

VACCINE DELIVERY RESEARCH DIGEST

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

REPORT TO THE BILL & MELINDA GATES FOUNDATION

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APPENDIX



1. <u>The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered</u> <u>by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled,</u> <u>phase 1 trial.</u>

Rouphael NG, Paine M, Mosley R, Henry S, McAllister DV, Kalluri H et al.

Lancet. 2017 Jun 27. [Epub ahead of print]

PubMed PMID: 28666680

ABSTRACT (Abridged)

BACKGROUND: Microneedle patches provide an alternative to conventional needle-and-syringe immunisation, and potentially offer improved immunogenicity, simplicity, cost-effectiveness, acceptability, and safety. We describe safety, immunogenicity, and acceptability of the first-in-man study on single, dissolvable microneedle patch vaccination against influenza.

METHODS: The TIV-MNP 2015 study was a randomised, partly blinded, placebo-controlled, phase 1, clinical trial at Emory University that enrolled non-pregnant, immunocompetent adults from Atlanta, GA, USA, who were aged 18-49 years, naive to the 2014-15 influenza vaccine, and did not have any significant dermatological disorders. Participants were randomly assigned (1:1:1:1) to four groups and received a single dose of inactivated influenza vaccine (fluvirin: 18 µg of haemagglutinin per H1N1 vaccine strain, 17 μ g of haemagglutinin per H3N2 vaccine strain, and 15 μ g of haemagglutinin per B vaccine strain) (1) by microneedle patch or (2) by intramuscular injection, or received (3) placebo by microneedle patch, all administered by an unmasked health-care worker; or received a single dose of (4) inactivated influenza vaccine by microneedle patch self-administered by study participants. Because of the nature of the study, participants were not masked to the type of vaccination method (ie, microneedle patch vs intramuscular injection). Primary safety outcome measures are the incidence of study productrelated serious adverse events within 180 days, grade 3 solicited or unsolicited adverse events within 28 days, and solicited injection site and systemic reactogenicity on the day of study product administration through 7 days after administration, and secondary safety outcomes are new-onset chronic illnesses within 180 days and unsolicited adverse events within 28 days, all analysed by intention to treat. Secondary immunogenicity outcomes are antibody titres at day 28 and percentages of seroconversion and seroprotection, all determined by haemagglutination inhibition antibody assay. The trial is completed and registered with ClinicalTrials.gov, number NCT02438423.

FINDINGS: In Sept, 2015, 100 participants were enrolled and randomly assigned to a group. There were no treatment-related serious adverse events, no treatment-related unsolicited grade 3 or higher adverse events, and no new-onset chronic illnesses. Among vaccinated groups (vaccine via health-care worker administered microneedle patch or intramuscular injection, or self-administered microneedle patch), overall incidence of solicited adverse events (n=89 vs n=73 vs n=73) and unsolicited adverse events (n=18 vs n=12 vs n=14) were similar. Reactogenicity was mild, transient, and most commonly reported as tenderness (15 [60%] of 25 participants) and pain (11 [44%] of 25) after intramuscular injection; and as tenderness (33 [66%] of 50), erythema (20 [40%] of 50), and pruritus (41 [82%] of 50]) after vaccination by microneedle patch application. The geometric mean titres were similar at day 28 between the microneedle patch administered by a health-care worker versus the intramuscular route for the H1N1 strain (1197 [95% CI 855-1675] vs 997 [703-1415]; p=0.5), the H3N2 strain (287 [192-430] vs 223 [160-312]; p=0.4), and the B strain (126 [86-184] vs 94 [73-122]; p=0.06). Similar geometric mean titres were reported in participants who self-administered the microneedle patch (all p>0.05). The seroconversion percentages were significantly higher at day 28 after microneedle patch vaccination compared with placebo (all p<0.0001) and were similar to intramuscular injection (all p > 0.01).

INTERPRETATION: Use of dissolvable microneedle patches for influenza vaccination was well tolerated and generated robust antibody responses.

WEB: <u>https://dx.doi.org/ 10.1016/S0140-6736(17)30575-5</u> IMPACT FACTOR: 47.83



CITED HALF-LIFE: 9.0

START Scientific Comment: This is the first study in humans to demonstrate the safety and immunogenicity of dissolvable microneedle patch for influenza vaccination. This study was preceded by a similar intradermal hollow microneedle device vaccine--Fluzone Intradermal Quadrivalent Influenza Vaccine, developed by Sanofi Pastor but is distinguished by microneedles that dissolve after application leaving behind a patch backing that can be discarded as non-sharps waste thereby eliminating sharps wastes. The vaccine remains stable for upwards of 12 months at 5°C, 25°C, and 40°C making it suitable for distribution and storage outside of the cold chain. Authors reported participants in IM_{IIV} group received 15 µg of vaccine product for each strain and though doses were slightly lower among MNP groups, there was no significant difference between the dose of each strain delivered by the MNP_{IIV-HCW} and MNP_{IIV-self} groups (p>0.60). The MNP_{IIV-HCW} group demonstrated greatest proportion of seroconverted participants for H3N2 and B strains at day 28 (figure 5) and day 180 (appendix) and the MNP_{IIV-HCW} demonstrated the greatest proportion of seroconverted participants for H1N1 at day 28 (figure 5) and 180 (appendix). Overall immunological responses were similar in vaccinated groups when compared to control. Previous studies have reported targeting antigen-presenting cells in the skin may confer an enhanced immunogenicic effects to microneedle delivery relative to intramuscular delivery though this study was not powered to make such a comparison.

A total of 13 treatment-related adverse events were reported in 8 participants seven days post vaccination (Figure 3). Local reactogenicity events were reported more often in the MNPIIV groups than in the IMIIV group but were generally mild and self-limiting. Authors report there was no difference in the severity or frequency of SAEs associated with treatment among the three treatment groups receiving inactivated influenza vaccines. Excluding controls, the incidence of solicited and unsolicited adverse events (MNP_{IIV-HCW}: n=18, IM_{IIV}: n=12, & MNP_{IIV-self}: n=14) were similar across groups (solicited :MNP_{IIV-HCW} n=89, IM_{IIV} n=73, & MNP_{IIV-self}: n=73 vs unsolicited: MNP_{IIV-HCW} n=18, IM_{IIV} n=12, & MNP_{IIV-self} n=14). No serious adverse events (SAEs) or dropouts due to SAEs related to any treatment were reported during the study, though 41% of participants provided unsolicited reports of adverse events. Authors report that by the conclusion of the study the proportion of participants receiving MNPs wishing to receive MNPs in the future (relative to intranasal, intramuscular, or no vaccine) grew from 56% to 70%. However, in choosing to restrict the pool of eligible individuals to those who were not vaccinated during the 2015-2016 season authors may have inadvertently selected individuals who would be less inclined to prefer IM vaccines given their history. High pre-vaccination titres observed in the study population make it difficult to compare the effect across groups.



2. <u>Immunogenicity and safety of three aluminium hydroxide adjuvanted vaccines with</u> reduced doses of inactivated polio vaccine (IPV-AI) compared with standard IPV in young infants in the Dominican Republic: a phase 2, non-inferiority, observer-blinded, randomised, and controlled dose investigation trial.

Rivera L, Pedersen RS, Peña L, Olsen KJ, Andreasen LV, Kromann I, Nielsen PI et al.

Lancet Infect Dis. 2017 Jul [Epub 2017 Apr 25]

PMID: 28454674

ABSTRACT

BACKGROUND: Cost and supply constraints are key challenges in the use of inactivated polio vaccine (IPV). Dose reduction through adsorption to aluminium hydroxide (Al) is a promising option, and establishing its effectiveness in the target population is a crucial milestone in developing IPV-Al. The aim of this clinical trial was to show the non-inferiority of three IPV-Al vaccines to standard IPV. **METHODS:** In this phase 2, non-inferiority, observer-blinded, randomised, controlled, single-centre trial in the Dominican Republic, healthy infants aged 6 weeks, not previously polio vaccinated, were allocated after computer-generated randomisation by block-size of four, to receive one of four IPV formulations (three-times reduced dose [1/3 IPV-A]], five-times reduced dose [1/5 IPV-A]], ten-times reduced dose [1/10 IPV-Al], or IPV) intramuscularly in the thigh at 6, 10, and 14 weeks of age. The primary outcome was seroconversion for poliovirus types 1, 2, and 3 with titres more than or equal to four-fold higher than the estimated maternal antibody titre and more than or equal to 8 after three vaccinations. Noninferiority was concluded if the lower two-sided 90% CI of the seroconversion rate difference between IPV-Al and IPV was greater than -10%. The safety analyses were based on the safety analysis set (randomly assigned participants who received at least one trial vaccination) and the immunogenicity analyses were based on the per-protocol population. This study is registered with Clinical Trials.gov registration, number NCT02347423.

FINDINGS: Between Feb 2, 2015, and Sept 26, 2015, we recruited 824 infants. The per-protocol population included 820 infants; 205 were randomly assigned to receive 1/3 IPV-Al, 205 to receive 1/5 IPV-Al, 204 to receive 1/10 IPV-Al, and 206 to receive IPV. The proportion of individuals meeting the primary endpoint of seroconversion for poliovirus types 1, 2, and 3 was already high for the three IPV-Al vaccines after two vaccinations, but was higher after three vaccinations (ie, after completion of the expanded programme of immunisation schedule): 1/3 IPV-Al 98·5% (n=202, type 1), 97·6% (n=200; type 2), and 99·5% (n=204, type 3); 1/5 IPV-Al: 99·5% (n=204, type 1), 96·1% (n=197, type 2), and 98·5% (n=202, type 3); and 1/10 IPV-Al: 98·5% (n=201, type 1), 94·6% (n=193, type 2), and 99·5% (n=203, type 3). All three IPV-Al were non-inferior to IPV, with absolute differences in percentage seroconversion for each poliovirus type being greater than -10% (1/3 IPV-Al type 1, -1·46 [-3·60 to 0·10], type 2, -0·98 [-3·62 to 1·49], and type 3, -0·49 [-2·16 to 0·86]; 1/5 IPV-Al type 1, -0·49 [-2·16 to 0·86], type 2, -2·45 [-5·47 to 0·27], and type 3, -0·49 [-2·17 to 0·86]). Three serious adverse events occurred that were unrelated to the vaccine.

INTERPRETATION: The lowest dose (1/10 IPV-Al) of the vaccine performed well both after two and three doses. Based on these results, this new vaccine is under investigation in phase 3 trials.

WEB: https://dx.doi.org/10.1016/S1473-3099(17)30177-9

IMPACT FACTOR: 19.86

CITED HALF-LIFE: 4.4

START Scientific Comment: This study demonstrates reduced doses of IPV can be injected intradermally without adjuvants or intramuscularly with aluminum hydroxide adjuvant, with similar immunogenicity results under the recommended EPI schedule. Complete safety evaluation of IPV-Al and 6-month follow-up titre measurement to obtain information on long-term protection rates are currently underway in phase 3 clinical trials.



3. <u>Reduced schedules of 4CMenB vaccine in infants and catch-up series in children:</u> <u>Immunogenicity and safety results from a randomised open-label phase 3b trial.</u>

Martinón-Torres F, Safadi MAP, Martinez AC, Marquez PI, Torres JCT, Weckx LY et al.

Vaccine. 2017 Jun [Epub 2017 May 19]

PMID: 28533054

ABSTRACT

BACKGROUND: This study evaluated the immunogenicity and safety of a licensed meningococcal serogroup B vaccine (4CMenB) administered alone according to reduced schedules in infants or catch-up series in children.

METHODS: In this open-label, multicentre, phase 3b study (NCT01339923), infants randomised 1:1:1 received 4CMenB: 2+1 doses at $3\frac{1}{2}$ -5-11 months or 6-8-11 months of age, 3+1 doses at ages $2\frac{1}{2}$ - $3\frac{1}{2}$ -5-11 months. Children aged 2-10 years received 2 catch-up doses administered 2 months apart. Immune responses were measured by hSBA assays against 4 strains specific for vaccine components fHbp, NadA, PorA and NHBA. Sufficiency of immune responses was defined in groups with 2+1 doses schedules as a lower limit \geq 70% for the 97.5% confidence interval of the percentage of infants with hSBA titres \geq 4, 1month post-dose 2 for fHbp, NadA, PorA. Adverse events were collected for 7days post-vaccination; serious adverse events (SAEs) throughout the study.

RESULTS: 754 infants and 404 children were enrolled. Post-primary vaccination, 98-100% of infants across all groups developed hSBA titres \geq 4 for fHbp, NadA, PorA, and 48-77% for NHBA. Sufficiency of immune responses in infants receiving 2+1 schedules was demonstrated for fHbp, NadA, PorA after 2 doses of 4CMenB, as pre-specified criteria were met. Following receipt of 2 catch-up doses, 95-99% of children developed hSBA titres \geq 4 for 4CMenB components. Similar safety profiles were observed across groups. A total of 45 SAEs were reported, 3 of which were related to vaccination.

CONCLUSION: Reduced infant schedules and catch-up series in children were immunogenic and safe, having the potential to widen 4CMenB vaccine coverage.

WEB: https://dx.doi.org/ 10.1016/j.vaccine.2017.05.023

IMPACT FACTOR: 3.24

CITED HALF-LIFE: 6.0

START Scientific Comment: The study was conducted between 2011 and 2014 in 26 centers across Brazil, Peru, Hungary, and Spain. Healthy infants and children were allocated into four groups according to age (Group 1: 2.5 mo, Group 2: 3.5 mo, Group 3: 6 mo, and Group 4: 2-10 yrs) at enrollment. Children were randomized 1:1 into a and b parallel sub-groups for groups 1-3. Groups 1a-3a received the reduced 2+1 dose schedule and Group 1b-3b received the 3+1 dose schedule. In Group 4 children were non-randomly subdivided into two age strata (Group 4a: 2–5 years; 4b: 6–10 yrs.) to observe the effect of 2 catch-up doses administered 2 months apart. Infants/children in the same group received the same vaccination schedule and results were pooled for analysis. No formal hypotheses are were tested in this study. Primary aim of the study was to demonstrate immunogenicity of the 4CMenB vaccine 3 reference strains specific for fHbp, NadA and PorA at 1 month after the 2-dose primary vaccination series in healthy infants from Groups 2 and 3. Secondary aims included assessing the immune responses induced by 3-dose 4CMenB primary vaccination schedule in Group 1, immune responses following a booster dose in infants, the immunogenicity of the 2-dose catch-up series in children aged 2–10 years in Group 4, immune response induced by the fHbp, NadA, PorA vaccine components across groups over time, and the safety and tolerability of the vaccine. Safety analyses reported are descriptive. Investigators found safety profiles were similar across all groups and authors note the highest reactogenicity and highest rate of AEs were observed following the administration of the first dose. Unsolicited AEs were reported in 75%–79% of infants across the Groups 1–3 of which 16%–25% may be attributed to treatment (see supp. table 2). In Group 4, fewer AEs were reported in children aged 6–10 years (34%) than in children aged 2-5 years (56%). Interpretation of safety results may be biased due to the open-label study design as it may have encouraged increased rate of adverse events reported.



4. Implementation of a human papillomavirus vaccination demonstration project in Malawi: successes and challenges.

Msyamboza KP, Mwagomba BM, Valle M, Chiumia H, Phiri T.

BMC Public Health. 2017 Jun 26

PMID: 28651574

ABSTRACT

BACKGROUND: Cervical cancer is a major public health problem in Malawi. The age-standardized incidence and mortality rates are estimated to be 75.9 and 49.8 per 100,000 population, respectively. The availability of the human papillomavirus (HPV) vaccine presents an opportunity to reduce the morbidity and mortality associated with cervical cancer. In 2013, the country introduced a school-class-based HPV vaccination pilot project in two districts. The aim of this study was to evaluate HPV vaccine coverage, lessons learnt and challenges identified during the first three years of implementation. **METHODS:** This was an evaluation of the HPV vaccination project targeting adolescent girls aged 9–13 years conducted in Malawi from 2013 to 2016. We analysed programme data, supportive supervision reports and minutes of National HPV Task Force meetings to determine HPV vaccine coverage, reasons for partial or no vaccination and challenges. Administrative coverage was validated using a community-based coverage survey.

RESULTS: A total of 26,766 in-school adolescent girls were fully vaccinated in the two pilot districts during the first three years of the programme. Of these; 2051 (7.7%) were under the age of 9 years, 884 (3.3%) were over the age of 13 years, and 23,831 (89.0%) were aged 9–13 years (the recommended age group). Of the 765 out-of-school adolescent girls aged 9–13 who were identified during the period, only 403 (52.7%) were fully vaccinated. In Zomba district, the coverage rates of fully vaccinated were 84.7%, 87.6% and 83.3% in year 1, year 2 and year 3 of the project, respectively. The overall coverage for the first three years was 82.7%, and the dropout rate was 7.7%. In Rumphi district, the rates of fully vaccinated coverage were 90.2% and 96.2% in year 1 and year 2, respectively, while the overall coverage for the first year was validated using a community-based cluster coverage survey. The majority of the coverage results were statistically similar, except for in Rumphi district, where community-based 3-dose coverage was higher than the corresponding administrative-coverage (94.2% vs 90.2%, *p* < 0.05), and overall (in both districts), facility-based 1-dose coverage was higher than the corresponding community-based (94.6% vs 92.6%, *p* < 0.05). Transferring out of the district, dropping out of school and refusal were some of the reasons for partial or no uptake of the vaccine.

CONCLUSION: In Malawi, the implementation of a school-class-based HPV vaccination strategy was feasible and produced high (>80%) coverage. However, this strategy may be associated with the vaccination of under- and over-aged adolescent girls who are outside of the vaccine manufacturer's stipulated age group (9–13 years). The health facility-based coverage for out-of-school adolescent girls produced low coverage, with only half of the target population being fully vaccinated. These findings highlight the need to assess the immunogenicity associated with the administration of a two-dose schedule to adolescent girls younger or older than 9–13 years and effectiveness of health facility-based strategy before rolling out the programme.

WEB: https://dx.doi.org/ 10.1186/s12889-017-4526-y

IMPACT FACTOR: 2.27

CITED HALF-LIFE: 4.6

START Scientific Comment: Authors found that despite targeting girls in standard/grade 4 level school-class-based strategy, the approach resulted in vaccination of girls outside the vaccine manufacturers' stipulated age group of 9–13 years. Investigators found that among schools located in urban regions 21% of girls in standard 4 were <9 years, while girls aged \geq 14 years in standard 4 were more likely to be observed in schools located in rural areas. The safety and relative immunogenicity of 2-dose schedule in girls \leq 8 yrs or \geq 14 compared to 9-13 age groups are not well established though authors report no serious adverse events were reported in this age group.



5. <u>Impact of isoniazid preventive therapy on the evaluation of long-term effectiveness of infant MVA85A vaccination</u>.

Bunyasi EW, Luabeya AKK, Tameris M, Geldenhuys H, Mulenga H, Landry BS et al.

Int J Tuberc Lung Dis. 2017 Jul 1

PMID: 28633702

ABSTRACT

SETTING: South Africa.

OBJECTIVE: To evaluate the long-term effectiveness of infant modified vaccinia Ankara virus-expressing antigen 85A (MVA85A) vaccination against tuberculosis (TB).

DESIGN: We analysed data from a double-blind randomised placebo-controlled Phase 2b MVA85A infant TB vaccine trial (2009-2012), with extended post-trial follow-up (2012-2014). Isoniazid preventive therapy (IPT) was provided by public health services according to national guidelines. The primary outcome was curative treatment for TB disease. Survival analysis and Poisson regression were used for study analysis.

RESULTS: Total follow-up was 10 351 person-years of observation (pyo). Median follow-up age was 4.8 years (interquartile range 4.4-5.2). There were 328 (12%) TB cases. TB disease incidence was 3.2/100 pyo (95%CI 2.8-3.5) overall, and respectively 3.3 (95%CI 2.9-3.9) and 3.0 (95%CI 2.6-3.5)/100 pyo in the MVA85A vaccine and placebo arms. A total of 304 children (11%) received IPT, with respectively 880 and 9471 pyo among IPT and non-IPT recipients. There were 23 (7.6%) TB cases among 304 IPT recipients vs. 305 (12.9%) among 2374 non-IPT recipients (P = 0.008). IPT effectiveness was 85% (95%CI 76-91).

CONCLUSION: Extended follow-up confirms no long-term effectiveness of infant MVA85A vaccination, but a six-fold reduction in TB risk can be attributed to IPT. National TB programmes in high TB burden countries should ensure optimal implementation of IPT for eligible children.

WEB: https://dx.doi.org/ 10.5588/ijtld.16.0709

IMPACT FACTOR: 2.47

CITED HALF-LIFE: 7.1

START Scientific Comment: To address primary and secondary objectives authors utilized two independent categories of exposure stratified by the presence of latent TB infection (LTBI). The first exposure category was defined as, 'vaccination' (vaccine/placebo) and the second 'IPT' (documented to have started/initiated vs. not started). Authors define date of LTBI as was the earliest date of a positive test. Children who were TST/QFT-negative without subsequent conversion were classified as non-LTBI. Authors performed a survival analysis to explore vaccine and IPT effectiveness. The initiating event for children documented to have started IPT was the date of IPT initiation, the date of LTBI in children who did not receive IPT, and the first negative TST/QFT result in children without LTBI. Survival time culminated on the date of the first diagnosis of TB disease, administrative censorship, death or migration. The study population had a high incidence of TB disease with a third of the overall disease burden observed among children with LTBI. Investigators found IPT administration to children with LTBI reduces the risk of TB disease from 16-fold to 2.5-fold greater than children without LTBI. 1 TB case was prevented for every 4 children with LTBI receiving IPT. The lack of an observed effect for MVA85A boost vaccination may be associated with the method of TB surveillance and case detection during the post-trial period. Without access to standardized clinical, radiographic and microbiological data investigators define cases according to whether or not an individual received anti-TB treatment from an attending clinician. TB incidence during the post trial period in the post-trial period may therefore have been underestimated due to the use of passive surveillance methods compared with active surveillance for in-trial incidence of TB.



6. Impact and cost-effectiveness of rotavirus vaccination in Bangladesh.

Pecenka C, Parashar U, Tate JE, Khan JAM, Groman D, Chacko S et al.

Vaccine. 2017 Jul 13 [Epub 2017 Jun 13] PMID: 28623028

ABSTRACT

INTRODUCTION: Diarrheal disease is a leading cause of child mortality globally, and rotavirus is responsible for more than a third of those deaths. Despite substantial decreases, the number of rotavirus deaths in children under five was 215,000 per year in 2013. Of these deaths, approximately 41% occurred in Asia and 3% of those in Bangladesh.

BACKGROUND: While Bangladesh has yet to introduce rotavirus vaccination, the country applied for Gavi support and plans to introduce it in 2018. This analysis evaluates the impact and cost-effectiveness of rotavirus vaccination in Bangladesh and provides estimates of the costs of the vaccination program to help inform decision-makers and international partners.

METHODS: This analysis used Pan American Health Organization's TRIVAC model (version 2.0) to examine nationwide introduction of two-dose rotavirus vaccination in 2017, compared to no vaccination. Three mortality scenarios (low, high, and midpoint) were assessed. Benefits and costs were examined from the societal perspective over ten successive birth cohorts with a 3% discount rate. Model inputs were locally acquired and complemented by internationally validated estimates.

RESULTS: Over ten years, rotavirus vaccination would prevent 4000 deaths, nearly 500,000 hospitalizations and 3 million outpatient visits in the base scenario. With a Gavi subsidy, cost/disability adjusted life year (DALY) ratios ranged from \$58/DALY to \$142/DALY averted. Without a Gavi subsidy and a vaccine price of \$2.19 per dose, cost/DALY ratios ranged from \$615/DALY to \$1514/DALY averted.

CONCLUSION: The discounted cost per DALY averted was less than the GDP per capita for nearly all scenarios considered, indicating that a routine rotavirus vaccination program is highly likely to be cost-effective. Even in a low mortality setting with no Gavi subsidy, rotavirus vaccination would be cost-effective. These estimates exclude the herd immunity benefits of vaccination, so represent a conservative estimate of the cost-effectiveness of rotavirus vaccination in Bangladesh.

WEB: https://dx.doi.org/ 10.1016/j.vaccine.2017.05.087

IMPACT FACTOR: 3.24

CITED HALF-LIFE: 6.0

START Scientific Comment: Live births and life expectancy at birth were drawn from United Nations Populations Division. Investigators also used the United Nations Inter-agency Group for Child Mortality Estimation data for infant and child mortality data in Bangladesh during the 2005-2015 period to project infant and child mortality rates through 2026. Incidence and severity of rotavirus were drawn from meta-analysis and are consistent with findings from RotaTeq vaccine clinical trials in Bangladesh and in Vietnam. To address the wide range of rotavirus deaths in Bangladesh reported in the literature the authors choose to model the estimated lower bound, midpoint and upper bound (1000, 1850, & 2700 deaths/year). Authors used national vaccine coverage rates reported in DTP1, DPT2, and DTP3 campaigns to estimate potential rotavirus vaccine coverage and vaccine efficacy estimates are drawn from unpublished analysis of the Rotarix trial in Bangladesh. Authors used estimated 1-year vaccine efficacy for severe and non-severe disease ranges, at 48% and 45.2%, respectively, and findings from unpublished Rotraix trial which suggest a 36% reduction for each subsequent year. Vaccine prices were estimated from Gavi Alliance projection of co-financing shares overtime in Bangladesh. With the Gavi subsidy the price per dose is \$0.16 in 2017 and increases by 15% per year to \$0.55 in 2026. Authors include and additional 3% for handling, 2% for delivery, and 5% lost due to vaccine wastage. Table 2 illustrates government and household costs per visit for severe and non-severe rotavirus cases are greater in inpatient settings and household costs are estimated to be nearly 5x greater the cost per visit incurred by the government.



7. WHO position on the use of fractional doses - June 2017, addendum to vaccines and vaccination against yellow fever WHO: Position paper - June 2013.

World Health Organization Vaccine. 2017 Jul 6. [Epub ahead of print] PMID: 28689653

ABSTRACT

This article presents the World Health Organization's (WHO) recommendations on the use of fractional doses of yellow fever vaccines excerpted from the "Yellow fever vaccine: WHO position on the use of fractional doses - June 2017, Addendum to Vaccines and vaccination against yellow fever WHO: Position Paper - June 2013", published in the Weekly Epidemiological Record [1,2]. This addendum to the 2013 position paper pertains specifically to use of fractional dose YF (fYF) vaccination (fractional dose yellow fever vaccination refers to administration of a reduced volume of vaccine dose, which has been reconstituted as usual per manufacturer recommendations) in the context of YF vaccine supply shortages beyond the capacity of the global stockpile. The current WHO position on the use of yellow fever (YF) vaccine is set out in the 2013 WHO position paper on vaccines and vaccination against YF and those recommendations are unchanged. Footnotes to this paper provide a number of core references including references to grading tables that assess the quality of the scientific evidence, and to the evidence-to-recommendation table. In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with WHO's current position on the use of vaccines in the global context. Recommendations on the use of Yellow Fever vaccines were discussed by SAGE in October 2016; evidence presented at these meetings can be accessed at:

www.who.int/immunization/sage/meetings/2016/October/presentations_background_docs/en/.

WEB: https://dx.doi.org/ 10.1016/j.vaccine.2017.06.087

IMPACT FACTOR: 3.24 CITED HALF-LIFE: 6.0

START Scientific Comment: In 2016, a sharp increase in the demand for YF vaccine following a series of large YF outbreaks in central Africa threated to drain the global stockpile and curtail immunization programs in high-risk areas. As a result, fractional dosing of YF vaccination was implemented to stretch the available vaccine products to ensure populations at risk were vaccinated and reduce the risk of an urban breakout or international transmission. The potency of standard YF doses exceeds the WHO minimum recommend potency of YF. Fractional YF (fYF) doses may confer similar safety, immunogenicity and effectiveness to that of the standard dosage, making fYF an attractive dose-sparing strategy. Based on available clinical data WHO recommends a minimum doses should contain 3000 IU/dose and no less than 1000 IU/dose. Countries may determine the most suitable volume to be used as a fractional dose for their needs, however practical difficulties in delivering doses <0.1mL precludes the use of smaller volumes. Vaccines should be reconstituted according to manufacture specifications and never diluted. fYF doses should be delivered subcutaneously or intramuscularly using auto-disable syringes. Reconstituted vaccines are heat sensitive and must be kept at a constant temperature between 2-8 °C and discarded after 6 hours. To prevent contamination due to repeated vial septum perforation, vials containing >10 standard 0.5 mL doses should not be used for fYF. Children <2 yrs, pregnant women, and HIV-infected individuals should continue to receive the standard YF dose.



8. <u>Efforts to monitor Global progress on individual and community demand for</u> <u>immunization: Development of definitions and indicators for the Global Vaccine Action</u> <u>Plan Strategic Objective 2</u>.

Hickler B, MacDonald NE, Senouci K, Schuh HB

Vaccine. 2017 Jun 16 [Epub 2017 May] PMID: 28536028

ABSTRACT

The Second Strategic Objective of the Global Vaccine Action Plan, "individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility", differs from the other five in that it does not focus on supply-side aspects of immunization programs but rather on public demand for vaccines and immunization services. This commentary summarizes the work (literature review, consultations with experts, and with potential users) and findings of the UNICEF/World Health Organization Strategic Objective 2 informal Working Group on Vaccine Demand, which developed a definition for demand and indicators related to Strategic Objective 2. Demand for vaccines and vaccination is a complex concept that is not external to supply systems but rather encompasses the interaction between human behaviors and system structure and dynamics.

WEB: https://dx.doi.org/ 10.1016/j.vaccine.2017.04.056

IMPACT FACTOR: 3.24 CITED HALF-LIFE: 6.0

START Scientific Comment: The informal Working Group on Vaccine Demand (iWGVD) members attempted to define the scope of the term "demand" in immunization literature and found "demand" was typically used in reference to three major categories: classic economic interpretations of supply and demand, immunization system structure and operations, and the attitude and behavior of individuals and groups of actors who comprise these systems. The authors assert that distinguishing between system/service dynamics and demand did not capture the complex interaction between human behaviors and system dynamics (figures 1 and 2). iWGVD sought to shift the definition of demand in the context of SO2 from passive terminology e.g. *acceptance* to more active terminology e.g. *quality of services* and *acceptability*. Defining vaccination demand in terms of a set of behaviors rather than an attitude became the first step towards bridging the intention-activation gap. iWGVD members defined demand as

"...the actions of individuals and communities to seek, support, and/or advocate for vaccines and immunization services. Demand is dynamic and varies by context, vaccine, immunization services provided, time, and place. Demand is fostered by governments, immunization program managers, public and private sector providers, local leadership, and civil society organizations hearing and acting on the voices of individuals and communities."

In addition to outcome measures such as coverage, dropout rate, and timeliness, iWGVD included a combination of process measures related to national immunization program investments in activities to stimulate and sustain demand to help define indicators illustrating alignment with GVAP SO2 aims. The four indicators are designed to assist programs in evaluating the extent to which investments fostered and sustained demand along with indirect measures of program success in raising coverage, reducing dropouts and improving timeliness of completion of the childhood vaccine schedule.



9. The importance of vaccine supply chains to everyone in the vaccine world.

Lee BY, Haidari LA. Vaccine. 2017 Jun 16. [Epub ahead of print]

PMID: 28629921

ABSTRACT

While the focus of many in the vaccine world has been on developing new vaccines and measuring their effects on humans, failure to understand and properly address vaccine supply chain issues can greatly reduce the impact of any vaccine. Therefore, everyone involved in vaccine decision-making may want to take into account supply chains when making key decisions. In fact, considering supply chain issues long before a vaccine reaches the market can help design vaccines and vaccine programs that better match the system. We detail how vaccine supply chains may affect the work and decision making of ten examples of different members of the vaccine community: preclinical vaccinologists, vaccine clinical trialists, vaccine package designers, health care workers, epidemiologists and disease surveillance experts, policy makers, storage equipment manufacturers, other technology developers, information system specialists, and funders. We offer ten recommendations to help decision makers better understand and address supply chains.

WEB: https://dx.doi.org/10.1016/j.vaccine.2017.05.096

IMPACT FACTOR: 3.24 CITED HALF-LIFE: 6.0

START Scientific Comment: Biological characteristics of a vaccine may impact the operation vaccine supply chains. Authors provide a series of examples illustrating the relative influence of vaccine stakeholders in their ability to exacerbate or assuage problems in the vaccine supply chain. Preclinical vaccinologist may consider the impact of multiple dosages that would increase the overall volume of vaccine doses overwhelming supply chain and resulting in bottlenecks. The development of thermostable vaccines may serve to relive such bottlenecks by avoiding constraints of the cold chain delivery. Vaccine clinical trialists should consider the system-wide effects that various target populations may have and the potential need for supply chain strengthening. For example blockages from the additional volume of seasonal vaccines targeting special populations (e.g. flu vaccines among the elderly) may disrupt the flow of other vaccines in the region. In models evaluating the impact of Merck and GlaxoSmithKline redesign of vaccine packages illustrated introducing rotavirus vaccine in various packaging sizes, showing dramatic, system-wide reductions in stockouts when hanging the size of a single vaccine.

Table 1 illustrates the 10 recommendations and corresponding examples of possible actions to help decision makers better understand and address vaccine supply chains. Authors posit communicating vaccine supply chain needs to a broader community may be facilitated with the development of Target Product Profiles (TPPs), a menu of desirable characteristics, features and attributes of products to tailor product development according to common constraints of the vaccine supply chain.



10. <u>Evaluation of vaccination strategies for SIR epidemics on random networks incorporating household structure</u>.

Ball F, Sirl D. J Math Biol. 2017 Jun 20.[Epub ahead of print] PMID: 28634747

ABSTRACT

This paper is concerned with the analysis of vaccination strategies in a stochastic susceptible \rightarrow infected \rightarrow removed model for the spread of an epidemic amongst a population of individuals with a random network of social contacts that is also partitioned into households. Under various vaccine action models, we consider both household-based vaccination schemes, in which the way in which individuals are chosen for vaccination depends on the size of the households in which they reside, and acquaintance vaccination, which targets individuals of high degree in the social network. For both types of vaccination scheme, assuming a large population with few initial infectives, we derive a threshold parameter which determines whether or not a large outbreak can occur and also the probability of a large outbreak and the fraction of the population infected by a large outbreak. The performance of these schemes is studied numerically, focusing on the influence of the household size distribution and the degree distribution of the social network. We find that acquaintance vaccination can significantly outperform the best household-based scheme if the degree distribution of the social network is heavy-tailed. For householdbased schemes, when the vaccine coverage is insufficient to prevent a major outbreak and the vaccine is imperfect, we find situations in which both the probability and size of a major outbreak under the scheme which minimises the threshold parameter are larger than in the scheme which maximises the threshold parameter.

WEB: https://dx.doi.org/ 10.1007/s00285-017-1139-0

IMPACT FACTOR: 1.57 **CITED HALF-LIFE:** >10.0

START Scientific Comment: Vaccine allocation methods described by authors include (i) uniformly chosen individuals (Ind UAR), (ii) uniformly chosen households (HH UAR), (iii & iv) 'best' and 'worst' household-based allocation (HH Best and HH Worst), (v & vi) 'best' and 'worst' acquaintance vaccination (Acq Best and Acq Worst). Figures 1-3 Plot the post-vaccination threshold parameter (Rv) final proportion of the total population infected (z) as a function of the vaccine coverage for six different vaccine allocation schemes under varving degrees of vaccine effectiveness. Figure 1 models differences in vaccine allocation methods in the presence of a perfect vaccine. Figure 2 models differences in allocation methods given an all-or-nothing vaccine action model with 70% vaccine efficacy. Figure 3 models differences in allocation methods given a non-random vaccine action model with a relative susceptibility of 0.5 and infectivity of 0.6. Authors vary combinations of household size and network degree distribution while keeping all other parameters fixed. When the network degree distribution demonstrates low variability (e.g. the Poisson case) good household schemes appear to perform as well as acquaintance vaccination, however acquaintance vaccination outperforms the household based schemes when network degree distribution increases in variability (e.g. the cutoff power law). The authors note that when the epidemic exceeds the threshold, optimizing vaccine allocation based on the post-vaccination threshold parameter (R_v) may not result in the lowest possible final proportion of the total population infected (z). Authors found that when vaccine coverage is too low to prevent a large outbreak comparing optimal household allocation strategies may depend on whether the post vaccination R_v is used or z. Overall, authors find that while acquaintance vaccination may offer more benefits to household vaccination allocation, ethical considerations ultimately make the practice of this allocation strategy untenable in human populations. Future work may explore similar allocation regime targeting highly connected individuals.



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]) ("2017/6/15"[PDAT] : "2017/7/14"[PDAT]))

* August 2, 2017, this search of English language articles published between June 15, 2017 and July 14, 2017 and indexed by the US National Library of Medicine resulted in 219 unique manuscripts.

