VACCINE DELIVERY RESEARCH DIGEST

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH & TRAINING (START) CENTER

REPORT TO THE BILL & MELINDA GATES FOUNDATION

PRODUCED BY: MESIC A, BABIGUMIRA JB

SEPTEMBER 2020

Want the Vaccine Delivery Research Digest delivered directly to your inbox?
Subscribe on the Digest website: http://uwstartcenter.org/publication-digests/vaccine-digest/

START CENTER
STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER
Department of Global Health | University of Washington

List of Articles

1 Etiology of Pediatric Meningitis in West Africa Using Molecular Methods in the Era of Conjugate Vaccines against Pneumococcus, Meningococcus, and Haemophilus influenzae Type b

{Abstract & START Commentary} {Full Article}

- A sentinel-based meningitis surveillance study that used a customized probe-based PCR system to target 35 meningitis and encephalitis pathogens for case ascertainment.

2 Hospital-based surveillance for Japanese encephalitis in Bangladesh, 2007-2016: Implications for introduction of immunization

{Abstract & START Commentary} {Full Article}

- A hospital-based surveillance study for Japanese encephalitis.

3 Introduction of birth dose of hepatitis B virus vaccine to the immunization program in Ethiopia: an economic evaluation

{Abstract & START Commentary} {Full Article}

- A modelling study of a decision analytic model that estimates intervention costs and health impact of the Hepatitis B vaccine.

4 Risk-based Vaccines and the Need for Risk-based Subnational Vaccination Strategies for Introduction

{Abstract & START Commentary} {Full Article}

- A commentary focused on describing ways in which subnational strategies for introducing risk-based vaccines could be improved.

5 Decision Making and Implementation of the First Public Sector Introduction of Typhoid Conjugate Vaccine-Navi Mumbai, India, 2018

{Abstract & START Commentary} {Full Article}

- A study describing the decision-making process, campaign implementation, administrative coverage, and delivery costs of typhoid conjugate vaccine.

6 Achieving coordinated national immunity and cholera elimination in Haiti through vaccination: a modelling study

{Abstract & START Commentary} {Full Article}

- A modelling study presenting the impact of five prospective oral cholera vaccination campaigns for a 10-year period to determine the probability of and time to elimination, the effect and coverage of mass vaccination, and the percentage of cases averted.

7 Environmental Surveillance as a Tool for Identifying High-risk Settings for Typhoid Transmission {Abstract & START Commentary} {Full Article}

- A commentary presenting the benefits, challenges, and recent advances in using environmental surveillance for typhoid transmission.

8 Health economic assessment of a rabies pre-exposure prophylaxis program compared with post-exposure prophylaxis alone in high-risk age groups in the Philippines {Abstract & START Commentary} {Full Article}

- A prospective cohort study assessing the incidence of animal bites in active and passive surveillance systems and the impact of rabies prevention.

9 Introduction of multi-dose PCV 13 vaccine in Benin: from the decision to vaccinators experience {Abstract & START Commentary} {Full Article}

- A qualitative study assessing the process and experience of introducing the multi-dose pneumococcal conjugate vaccine in Benin.

10 Efficacy after 1 and 2 doses of CYD-TDV in dengue endemic areas by dengue serostatus {Abstract & START Commentary} {Full Article}

- A post-hoc analysis of data from of two-Phase III studies of a live, attenuated dengue vaccine which aimed to understand the efficacy after the first and second dose among seropositive and seronegative participants.

Appendix

Details of Articles

1. Etiology of Pediatric Meningitis in West Africa Using Molecular Methods in the Era of Conjugate Vaccines against Pneumococcus, Meningococcus, and Haemophilus influenzae Type b

Kwambana-Adams BA, Liu J, Okoi C, et al.

Am J Trop Med Hyg. 2020;103(2):696-703

PubMed ID: 32458777

ABSTRACT

Despite the implementation of effective conjugate vaccines against the three main bacterial pathogens that cause meningitis, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and *Neisseria meningitidis* serogroup A, the burden of meningitis in West Africa remains high. The relative importance of other bacterial, viral, and parasitic pathogens in central nervous system infections is poorly characterized. Cerebrospinal fluid (CSF) specimens were collected from children younger than 5 years with suspected meningitis, presenting at pediatric teaching hospitals across West Africa in five countries including Senegal, Ghana, Togo, Nigeria, and Niger. Cerebrospinal fluid specimens were initially tested using bacteriologic culture and a triplex real-time polymerase chain reaction (PCR) assay for *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* used in routine meningitis surveillance. A custom TaqMan Array Card (TAC) assay was later used to detect 35 pathogens including 15 bacteria, 17 viruses, one fungus, and two protozoans. Among 711 CSF specimens tested, the pathogen positivity rates were 2% and 20% by the triplex real-time PCR (three pathogens) and TAC (35 pathogens), respectively. TAC detected 10 bacterial pathogens, eight viral pathogens, and *Plasmodium*. Overall, *Escherichia coli* was the most prevalent (4.8%), followed by *S. pneumoniae* (3.5%) and *Plasmodium* (3.5%). Multiple pathogens were detected in 4.4% of the specimens. Children with human immunodeficiency virus (HIV) and *Plasmodium* detected in CSF had high mortality. Among 220 neonates, 17% had at least one pathogen detected, dominated by gram-negative bacteria. The meningitis TAC enhanced the detection of pathogens in children with meningitis and may be useful for case-based meningitis surveillance.

WEB: 10.4269/ajtmh.19-0566
IMPACT FACTOR: 2.216
CITED HALF-LIFE: 10.7

START COMMENTARY

In the following sentinel-based meningitis surveillance study, Kwambana-Adams *et al.* collected cerebrospinal fluid (CSF) from children under five in Senegal, Ghana, Togo, Nigeria, and Niger from 2017 and 2018 after the rollout of the pneumococcal conjugate vaccine (PCV), the meningococcal A protein–polysaccharide conjugate vaccine (MenAfriVac), and the Hib conjugate vaccine. The authors used the TaqMan Array Card (TAC), a probe-based PCR system that can detect bacterial, viral, protozoan, and fungal pathogens, and customized the TAC assay to target 35 meningitis and encephalitis pathogens for case ascertainment. This article contributes to the literature as meningitis diagnosis and surveillance have historically been hindered by low pathogen yields from bacterial culture, which limits the ability to detect meningeal pathogens. Improving diagnostics and surveillance has been indicated as a priority for the WHO's elimination of epidemic meningitis in Africa by 2030.

Key findings include that the leading pathogen detected varied across settings, and that antibiotic usage affected pathogen detection. In Togo, *Plasmodium* was the most common pathogen (5% of specimens). In Ghana and Niger, the most common pathogen was *S. pneumoniae* (6.3% and 13%, respectively), whereas *E. coli* was the most common in Nigeria and Senegal (14% and 16%, respectively). About 41% of patients reported antibiotic use before admission, which did not affect the overall bacterial pathogen detection. However, for specific pathogens, namely E. coli and Plasmodium, there were significantly lower rates in those that reported use of antibiotics (3.4% vs. 8.0%, P=0.038 for *E. coli*; and 0.5% vs. 3.7% for *Plasmodium*, P=0.033).

Key limitations that affect the representativeness of this study include the lack of nationwide case-based surveillance across the five countries, the inability to test all CSF specimens (i.e. only 65% of the samples had sufficient volume for testing), and the differences in case ascertainment, which could be a result of co-infections and overlap of case definitions with other febrile illness. However, despite these limitations, this study shows the ability of molecular detection to enhance case ascertainment for meningitis surveillance programs in endemic settings.

Return to List of Articles

2. Hospital-based surveillance for Japanese encephalitis in Bangladesh, 2007-2016: Implications for introduction of immunization

Paul KK, Sazzad HMS, Rahman M, et al.

Int J Infect Dis. 2020;99:69-74.

PubMed ID: 32721530

ABSTRACT

BACKGROUND: Japanese encephalitis (JE) virus is recognized as a major cause of encephalitis in Bangladesh. The World Health Organization (WHO) recommends human immunization as the most effective means to control JE. Several WHO-prequalified vaccines are available to prevent JE but no vaccination program has been implemented in Bangladesh.

METHODS: We conducted hospital-based surveillance for acute meningitis-encephalitis syndrome (AMES) to describe JE epidemiology and help inform policy decisions about possible immunization strategies for Bangladesh.

RESULTS: During 2007–2016, a total of 6543 AMES patients were identified at four tertiary hospitals. Of the 6525 patients tested, 548 (8%) were classified as JE cases. These 548 patients resided in 36 (56%) out of 64 districts of Bangladesh, with the highest proportion of JE cases among AMES patients (12% and 7%) presenting at two hospitals in the northwestern part of the country. The median age of JE cases was 30 years, and 193 (35%) were aged ⩽15 years. The majority of JE cases (80%) were identified from July through November.

CONCLUSIONS: Surveillance results suggest that JE continues to be an important cause of meningo-encephalitis in Bangladesh. Immunization strategies including JE vaccine introduction into the routine childhood immunization program or mass vaccination in certain age groups or geographic areas need to be examined, taking into consideration the cost-effectiveness ratio of the approach and potential for decreasing disease burden.

WEB: 10.1016/j.ijid.2020.07.026

IMPACT FACTOR: 3.202

CITED HALF-LIFE: 5.3

START COMMENTARY

From 2007 to 2016, Paul *et al.* conducted a hospital-based surveillance study for acute meningitis-encephalitis syndrome (AMES). Results indicate that most Japanese encephalitis (JE) cases were male (62% of 548) and most cases were under <30 years old (35%) though the median age varied

greatly across sites, from 11 years old at Chittagong Hospital to 40 at Khulna Hospital. The JE proportion of AMES cases was highest in participants aged 56-65 (20%, 82 of 406), and lowest among children under five (3%, 67 of 1925). The authors of the study observed seasonal increased in the second quarter of each year, with most cases from July to November with a peak in October, likely due to the abundance of *Culex tritaeniorhynchus* mosquitoes during the monsoon and post monsoon period. Authors note that current JE immunization programs, which focus on one-time catch up childhood immunization campaigns, may fall short. The current Gavi Alliance campaign for children 9 months and 14 years is expected to prevent one-third of all cases of JE. However, given that most cases are in adults, it would take years to see a reduction without additional targeted adult immunization campaigns

One key limitation to note were the differences in surveillance across hospitals, which affected the number of JE cases identified and the temporo-spatial distribution of those cases. Rajshahi, Khulna, and Chittagong Medical College Hospitals began surveillance in September 2007, whereas Rangpur Medical College Hospital began in January 2010. Enrolment at Khulna medical hospital stopped at the end of 2010 and Chittagong Medical College did not conduct surveillance during 2011 and 2012. These differences in surveillance could have greatly affected the results of this study.

Return to List of Articles

3. Introduction of birth dose of hepatitis B virus vaccine to the immunization program in Ethiopia: an economic evaluation

Memirie ST, Desalegn H, Naizgi M, et al.
Cost Eff Resour Alloc. 2020;18:23.
PubMed ID: 32704237

ABSTRACT

BACKGROUND: Hepatitis B virus (HBV) infection is an important cause of morbidity and mortality with a very high burden in Africa. The risk of developing chronic infection is marked if the infection is acquired perinatally, which is largely preventable through a birth dose of HBV vaccine. We examined the cost-effectiveness of a birth dose of HBV vaccine in a medical setting in Ethiopia.
METHODS: We constructed a decision analytic model with a Markov process to estimate the costs and effects of a birth dose of HBV vaccine (the intervention), compared with current practices in Ethiopia. Current practice is pentavalent vaccination (DPT-HiB-HepB) administered at 6, 10 and 14 weeks after birth. We used disability-adjusted life years (DALYs) averted to quantify the health

benefits while the costs of the intervention were expressed in 2018 USD. Analyses were based on Ethiopian epidemiological, demographic and cost data when available; otherwise we used a thorough literature review, in particular for assigning transition probabilities.
RESULTS: In Ethiopia, where the prevalence of HBV among pregnant women is 5%, adding a birth dose of HBV vaccine would present an incremental cost-effectiveness ratio (ICER) of USD 110 per DALY averted. The estimated ICER compares very favorably with a willingness-to-pay level of 0.31 times gross domestic product per capita (about USD 240 in 2018) in Ethiopia. Our ICER estimates were robust over a wide range of epidemiologic, vaccine effectiveness, vaccine coverage and cost parameter inputs.
CONCLUSIONS: Based on our cost-effectiveness findings, introducing a birth dose of HBV vaccine in Ethiopia would likely be highly cost-effective. Such evidence could help guide policymakers in considering including HBV vaccine into Ethiopia's essential health services package.
WEB: 10.1186/s12962-020-00219-7
IMPACT FACTOR: 1.413
CITED HALF-LIFE: 7.8

START COMMENTARY

Memirie *et al.* constructed a decision analytic model with a Markov process to estimate intervention costs and health impact of a hepatitis B virus (HBV) infected individual over a lifetime. Two strategies that were used for this include a novel strategy of four doses called Hep B-BD vaccine plus, in which all infants receive HepB-BD vaccine (monovalent) within 24 hours of delivery (assuming 50% of births occur with a skilled attendant) and continue on with the pentavalent vaccine (DPT-HiB-HepB) series starting at the age of 6 weeks. The second strategy is the current HepB-BD vaccine strategy, which is rolled out to a birth cohort at 6, 10 and 13 weeks after birth. Table 1 provides detailed information on the base assumptions and ranges for sensitivity analyses for key epidemiological parameters for HBV infection; Table 2 provides disability weights for different disease states; And, table 3 provides base assumptions and ranges for sensitivity analyses for HBV vaccination and intervention costs, both of which are critical to the Markov model.

Results indicate that the first strategy, with an additional HepB-BD vaccine would have an incremental cost-effectiveness ratio (ICER) of USD110 per DALY averted, which is lower than the willingness-to-pay threshold (i.e. less than three times the GBP per capita in Ethiopia), making this strategy highly cost-effective. The model indicated that combinations of 'vaccine effectiveness' and other parameters would increase ICERs. Vaccine effectiveness combined with 'average cost per vaccination child' would result in an ICER of USD262 per DALY averted, whereas combined with 'prevalence of HBV infection among mothers', it would result in an ICER of USD421 per DALY averted. Combined with "vaccine utilization" it would result in an ICER of USD663 per DALY averted.

Overall, this strategy would avert 10,020 DALYs for a cost of USD2.5 million for a birth cohort of 3.34 million. Key limitations of this study are related to assumptions. Assumptions around cost may not include all components of immunization programs such as the cost of outreach strategies, transport, and additional health staff. Further, some assumptions around vaccine effectiveness and costs of health states and treatment were not specific to Ethiopia.

Return to List of Articles

4. Risk-based Vaccines and the Need for Risk-based Subnational Vaccination Strategies for Introduction

Muhib FB, Pecenka CJ, Marfin AA.
Clin Infect Dis. 2020;71(Supplement_2):S165-S171.
PubMed ID: 32725237

ABSTRACT

BACKGROUND: Most vaccines in the Expanded Program on Immunization are universal childhood vaccines (eg, measles and rotavirus vaccines). Other vaccines such as typhoid conjugate (TCV) and Japanese encephalitis vaccines are risk based and only used in countries where populations are at risk of these diseases. However, strategies to introduce risk-based vaccines are becoming complex due to increasing intracountry variability in disease incidence. There is a need to assess whether subnational vaccine strategies are appropriate.
CRITERIA, CHALLENGES, AND BENEFITS: Subnational strategies consider intracountry heterogeneous risk and prioritize vaccination only in those areas that are at risk; there is no intent to introduce the vaccine nationally. The following variables should be considered to determine appropriateness of subnational strategies: disease burden, outbreak potential, treatment availability and costs, cost-effectiveness, and availability of other preventive interventions. We propose criteria for each variable and use a hypothetical country considering TCV introduction to show how criteria are applied to determine if a subnational strategy is appropriate. Challenges include granularity of disease-burden data, political challenges of vaccinating only a portion of a population, and potentially higher costs of introduction. Benefits include targeted reduction of disease burden, increased equity for marginalized populations, and progress on development goals.
CONCLUSIONS: In the absence of perfect information at the national level, adopting a subnational vaccine strategy can provide country decision makers with an alternative to national vaccine introduction. Given the changing nature of communicable disease burden, subnational vaccination

may be a tool to effectively avert mortality and morbidity while maximizing the use of available health and financial resources.

WEB: 10.1093/cid/ciaa483
IMPACT FACTOR: 8.313
CITED HALF-LIFE: 8.3

START COMMENTARY

Muhib *et al.* describe ways to improve subnational strategies for introducing risk-based vaccines based on disease incidence. Risk based vaccines include those for disease that are not uniformly distributed globally including typhoid, cholera, yellow fever, meningococcal disease, Japanese encephalitis (JE), and tick-borne encephalitis. Criteria which should be evaluated when considering the introduction of a vaccine sub-nationally includes the burden of disease, the outbreak potential, treatment availability and cost, the availability of other preventive measures, and cost effectiveness. These criteria, and related indicators are outlined in depth in Table 1. These criteria allow decision-makers in country to determine where within a country, or for which population, a vaccine might be most appropriate, which is hugely beneficial given heterogenous distribution of disease and economic and infrastructure resources within countries. Muhib *et al.* highlight some issues that may arise when employing this strategy, including a lack of high-quality disease incidence data in some settings, political challenges, and costs related to vaccine delivery to target populations or geographies. Despite the challenges, sub-national vaccine strategies that target highly affected populations and areas could be impactful by reducing disease burden and increasing equity, vaccine impact, and cost-effectiveness. One key limitation of this study that the list of criteria (Table 1) may not be exhaustive; there are other factors such as environmental changes which influence disease incidence and may be important to consider.

Return to List of Articles

5. Decision Making and Implementation of the First Public Sector Introduction of Typhoid Conjugate Vaccine-Navi Mumbai, India, 2018

Date K, Shimpi R, Luby S, et al.

Clin Infect Dis. 2020;71(Supplement_2):S172-S178.
PubMed ID: 32725235

ABSTRACT

BACKGROUND: Typhoid fever prevention and control efforts are critical in an era of rising antimicrobial resistance among typhoid pathogens. India remains one of the highest typhoid disease burden countries, although a highly efficacious typhoid conjugate vaccine (TCV), prequalified by the World Health Organization in 2017, has been available since 2013. In 2018, the Navi Mumbai Municipal Corporation (NMMC) introduced TCV into its immunization program, targeting children aged 9 months to 14 years in 11 of 22 areas (Phase 1 campaign). We describe the decision making, implementation, and delivery costing to inform TCV use in other settings.
METHODS: We collected information on the decision making and campaign implementation in addition to administrative coverage from NMMC and partners. We then used a microcosting approach from the local government (NMMC) perspective, using a new Microsoft Excel–based tool to estimate the financial and economic vaccination campaign costs.
RESULTS: The planning and implementation of the campaign were led by NMMC with support from multiple partners. A fixed-post campaign was conducted during weekends and public holidays in July–August 2018 which achieved an administrative vaccination coverage of 71% (ranging from 46% in high-income to 92% in low-income areas). Not including vaccine and vaccination supplies, the average financial cost and economic cost per dose of TCV delivery were $0.45 and $1.42, respectively.
CONCLUSION: The first public sector TCV campaign was successfully implemented by NMMC, with high administrative coverage in slums and low-income areas. Delivery cost estimates provide important inputs to evaluate the cost-effectiveness and affordability of TCV vaccination through public sector preventive campaigns.
WEB: 10.1093/cid/ciaa597
IMPACT FACTOR: 8.313
CITED HALF-LIFE: 8.3

START COMMENTARY

In this study, Date *et al.* describe the decision-making process, campaign implementation, administrative coverage, and delivery costs of Typhoid Conjugate Vaccine (TCV) in Navi Mumbai, India. This article contributes an understanding of implementation of TCV, which have been shown to have potential for substantially reducing the burden of typhoid. The authors describe in detail the key decisions related to implementation including a description and rational for the introduction of TCV, the target population (9 months to 14 years old) and the two-phase roll-out. Further, authors describe the implementation of the vaccine, which included a vaccination session for every 150 children, various vaccination sites (health posts, immunization clinics, residential offices, and community center), and social mobilization activities. Overall, 113,420 children received the coverage (71% coverage) and 222 vaccine recipients reported adverse events. Of those, 95% were mild (i.e. pain, fever, and swelling) and no deaths were reported. Rapid convenience monitoring of

495 vaccination sessions was employed to check quality indicators, which ranged from 89%-100%, indicating high quality. To confirm coverage, 328 sub-areas and 6560 were selected for household monitoring and 86% of children were vaccinated, indicating high coverage. Unsurprisingly, vaccine delivery costs depended on vaccination coverage. The financial costs per dose ranged from $0.44 to $0.60 whereas the average economic cost per dose was $1.30 to $3.93. Limitations of this study to note include convenience sampling to check for quality of the vaccination sessions, which may have introduce some selection bias. Further, the cost estimates did not include the cost of the vaccine and vaccination supplies, which may mean it underestimates the real financial and economic cost of a TCV campaign. However, the successful public sector implementation of TCV in this study provides a promising example for similar settings with a high typhoid burden.

Return to List of Articles

6. Achieving coordinated national immunity and cholera elimination in Haiti through vaccination: a modelling study

Lee EC, Chao DL, Lemaitre JC, et al.

Lancet Glob Health. 2020;8(8):e1081-e1089.
PubMed ID: 32710864

ABSTRACT

BACKGROUND: Cholera was introduced into Haiti in 2010. Since then, more than 820 000 cases and nearly 10 000 deaths have been reported. Oral cholera vaccine (OCV) is safe and effective, but has not been seen as a primary tool for cholera elimination due to a limited period of protection and constrained supplies. Regionally, epidemic cholera is contained to the island of Hispaniola, and the lowest numbers of cases since the epidemic began were reported in 2019. Hence, Haiti may represent a unique opportunity to eliminate cholera with OCV.
METHODS: In this modelling study, we assessed the probability of elimination, time to elimination, and percentage of cases averted with OCV campaign scenarios in Haiti through simulations from four modelling teams. For a 10-year period from January 19, 2019, to Jan 13, 2029, we compared a no vaccination scenario with five OCV campaign scenarios that differed in geographical scope, coverage, and rollout duration. Teams used weekly department-level reports of suspected cholera cases from the Haiti Ministry of Public Health and Population to calibrate the models and used common vaccine-related assumptions, but other model features were determined independently.
FINDINGS: Among campaigns with the same vaccination coverage (70% fully vaccinated), the median probability of elimination after 5 years was 0–18% for no vaccination, 0–33% for 2-year

campaigns focused in the two departments with the highest historical incidence, 0–72% for three-department campaigns, and 35–100% for nationwide campaigns. Two-department campaigns averted a median of 12–58% of infections, three-department campaigns averted 29–80% of infections, and national campaigns averted 58–95% of infections. Extending the national campaign to a 5-year rollout (compared to a 2-year rollout), reduced the probability of elimination to 0–95% and the proportion of cases averted to 37–86%.

INTERPRETATION: Models suggest that the probability of achieving zero transmission of Vibrio cholerae in Haiti with current methods of control is low, and that bolder action is needed to promote elimination of cholera from the region. Large-scale cholera vaccination campaigns in Haiti would offer the opportunity to synchronise nationwide immunity, providing near-term population protection while improvements to water and sanitation promote long-term cholera elimination.

WEB: 10.1016/S2214-109X(20)30310-7

IMPACT FACTOR: 21.597

CITED HALF-LIFE: 3.1

START COMMENTARY

In this modelling study, Lee *et al.* present the impact of five prospective Oral Cholera Vaccination (OCV) compared to the status quo (no vaccination) for a 10-year period in Haiti to determine the probability of and time to elimination, the effect and coverage of mass vaccination, and the percentage of cases averted. Each model was fit to common cholera incidence data and included six projections which included the status quo, and five scenarios that differed by deployment and vaccination coverage. Details regarding the scenarios and vaccine protection assumptions are illustrated in Figure 2. Only when the models included a nationwide vaccination campaign with a 2-year rollout projected some probability of elimination, and between 58% to 95% of infections averted over a 5-year period. Given the low probability of elimination in other scenarios (e.g. 0-18% chance of elimination under current conditions), it highlights the need for increased efforts to improve access to safe and sustainable water and sanitation in conjunction with mass OCV campaigns. This article contributes to the literature as it outlines the opportunity to use OCV to eliminate cholera, rather than use it as a temporary measure to respond to outbreaks. However, this opportunity would require a large-scale campaign with high population coverage in order to successfully eliminate cholera.

Return to List of Articles

7. Environmental Surveillance as a Tool for Identifying High-risk Settings for Typhoid Transmission

Andrews JR, Yu AT, Saha S, et al.
Clin Infect Dis. 2020;71(Supplement_2):S71-S78.
PubMed ID: 32725227

ABSTRACT

Enteric fever remains a major cause of morbidity in developing countries with poor sanitation conditions that enable fecal contamination of water distribution systems. Historical evidence has shown that contamination of water systems used for household consumption or agriculture are key transmission routes for *Salmonella* Typhi and *Salmonella* Paratyphi A. The World Health Organization now recommends that typhoid conjugate vaccines (TCV) be used in settings with high typhoid incidence; consequently, governments face a challenge regarding how to prioritize typhoid against other emerging diseases. A key issue is the lack of typhoid burden data in many low- and middle-income countries where TCV could be deployed. Here we present an argument for utilizing environmental sampling for the surveillance of enteric fever organisms to provide data on community-level typhoid risk. Such an approach could complement traditional blood culture-based surveillance or even replace it in settings where population-based clinical surveillance is not feasible. We review historical studies characterizing the transmission of enteric fever organisms through sewage and water, discuss recent advances in the molecular detection of typhoidal Salmonella in the environment, and outline challenges and knowledge gaps that need to be addressed to establish environmental sampling as a tool for generating actionable data that can inform public health responses to enteric fever.
WEB: 10.1093/cid/ciaa513
IMPACT FACTOR: 8.313
CITED HALF-LIFE: 8.3

START COMMENTARY

In this commentary, Andrews *et al*. present the case for using environmental surveillance for typhoid transmission, which is important given the scarcity of typhoid burden data due to inadequate diagnostics and limited laboratory capacity for blood cultures in low- and middle-income countries. Authors describe the methods for environmental surveillance, which include collecting samples from drinking water, sewage, air, or fomites to screen for pathogens. This method may be particularly useful given that contaminated water is a critical pathway for typhoidal *Salmonella* transmission and there is no animal reservoir for transmission. Though this seems like a promising method of surveillance, Andrews et. al highlight some of the challenges of this method such as technical difficulties relating to isolating the pathogens from water and environmental samples. However, if these challenges can be addressed through the advent of sensitive molecular techniques, this method of surveillance would be useful in limited resource settings where blood-culture based

surveillance data is insufficient, as a means of monitoring and measuring the effect of typhoidal prevention interventions, and to facilitate disease elimination and improvements in sanitation.

Return to List of Articles

8. Health economic assessment of a rabies pre-exposure prophylaxis program compared with post-exposure prophylaxis alone in high-risk age groups in the Philippines

Deray R, Rivera C, Gripon S, et al.
PLoS One. 2018;13(1):e0189596.
PubMed ID: 32450291

ABSTRACT

BACKGROUND: Rabies remains endemic in the Philippines. A study was conducted in El Nido, Palawan, Philippines to: (i) detect the true incidence of animal bites in school children aged 5–14 years using active surveillance and compare these data to estimates from the existing passive surveillance system, (ii) evaluate the impact of rabies prevention education and pre-exposure prophylaxis (PrEP) on animal bite incidence, and (iii) assess the health economic impact of the interventions.

METHODOLOGY AND PRINCIPAL FINDINGS: A cohort of 4,700 school children was followed-up for any suspect rabies exposures between January 2011 and December 2012. Data on animal bite incidence from the study cohort were compared to that obtained from a review of consultation records at the Animal Bite Treatment Center (ABTC). PrEP was offered to children in all 27 public elementary schools in El Nido (in January to February 2012). Teachers were given a manual for integrating rabies in the public elementary school curriculum during the school year 2012–13. Active surveillance of the cohort revealed a higher incidence of suspect rabies exposures than that from passive surveillance. Despite a decrease in the number of Category III bites, there was no significant decrease in overall bite incidence as a result of the interventions. However, there was an increase in rabies awareness among school children in all grade levels. There was also a high level of acceptability of PrEP. Children who received PrEP and subsequently were bitten only needed two booster doses for post-exposure prophylaxis, resulting in substantial cost-savings.

CONCLUSIONS/SIGNIFICANCE: The true burden of animal bites remains underestimated in ABTC records. PrEP is advantageous in selected population groups, i.e. school-aged children in rabies

endemic areas with limited access to animal and human rabies prevention services. Educating school children is beneficial. Strengthening veterinary interventions to target the disease at source is important.

WEB: 10.1016/j.ijid.2020.05.062
IMPACT FACTOR: 2.740
CITED HALF-LIFE: 5.6

START COMMENTARY

Deray *et al.* followed a prospective cohort of 4,700 school children in the Philippines, a country in which dog rabies is endemic. The aim of the study was to better understand the incidence of animal bites and rabies, which is greatly underreported and underestimated globally. Authors assessed the incidence of animal bites in active and passive surveillance systems, the impact of rabies interventions (which included pre-exposure prophylaxis [PrEP] and disease prevention education), and the health economic impacts of the intervention. Key findings include that 82.3% of the study cohort received the complete three dose of anti-rabies PrEP, 10.1% received one or two doses, and 7% received no PrEP. Nearly all (4,663 of 4,666) parents reported children received education about rabies and there was a significant increase in the proportion of students who were aware of rabies by the end of the year (49% in the pre-test to 98% in the post test, $p<0.01$). One key finding of this study is that most children with animal bites did not seek treatment at an animal bite treatment center, and only 27% of bites were reported to animal bite treatment centers. It was estimated that introducing PrEP would result in cost savings of USD 17,133 over 10 years, but this cost savings relies on the reporting and treatment of all bites, which did not happen as part of this study. Some key limitations of this study are that this may not be generalizable to children that are not in the formal education system but are living in rabies endemic areas.

Return to List of Articles

9. Introduction of multi-dose PCV 13 vaccine in Benin: from the decision to vaccinators experience

Abdoulaye Alfa D, Houngnihin RA, Ilboudo GP, Dick N, Kaucley L, Essoh TA.
BMC Public Health. 2020;20(1):1216.
PubMed ID: 32770996

ABSTRACT

BACKGROUND: In 2011, Benin introduced the 13-valent pneumococcal conjugated vaccine (PCV13), in a single-dose vial, into its Expanded Programme for Immunisation (EPI) with support from Gavi. In April 2018, with the support of the Agence de Médecine Préventive Afrique (AMP) and other technical and financial partners, the single-dose vial was transitioned to a four-dose vial. Here we describe the decision-making process and the experience of the vaccinators during the change.
METHODS: We carried out semi-structured, individual interviews with 61 participants individuals involved in the EPI: 7 from central level, 5 from regional level, 7 from township level and 42 from district level. The interviews were recorded and transcribed, and the information categorised, using Nvivo software, and then analysed.
RESULTS: The Inter-agency Coordination Committee (ICC), the Benin National Advisory Committee for Vaccines and Vaccination, (BNACVV) and the World Health Organisation (WHO) (i.e., the traditional governance structures involved in vaccination decisions) were not involved in the decision to change to the four-dose vial for PCV13. The decision was taken by the EPI, supported by Gavi. The vaccination errors observed in the first months following the change in presentation were due to the absence of guidelines for changes in vaccine presentation and the central-level actors' perception that it was 'only a change in the vial', and therefore that the communication and training for a new vaccine were not required since the vaccine itself and its administration mode were unchanged.
CONCLUSIONS: It is important that the other countries eligible for Gavi support that are about to change to the multi-dose vial PCV13 presentation learn from Benin's experience. The main lessons learned are that changes in the presentation of an established vaccine should follow the same process as the introduction of a new vaccine, and that all stakeholders involved in vaccines and vaccination should participate in the decision-making process and implementation.
WEB: 10.1186/s12889-020-09326-9
IMPACT FACTOR: 2.521
CITED HALF-LIFE: 6.0

START COMMENTARY

In this qualitative study, Abdoulaye Alfa *et al.* explore the process of introducing the multi-dose pneumococcal conjugate vaccine (PCV13) vaccine to the Expanded Programme for Immunisation (EPI) in Benin. Authors describe the decision-making process, which involved key stakeholders in Benin (National Agency for Immunization) and external partners (UNICEF and Gavi). There were mixed views on the new PCV13 vaccine. Some vaccinators expressed confusion about the vaccine supplies, indicating that they did not realize that there were four doses in each vial, which may indicate that information sheets did not reach the vaccinators. Others noted there were issues with vaccine wastage, as the opening date was not indicated by vaccinators on each vial. However, many appreciated the smaller size as many clinics given it takes less storage space and the ease of

vaccine transport. This study describes some of the errors that were experienced in the first months of vaccination activities which were largely due to the perception that this should not be treated as a new vaccine and therefore, did not require a high level of communication and training. However, for other countries which may implement PCV13, Alfa *et al.* urge all stakeholders to take the lessons learned in Benin and apply them to their own decision-making process and implementation.

Return to List of Articles

10. Efficacy after 1 and 2 doses of CYD-TDV in dengue endemic areas by dengue serostatus

Dayan GH, Langevin E, Forrat R, et al.

Vaccine. 2020;S0264-410X(20)30987-7. doi:10.1016/j.vaccine.2020.07.056
PubMed ID: 32773243

ABSTRACT

A simplified dose regimen of the live, attenuated, tetravalent dengue vaccine (CYD-TDV) could have the potential to facilitate easier implementation of immunization programs against symptomatic virologically-confirmed dengue (VCD) in dengue seropositive individuals aged ⩾ 9 years. This post-hoc analysis of two Phase III studies (CYD14 [NCT01373281] and CYD15 [NCT01374516]) in dengue endemic areas assessed the efficacy of CYD-TDV by dengue serostatus between dose 1 and 2 (at Month [M] 6), between dose 2 and 3 (at M12), and from dose 3 to M25. Baseline dengue serostatus (seropositive or seronegative) was determined based on measured dengue neutralizing antibody titers with the 50% plaque reduction neutralization test (PRNT50) or ascertained by logistic regression-based multiple imputation (MI) to predict PRNT50. Vaccine efficacy against symptomatic VCD was assessed by age and baseline dengue serostatus using a case-cohort framework. Dengue neutralizing antibody geometric mean titers (GMTs) were measured with the PRNT50 at 28 days post-dose 2 and 3. Vaccine efficacy estimates in seropositive participants aged ⩾ 9 years at post-dose 1, 2, and 3 were 80.5% (95% CI, 66.2, 88.7), 82.0% (95% CI, 70.5, 89.0), and 75.2% (95% CI, 65.9, 81.9), respectively. In seropositive participants aged < 9 years, vaccine efficacy estimates were 48.5% (95% CI, -24.3, 78.6), 68.3% (95% CI, 34.5, 84.7), and 65.3% (95% CI, 40.2, 79.9), respectively. CYD-TDV efficacy was null to modest after any dose in seronegative participants, regardless of age group. Seropositive participants aged ⩾ 9 years in the CYD-TDV group had GMTs post-dose 3 that did not exceed those observed post-dose 2. In conclusion, CYD-TDV has high efficacy against VCD from the first dose through to M25, with estimates at post-dose 1 and 2 similar to or higher than those at post-dose 3 in seropositive participants aged ⩾ 9 years, consistent with immunogenicity data.

WEB: 10.1016/j.vaccine.2020.07.056
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

In this post-hoc analysis, Dayan *et al.* assess the efficacy of a live, attenuated dengue vaccine (CYD-TDV) by dengue serostatus during the six-month interval between dose 1 and 2, between dose 2 and 3, and from dose 3 to the 25th month after (M25) using data from two Phase III studies (CYD14 in the Asia-Pacific region and CYD15 in Latin America). This article contributes to the literature, as it is the first study to assess CYD-TDV efficacy after one or two doses, which would reduce vaccine-associated costs, which is particularly important for low- and middle-income countries. In Figure 1, authors present the vaccine efficacy for each time interval for each study and the pooled vaccine efficacy across studies. Key takeaways from this study include that vaccine efficacy could not be demonstrated in seronegative participants of any age at any time point, and that for dengue seropositive participants 9 years and over, CTD-TDV conferred protection against VCD from the first dose to the M25. Given that vaccine efficacy post-dose 1 and 2 were similar to those observed post-dose 3, there may be some rationale for a vaccine schedule with fewer doses, which would reduce costs, ease vaccine implementation, and likely result in increased coverage and vaccine schedule compliance. However, this would need to be assessed further in studies that evaluate the durability of neutralizing antibody responses with fewer doses.

Return to List of Articles

Appendix

The literature search for the August 2020 Vaccine Delivery Research Digest was conducted on September 3rd, 2020. We searched English language articles indexed by the US National Library of Medicine and published between July 15, 2020 and August 14, 2020. The search resulted in 319 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]) ("2020/7/15"[PDAT] : "2020/08/14"[PDAT]))