VACCINE DELIVERY RESEARCH DIGEST

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

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1. OPTIMIZING ENERGY FOR A 'GREEN' VACCINE SUPPLY CHAIN.

Lloyd J, McCarney S, Ouhichi R, Lydon P, Zaffran M.

Vaccine. 2014 Nov 17. pii: S0264-410X(14)01443-1. [Epub ahead of print]

PMID: 25444811

ABSTRACT

This paper describes an approach piloted in the Kasserine region of Tunisia to increase the energy efficiency of the distribution of vaccines and temperature sensitive drugs. The objectives of an approach, known as the 'net zero energy' (NZE) supply chain were demonstrated within the first year of operation. The existing distribution system was modified to store vaccines and medicines in the same buildings and to transport them according to pre-scheduled and optimized delivery circuits. Electric utility vehicles, dedicated to the integrated delivery of vaccines and medicines, improved the regularity and reliability of the supply chains. Solar energy, linked to the electricity grid at regional and district stores, supplied over 100% of consumption meeting all energy needs for storage, cooling and transportation. Significant benefits to the quality and costs of distribution were demonstrated. Supply trips were scheduled, integrated and reliable, energy consumption was reduced, the recurrent cost of electricity was eliminated and the release of carbon to the atmosphere was reduced. Although the initial capital cost of scaling up implementation of NZE remain high today, commercial forecasts predict cost reduction for solar energy and electric vehicles that may permit a step-wise implementation over the next 7-10 years. Efficiency in the use of energy and in the deployment of transport is already a critical component of distribution logistics in both private and public sectors of industrialized countries. The NZE approach has an intensified rationale in countries where energy costs threaten the maintenance of public health services in areas of low population density. In these countries where the mobility of health personnel and timely arrival of supplies is at risk, NZE has the potential to reduce energy costs and release recurrent budget to other needs of service delivery while also improving the supply chain.

WEB: http://dx.doi.org/10.1016/j.vaccine.2014.10.053

IMPACT FACTOR: 3.49

CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: Table 1 shows the interventions utilized to replace existing practices with strategies that reduce energy consumption. Figure 2 demonstrates the difference in costs associated with vaccine transportation and storage at the district and regional levels at baseline, and after the interventions were implemented. As shown in Figure 4, the intervention achieved the goal of a positive energy balance over the course of 1 year, with the amount of energy consumed exceeding energy produced in only one district for 3 months of the year (January- March). The missing element in the rationale for scale-up of net zero energy and a limitation of this study is a credible economic argument setting the necessary capital investment against whole-life gains in recurrent expenditure on energy.

2. RECOMMENDATIONS REGARDING THE DEVELOPMENT OF COMBINED ENTEROTOXIGENIC *ESCHERICHA COLI* AND *SHIGELLA* VACCINES FOR INFANTS.

Walker RI, Clifford A.

Vaccine. 2014 Dec 8. pii: S0264-410X(14)01605-3. [Epub ahead of print]

PMID: 25500172

ABSTRACT

PATH hosted a workshop on October 14 and 15, 2013 in Washington, DC to solicit expert opinions on the potential merits and challenges of developing combined enterotoxigenic *Escherichia coli* (ETEC) and *Shigella* vaccine products to benefit children in developing countries. This article summarizes the key issues raised during the workshop and provides an analysis of the recommendations regarding the strategic, clinical and regulatory, and manufacturing considerations for the development of a combined enteric vaccine, which aim to guide future vaccine development efforts and donor investment strategies in this area. Notwithstanding the potential technical, legal, financial, and other constraints that would be faced in developing a combined ETEC/*Shigella* vaccine, it is clear that this is the preferred approach over standalone products. There are many advantages to a combined vaccine, such as the potential cost-effectiveness and easier logistics of introducing a combined vaccine instead of two standalone vaccines in low-resource, endemic countries.

WEB: http://dx.doi.org/10.1016/j.vaccine.2014.11.048

IMPACT FACTOR: 3.49

CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: The authors demonstrate the proposed pathway for the development of the combined ETEC/*Shigella* vaccine in Figure 1. The recommendation is for the ETEC vaccine to go to market first while the combined vaccine is still in development. While this article highlights many positive aspects of creating a combined ETEC/*Shigella* vaccine, there are also drawbacks to this approach that the article discusses. One consideration is the timing of the vaccine, as ETEC and *Shigella* incidence peaks in children at different ages, and adding further clinic visits to the standard vaccine schedule is unlikely to be successful. Additionally, development may be challenged due intellectual property issues; a combined vaccine may require cooperation from multiple companies that will likely prioritize the development of a single-agent vaccine.

3. COMPARATIVE EFFECTIVENESS OF DIFFERENT STRATEGIES OF ORAL CHOLERA VACCINATION IN BANGLADESH: A MODELING STUDY.

Dimitrov DT, Troeger C, Halloran ME, Longini IM, Chao DL.

PLoS Negl Trop Dis. 2014 Dec 4;8(12):e3343. eCollection 2014.

PMID: 25473851

ABSTRACT

BACKGROUND: Killed, oral cholera vaccines have proven safe and effective, and several large-scale mass cholera vaccination efforts have demonstrated the feasibility of widespread deployment. This study uses a mathematical model of cholera transmission in Bangladesh to examine the effectiveness of potential vaccination strategies.

METHODS AND FINDINGS: We developed an age-structured mathematical model of cholera transmission and calibrated it to reproduce the dynamics of cholera in Matlab, Bangladesh. We used the model to predict the effectiveness of different cholera vaccination strategies over a period of 20 years. We explored vaccination programs that targeted one of three increasingly focused age groups (the entire vaccine-eligible population of age one year and older, children of ages 1 to 14 years, or preschoolers of ages 1 to 4 years) and that could occur either as campaigns recurring every five years or as continuous ongoing vaccination efforts. Our modeling results suggest that vaccinating 70% of the population would avert 90% of cholera cases in the first year but that campaign and continuous vaccination strategies differ in effectiveness over 20 years. Maintaining 70% coverage of the population would be sufficient to prevent sustained transmission of endemic cholera in Matlab, while vaccinating periodically every five years is less effective. Selectively vaccinating children 1-14 years old would prevent the most cholera cases per vaccine administered in both campaign and continuous strategies.

CONCLUSIONS: We conclude that continuous mass vaccination would be more effective against endemic cholera than periodic campaigns. Vaccinating children averts more cases per dose than vaccinating all age groups, although vaccinating only children is unlikely to control endemic cholera in Bangladesh. Careful consideration must be made before generalizing these results to other regions.

WEB: http://dx.doi.org/10.1371/journal.pntd.0003343

IMPACT FACTOR: 4.49

CITED HALF-LIFE: 2.50

UW EDITORIAL COMMENT: Figure 2 shows the distribution of reported cholera cases per month in Matlab from 1997 – 2001 and how the mathematical model was fitted to the seasonal and age distribution of cases. Figure 3 shows the results of the model predictions, comparing a one-time mass vaccination, vaccination campaigns every 5 years, and continuous vaccination over a 20 year period. Figure 4 then looks at the 5 year campaign and continuous vaccination strategies, comparing differing levels of vaccine coverage and age groups. The authors note that this model is based on an endemic setting, and the incidence distribution is likely different than in a cholera epidemic.

4. INTERVENTIONS AIMED AT COMMUNITIES TO INFORM AND/OR EDUCATE ABOUT EARLY CHILDHOOD VACCINATION.

Saeterdal I, Lewin S, Austvoll-Dahlgren A, Glenton C, Munabi-Babigumira S.

Cochrane Database Syst Rev. 2014 Nov 19; 11:CD010232.

PMID: 25408540

ABSTRACT

BACKGROUND: A range of strategies are used to communicate with parents, caregivers and communities regarding child vaccination in order to inform decisions and improve vaccination uptake. These strategies include interventions in which information is aimed at larger groups in the community, for instance at public meetings, through radio or through leaflets. …

OBJECTIVES: To assess the effects of interventions aimed at communities to inform and/or educate people about vaccination in children six years and younger.

RESULTS: We included two cluster-randomised trials that compared interventions aimed at communities to routine immunisation practices. In one study from India, families, teachers, children and village leaders were encouraged to attend information meetings where they received information about childhood vaccination and could ask questions. In the second study from Pakistan, people who were considered to be trusted in the community were invited to meetings to discuss vaccine coverage rates in their community and the costs and benefits of childhood vaccination. They were asked to develop local action plans and to share the information they had been given and continue the discussions in their communities. The trials show low certainty evidence that interventions aimed at communities to inform and educate about childhood vaccination may improve knowledge of vaccines or vaccine-preventable diseases among intervention participants (adjusted mean difference 0.121, 95% confidence interval (CI) 0.055 to 0.189). These interventions probably increase the number of children who are vaccinated. …

CONCLUSION: This review provides limited evidence that interventions aimed at communities to inform and educate about early childhood vaccination may improve attitudes towards vaccination and probably increase vaccination uptake under some circumstances. However, some of these interventions may be resource intensive when implemented on a large scale and further rigorous evaluations are needed. These interventions may achieve most benefit when targeted to areas or groups that have low childhood vaccination rates.

WEB: http://dx.doi.org/10.1002/14651858.CD010232.pub2

IMPACT FACTOR: 5.94

CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: This review provided limited evidence due to only two studies being utilized in the analysis. Figure 4 compares interventions aimed at communities to routine immunization practices.

5. INTEGRATION OF VACCINE SUPPLY CHAINS WITH OTHER HEALTH COMMODITY SUPPLY CHAINS: A FRAMEWORK FOR DECISION MAKING.

Yadav P, Lydon P, Oswald J, Dicko M, Zaffran M.

Vaccine. 2014 Nov 28;32(50):6725-6732. Epub 2014 Oct 23.

PMID: 25446826

ABSTRACT

One of the primary objectives of National Immunization Programs is to strengthen and optimize immunization supply chains so that vaccines are delivered to the end recipients effectively, efficiently and sustainably. As a result of larger investments in global health and a wider portfolio of vaccines, global agencies are recognizing the need for vaccine supply chains to operate at their most optimal levels. Integration with other supply chains is often presented as a strategy to improve efficiency. However, it remains unclear if the proposed benefits from integration of vaccine supply chains with other supply chains will outweigh the costs. This paper provides a framework for deciding where such integration offers the most significant benefits. It also cautions about the pitfalls of integration as a one size fits all strategy. It also highlights the need for systematic collection of cost and efficiency data in order to understand the value of integration and other such initiatives.

WEB: http://dx.doi.org/10.1016/j.vaccine.2014.10.001

IMPACT FACTOR: 3.49

CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: The authors used two examples of vaccine supply chain integration to determine which stages of the supply chain benefit from integration. Figure 1 shows the structure and stages of a vaccine supply chain through planning, storage, and transport. Table 1 provides an overview of which stages are currently integrated in various countries throughout Africa. Table 3 addresses some of the product attributes that are important to evaluate when considering supply chain integration, including varying demand due to variability in need and seasonality, and cold chain requirements. The article concludes that the greatest opportunity for integration is in transport and storage, while quantification, procurement, and ordering are more difficult to integrate across products.

6. GLOBAL, REGIONAL, AND NATIONAL ESTIMATES OF PNEUMONIA BURDEN IN HIV-INFECTED CHILDREN IN 2010: A META-ANALYSIS AND MODELLING STUDY.

Theodoratou E, McAllister DA, Reed C, Adeloye DO, Rudan I, Muhe LM, et al.

Lancet Infect Dis. 2014 Dec; 14(12):1250-8. Epub 2014 Nov 12.

PMID: 25455992

ABSTRACT

OBJECTIVES: Globally, pneumonia is a leading cause of mortality and morbidity in children younger than 5 years. Underlying HIV infection is an important risk factor for pneumonia morbidity and mortality in children. There are, however, no global or country level estimates of pneumonia burden in HIV-infected children. We assessed the role of HIV in pneumonia incidence and mortality and estimated the number of pneumonia cases and deaths in HIV-infected children younger than 5 years in 133 high pneumonia-burden countries in 2010.

METHODS: We estimated the risk of hospital admission and case fatality rate caused by pneumonia in HIV-infected children compared with HIV-uninfected children from a systematic review of studies published in Medline, Embase, and Global Health between Jan 1, 1980, and Aug 31, 2013. We estimated nationwide pneumonia incidence and mortality with two different models that incorporated several risk factors for paediatric pneumonia hospital admission and mortality (including HIV infection). We then estimated the number of pneumonia episodes and deaths that occurred in HIV-infected children in 2010.

FINDINGS: The odds ratio (OR) for hospital admission for all-cause pneumonia in HIV-infected children compared with HIV-uninfected children was 6·5 (95% CI 5·9-7·2). The risk of death was higher in children with pneumonia and HIV compared with those with pneumonia only (OR 5·9, 95% CI 2·7-12·7).. …

INTERPRETATION: Globally, a small proportion of pneumonia episodes and pneumonia deaths occur in HIV-infected children. However, in the highest HIV-burden countries in sub-Saharan Africa (ie, Swaziland, Lesotho, and Zimbabwe) up to a fifth of all pneumonia cases and 60% of pneumonia deaths occur in HIV-infected children. In these countries, major reductions in child pneumonia mortality can be achieved only if the systemic challenges plaguing the health system (poor coverage of early infant testing for HIV, of antiretroviral drugs in pregnant women and young children, of co-trimoxazole prophylaxis, and of pneumococcal vaccination) can be overcome.

WEB: http://dx.doi.org/10.1016/S1473-3099(14)70990-9

IMPACT FACTOR: 19.45

CITED HALF-LIFE: 4.80

UW EDITORIAL COMMENT: Figure 2 shows incidence of pneumonia that is attributable to HIV in children under 5 years old from 69 countries. Table 2 focuses on the 22 priority countries named in the UNAIDS Global Plan, showing proportion of pneumonia episodes and death attributed to HIV. These results suggest that priority countries that have not yet introduced the pneumococcal vaccine should consider doing so for HIV-infected children.

7. HEPATITIS B VACCINATION COVERAGE RATES AMONG ADULTS IN RURAL CHINA: ARE ECONOMIC BARRIERS RELEVANT?

Zhu D, Wang J, Wangen KR.

Vaccine. 2014 Nov 20; 32(49):6705-10. Epub 2013 Jul 8.

PMID: 23845801

ABSTRACT

BACKGROUND: Hepatitis B virus (HBV) infections cause major health problems in China. The Expanded Program of Immunization has succeeded in reducing infection rates among infants and children, but HBV vaccination coverage rates among adults remain low.

OBJECTIVE: The objective was to investigate how individual adult HBV vaccination decisions are influenced by economic factors, socioeconomic status, and demographic characteristics, and to assess how potential vaccination policies could affect HBV vaccination coverage rates among adults.

METHODS: We interviewed 22,618 adults, aged 15-59 years, from 7948 households, in 45 villages from 7 provinces. A questionnaire was used to collect information. The actual vaccine status was modeled using a polychotomous logistic regression with three outcomes; unvaccinated, partial vaccination, and complete vaccination. A subsample of unvaccinated adults gave responses to a hypothetical vaccination policy that offered HBV vaccination free of charge and various amounts of money to compensate for direct and indirect vaccination-related costs.

INTERPRETATION: The polychotomous logistic regression results suggest that vaccination user fees, time needed to get a vaccination, and vaccination-related travel costs were negatively associated with HBV vaccination coverage rates. Higher income was associated with higher coverage rates, and coverage rates decrease with age, with no significant difference between the genders. In the subsample that responded to the hypothetical policy, 55-72% (depending on the amount of money offered as compensation) stated they would accept a vaccination if it was offered free of charge.

CONCLUSIONS: Our polychotomous logistic regression results suggest that higher HBV vaccination coverage rates among adults are obtainable and that user fees, time needed to get a vaccination, and travel costs have acted as economic barriers to vaccination. This is supported by the responses to the hypothetical policy, which suggest that adult coverage rates could surge if HBV vaccine is offered at no cost.

WEB: http://dx.doi.org/10.1016/j.vaccine.2013.06.095

IMPACT FACTOR: 3.49

CITED HALF-LIFE: 4.90

UW EDITORIAL COMMENT: Table 2 presents the results of the polychotomous logistic regression, which found statistically significant associations between vaccination and travel costs, time needed to get the vaccination, and user fees. The study found a notable increase in willingness of adults to be vaccinated if compensation was offered to address these cost barriers (Figure 2).

8. QUANTIFYING THE IMPACT OF EXPANDED AGE GROUP CAMPAIGNS FOR POLIO ERADICATION.

Wagner BG, Behrend MR, Klein DJ, Upfill-Brown AM, Eckhoff PA, Hu H.

PLoS One. 2014 Dec 1; 9(12):e113538. eCollection 2014.

PMID: 25437014

ABSTRACT

A priority of the Global Polio Eradication Initiative (GPEI) 2013-2018 strategic plan is to evaluate the potential impact on polio eradication resulting from expanding one or more Supplementary Immunization Activities (SIAs) to children beyond age five-years in polio endemic countries. It has been hypothesized that such expanded age group (EAG) campaigns could accelerate polio eradication by eliminating immunity gaps in older children that may have resulted from past periods of low vaccination coverage. Using an individual-based mathematical model, we quantified the impact of EAG campaigns in terms of probability of elimination, reduction in polio transmission and age stratified immunity levels. The model was specifically calibrated to seroprevalence data from a polio-endemic region: Zaria, Nigeria. We compared the impact of EAG campaigns, which depend only on age, to more targeted interventions which focus on reaching missed populations. We found that EAG campaigns would not significantly improve prospects for polio eradication; the probability of elimination increased by 8% (from 24% at baseline to 32%) when expanding three annual SIAs to 5-14 year old children and by 18% when expanding all six annual SIAs. In contrast, expanding only two of the annual SIAs to target hard-to-reach populations at modest vaccination coverage-representing less than one tenth of additional vaccinations required for the six SIA EAG scenario-increased the probability of elimination by 55%. Implementation of EAG campaigns in polio endemic regions would not improve prospects for eradication. In endemic areas, vaccination campaigns which do not target missed populations will not benefit polio eradication efforts.

WEB: http://dx.doi.org/10.1371/journal.pone.0113538

IMPACT FACTOR: 3.53

CITED HALF-LIFE: 2.40

UW EDITORIAL COMMENT: Figure 2 shows the effect of expanding age groups and targeting in supplementary immunization activities (SIA) campaigns. The model found that with expanded age group (EAG) campaigns employed through 6 SIA per year, the probability of elimination increased by 16%, but falls to 8% with 3 EAG campaigns annually. Figure 5 shows the distribution of cases by age during previous polio outbreaks, looking separately at countries that have highly endemic polio, low endemic, and outbreaks. Figure 6 compares mucosal immunity in children 5-14 years old in EAG campaigns compared to standard campaigns. One limitation of this analysis is the assumption of homogenous mixing between low and high vaccine accessibility groups.

9. IDENTIFYING AN APPROPRIATE PCV FOR USE IN SENEGAL, RECENT INSIGHTS CONCERNING STREPTOCOCCUS PNEUMONIAE NP CARRIAGE AND IPD IN DAKAR.

Ba F, Seck A, Bâ M, Thiongane A, Cissé M, Seck K, et al.

BMC Infect Dis. 2014 Dec 4;14(1):627. [Epub ahead of print]

PMID: 25471219

ABSTRACT

BACKGROUND: Since 2000, the Global Alliance for Vaccines and Immunization (GAVI) and WHO have supported the introduction of the Pneumococcal Conjugate Vaccine (PCV) in the immunization programs of developing countries. The highest pneumococcal nasopharyngeal carriage rates have been reported (40-60%) in these countries, and the highest incidence and case fatality rates of pneumococcal infections have been demonstrated in Africa.

METHODS: Studies concerning nasopharyngeal pneumococcal carriage and pneumococcal infection in children less than 5 years old were conducted in Dakar from 2007 to 2008. Serotype, antibiotic susceptibility and minimum inhibitory concentrations were determined. In addition, among 17 overall publications, 6 manuscripts of the Senegalese literature published from 1972 to 2013 were selected for data comparisons.

RESULTS: Among the 264 children observed, 132 (50%) children generated a nasopharyngeal (NP) positive culture with Streptococcus pneumoniae. The five most prevalent serotypes, were 6B (9%), 19 F (9%), 23 F (7.6%), 14 (7.6%) and 6A (6.8%). Fifteen percent of the strains (20/132) showed reduced susceptibility to penicillin and 3% (4/132) showed reduced susceptibility to anti-pneumococcal fluoroquinolones. Among the 196 suspected pneumococcal infections, 62 (31.6%) Streptococcus pneumoniae were isolated. Vaccine coverage for PCV-7, PCV-10 and PCV-13, were 36.2% (17/47), 66% (31/47) and 70.2% (33/47) respectively. …

CONCLUSIONS: This study confirms a high rate of carriage and disease caused by Streptococcus pneumoniae serotypes contained within the current generation of pneumococcal conjugate vaccines and consistent with reports from other countries in sub-Saharan Africa prior to PCV introduction. Antimicrobial resistance in this small unselected sample confirms a low rate of antibiotic resistance. Case-fatality is high. Introduction of a high valency pneumococcal vaccine should be a priority for health planners with the establishment of an effective surveillance system to monitor post vaccine changes.

WEB: http://dx.doi.org/10.1186/s12879-014-0627-8

IMPACT FACTOR: 2.56

CITED HALF-LIFE: 3.40

UW EDITORIAL COMMENT: Figure 1 displays the results of the nasopharyngeal (NP) carriage study, showing which serotypes are most prevalent, and which are covered by each vaccine. Figure 2 shows the serotype coverage for each vaccine for NP carriage, invasive pneumococcal disease (IPD), and meningitis.

10. GLYCOCONJUGATE VACCINES: AN UPDATE.

Vella M1, Pace D.

Expert Opin Biol Ther. 2014 Dec 11:1-18. [Epub ahead of print]

PMID: 25496172

ABSTRACT

INTRODUCTION: Globally, the three main pathogens causing serious infections are *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis*. Over the last 5 years, new vaccines protecting against these bacteria have been developed and introduced in various countries. Areas covered: This review describes the recently licensed glycoconjugates being used to protect against these encapsulated bacteria. Immunogenicity and safety data that led to licensure or licensure expansion of these glycoconjugates are discussed in addition to the resultant impact on the disease burden.

EXPERT OPINION: The maintenance of robust immunisation programmes with high uptake rates is important in maintaining low rates of disease. Epidemiological surveillance systems are essential in monitoring any changes in infectious disease trends and in identifying emerging infections such as from non-typeable *H. influenzae*, pneumococcal serotype replacement disease and changes in the epidemiology of meningococcal serogroups. This is important to guide future vaccine development. Accessibility of these glycoconjugate vaccines in resource poor regions, which bear the highest disease burden from these pathogens, remains challenging largely due to high vaccine pricing. Recent aids from public and private funding, tiered vaccine pricing and the transfer of vaccine technology have helped in introducing these vaccines where they are most needed.

WEB: http://dx.doi.org/10.1517/14712598.2015.993375

IMPACT FACTOR: 3.65

CITED HALF-LIFE: 4.30

UW EDITORIAL COMMENT: This article provides an overview of the use, efficacy, and safety of glycoconjugate vaccines. Glycoconjugate vaccines are currently available for *Haemophilus influenzae* (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis*. While these vaccines have been available for 25 years, these pathogens continue to be a leading cause of disease in children in developing countries. Public and private funding has helped the introduction of the glycoconjugate Hib vaccine in low-income countries in the last 5 years, which is already impacting these countries. Further support is needed to provide these vaccines to low-income countries to see the same reduction in morbidity and mortality from *S. pneumonia* and *N. menigitidis* as has been realized in high-income countries.

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 ("2014/11/15"[PDAT] : "2014/12/14"[PDAT]))

*On January 5, 2015, this search of English language articles published between November 15, 2014 and December 14, 2014 and indexed by the US National Library of Medicine resulted in 157 unique manuscripts.