage rate among children visited later at home.

7. RISK FACTORS FOR DELAY IN AGE-APPROPRIATE VACCINATIONS AMONG GAMBIAN CHILDREN.

Odutola A, Afolabi MO, Ogundare EO, Lowe-Jallow YN, Worwui A, Okebe J et al.

ABSTRACT

BACKGROUND: Vaccination has been shown to reduce mortality and morbidity due to vaccine-preventable diseases. However, these diseases are still responsible for majority of childhood deaths worldwide especially in the developing countries. This may be due to low vaccine coverage or delay in receipt of age-appropriate vaccines. We studied the timeliness of routine vaccinations among children aged 12-59 months attending infant welfare clinics in semi-urban areas of The Gambia, a country with high vaccine coverage.

METHODS: A cross-sectional survey was conducted in four health centres in the Western Region of the Gambia. Vaccination dates were obtained from health cards and timeliness assessed based on the recommended age ranges for BCG (birth-8 weeks), Diphtheria-Pertussis-Tetanus (6 weeks-4 months; 10 weeks-5 months; 14 weeks-6 months) and measles vaccines (38 weeks-12 months). Risk factors for delay in age-appropriate vaccinations were determined using logistic regression. Analysis was limited to BCG, third dose of Diphtheria-Pertussis -Tetanus (DPT3) and measles vaccines.

RESULTS: Vaccination records of 1154 children were studied. Overall, 63.3% (95 % CI 60.6-66.1%) of the children had a delay in the recommended time to receiving at least one of the studied vaccines. The proportion of children with delayed vaccinations increased from BCG [5.8% (95 % CI 4.5-7.0%)] to DPT3 [60.4% (95 % CI 57.9%-63.0%)] but was comparatively low for the measles vaccine [10.8% (95 % CI 9.1%-12.5%)]. Mothers of affected children gave reasons for the delay, and their profile correlated with type of occupation, place of birth and mode of transportation to the health facilities.

CONCLUSION: Despite high vaccination coverage reported in The Gambia, a significant proportion of the children's vaccines were delayed for reasons related to health services as well as profile of mothers. These findings are likely to obtain in several countries and should be addressed by programme managers in order to improve and optimize the impact of the immunization coverage rates.

WEB: http://dx.doi.org/10.1186/s12913-015-1015-9

IMPACT FACTOR: 1.71

CITED HALF-LIFE: 4.50

UW EDITORIAL COMMENT: Table 1 shows the Gambian Expanded Programme on Immunization schedule (2011), including WHO recommendations on age for each vaccine, while Table 4 shows Median (IQR) age (in days) at vaccination for each vaccine from this study. Table 5 shows risk factors for delay in receipt of BCG, DPT3, Measles and delay of any vaccines. The authors recommend mHealth technologies, health worker training, and future appointment reminders as strategies that could increase immunization coverage.

8. EXPOSING CONCERNS ABOUT VACCINATION IN LOW- AND MIDDLE-INCOME COUNTRIES: A SYSTEMATIC REVIEW.

Cobos Muñoz D, Monzón Llamas L, Bosch-Capblanch X.

ABSTRACT

OBJECTIVES: Concerns about vaccination lead to under- and no-vaccination. Our objective is to synthesise and expose evidence on individuals' and communities' concerns about vaccination to influence current debates on strategies to improve vaccination coverage in low- and middle-income countries.

METHODS: Systematic literature review till February 2014, following standard methods. Published and grey literature that focused on individuals and community concerns on childhood vaccinations were selected.

RESULTS: 44 quantitative, qualitative and mixed-methods studies were included. Main reported concerns referred to perceptions of vaccine harms (e.g. attribution of fatal events). Other concerns included programme distrust (mainly due to rumours and conspiracies) and health system unfriendliness.

CONCLUSIONS: Concerns about vaccination are widespread and further worsen the challenges related to programmatic and health system barriers to vaccination. There is a disconnection between qualitative and quantitative research which misses the opportunity to quantify what is reported in the former. Strikingly, there is a wealth of evidence on concerns but much lesser evidence on interventions to address them. We welcome World Health Organization initiative to tackle vaccine hesitancy and call for the synthesis of evidence and production of guidance on strategies to address concerns on vaccination.

WEB: http://dx.doi.org/10.1007/s00038-015-0715-6

IMPACT FACTOR: 2.70

CITED HALF-LIFE: 3.90

UW EDITORIAL COMMENT: Table 1 lists the ten most frequently reported concerns about vaccination from studies with qualitative data: the top three concerns were general harm/adverse effects, distrust in medical community, and side effects of vaccines. Figure 2 shows a breakdown in concerns among geographic areas in the included studies. This study highlights the continued difficulty in identifying *interventions* to address vaccine concerns, and the evidence base in this area is slim. More research is needed to produce recommendations on how best to approach these concerns in low- and middle-income countries.

9. IMPLEMENTATION OF AN HPV VACCINATION PROGRAM IN ELDORET, KENYA: RESULTS FROM A QUALITATIVE ASSESSMENT BY KEY STAKEHOLDERS.

Vermandere H, Naanyu V, Degomme O, Michielsen K.

ABSTRACT

BACKGROUND: Cervical cancer strikes hard in low-resource regions yet primary prevention is still rare. Pilot projects have however showed that Human Papillomavirus (HPV) vaccination programs can attain high uptake. Nevertheless, a study accompanying a vaccination demonstration project in Eldoret, Kenya, revealed less encouraging outcomes: uptake during an initial phase targeting ten schools (i.e., 4000 eligible girls), was low and more schools had to be included to reach the proposed number of 3000 vaccinated girls. The previously conducted study also revealed that many mothers had not received promotional information which had to reach them through schools: teachers were sensitized by health staff and asked to invite students and parents for HPV vaccination in the referral hospital. In this qualitative study, we investigate factors that hampered promotion and vaccine uptake.

METHODS: Focus group discussions (FGD) with teachers (4) and fathers (3) were organized to assess awareness and attitudes towards the vaccination program, cervical cancer and the HPV vaccine, as well as a FGD with the vaccinators (1) to discuss the course of the program and potential improvements. Discussions were recorded, transcribed, translated, and analyzed using thematic analysis In addition, a meeting with the program coordinator was set up to reflect upon the program and the results of the FGD, and to formulate recommendations for future programs.

RESULTS: Cervical cancer was poorly understood by fathers and teachers and mainly linked with nonconforming sexual behavior and modern lifestyle. Few had heard about the vaccination opportunity: feeling uncomfortable to discuss cervical cancer and not considering it as important had hampered information flow. Teachers requested more support from health staff to address unexpected questions from parents. Non-uptake was also the result of distrust towards new vaccines. Schools entering the program in the second phase reacted faster: they were better organized, e.g., in terms of transport, while the community was already more familiarized with the vaccine.

CONCLUSIONS: Close collaboration between teachers and health staff is crucial to obtain high HPV vaccine uptake among schoolgirls. Promotional messages should, besides providing correct information, tackle misbeliefs, address stigma and stress the priority to vaccinate all, regardless of lifestyle. Monitoring activities and continuous communication could allow for detection of rumors and unequal uptake in the community.

UW EDITORIAL COMMENT: This study emphasizes the importance of appropriate promotional messaging, which both provides correct information and actively addresses rumors and common misconceptions about HPV transmission.

10. INTEGRATING VITAMIN A SUPPLEMENTATION AT 6 MONTHS INTO THE EXPANDED PROGRAM OF IMMUNIZATION IN SIERRA LEONE.

Hodges MH, Sesay FF, Kamara HI, Nyorkor ED, Bah M, Koroma AS et al.

ABSTRACT

Since 2004, twice-yearly mass vitamin A supplementation (VAS) has equitably reached over 85% of children 6-59 months old in Sierra Leone. However infants who turn 6 months after the event may wait until they are 11 months old to receive their first dose. The effectiveness of integrating VAS at 6 months into the Expanded Program of Immunization (EPI) in a revised child health card was studied. Health facilities matched according to staff cadre and work load were assigned to provide either a 'mini package' of VAS and infant and young child feeding (IYCF), a 'full package' of VAS, IYCF and family planning (FP), or 'child health card' only. 400 neonates were enrolled into each group, caregivers given the new child health card and followed until they were 12 months old. More infants in the full: 74.5% and mini: 71.7% group received VAS between 6 and 7 months of age compared with the new CH card only group: 60.2% (p = 0.002, p < 0.001 respectively). FP commodities were provided to 44.5% of caregivers in the full compared with <2.5% in the mini and new child health card only groups (p < 0.0001). Integration of VAS within the EPI schedule achieved >60% coverage for infants between 6 and 7 months of age. Provision of FP and/or IYCF further improved coverage. Funding was provided by the Canadian Department of Foreign Affairs, Trade and Development who had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

WEB: http://dx.doi.org/10.1007/s10995-015-1706-1

IMPACT FACTOR: 2.24

CITED HALF-LIFE: 4.70

UW EDITORIAL COMMENT: This study highlights the need for more training of community health volunteers, many of whom are either very young and preparing for more formal health education, or older with limited education. This is of particular importance as the Ministry of Health Services in Sierra Leone implements its 'Agenda for Prosperity,' which includes integrated routine child health services at the 6-month mark.

APPENDIX: PUBMED SEARCH TERMS

(((((vaccine[tiab] OR vaccines[tiab] OR vaccination[tiab] OR immunization[tiab] OR immunisation[tiab] OR vaccine[mesh] OR immunization[mesh]) AND (logistics[tiab] OR supply[tiab] OR "supply chain"[tiab] OR implementation[tiab] OR expenditures[tiab] OR financing[tiab] OR economics[tiab] OR "Cost effectiveness"[tiab] OR coverage[tiab] OR attitudes[tiab] OR belief[tiab] OR beliefs[tiab] OR refusal[tiab] OR "Procurement"[tiab] OR timeliness[tiab] OR systems[tiab])) OR ("vaccine delivery"[tiab])) NOT ("in vitro"[tiab] OR "immune response"[tiab] OR gene[tiab] OR chemistry[tiab] OR genotox*[tiab] OR sequencing[tiab] OR nanoparticle*[tiab] OR bacteriophage[tiab] OR exome[tiab] OR exogenous[tiab] OR electropor*[tiab] OR "systems biology"[tiab] OR "animal model"[tiab] OR cattle[tiab] OR sheep[tiab] OR goat[tiab] OR rat[tiab] OR pig[tiab] OR mice[tiab] OR mouse[tiab] OR murine[tiab] OR porcine[tiab] OR ovine[tiab] OR rodent[tiab] OR fish[tiab])) AND (English[LA]) AND ("2015/07/15"[PDAT] : "2015/08/14"[PDAT]))

*On September 21, 2015, this search of English language articles published between August 15, 2015 and September 14, 2015 and indexed by the US National Library of Medicine resulted in 201 unique manuscripts.