VACCINE DELIVERY RESEARCH DIGEST

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

REPORT TO THE BILL & MELINDA GATES FOUNDATION

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OCTOBER 2020

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Details of Articles

1. Fractional dose of intradermal compared to intramuscular and subcutaneous vaccination, a systematic review and meta-analysis

Schnyder JL, De Pijper CA, Garcia Garrido HM, et al.

Travel Med Infect Dis. 2020 Sep 6;37:101868.

PubMed ID: 32898704

ABSTRACT

BACKGROUND: Vaccine supply shortages are of global concern. We hypothesise that intradermal (ID) immunisation as an alternative to standard routes might augment vaccine supply utilisation without loss of vaccine immunogenicity and efficacy.

METHODS: We conducted a systematic review and meta-analysis searching Medline, Embase and Web of Science databases. Studies were included if: licensed, currently available vaccines were used; fractional dose of ID was compared to IM or SC immunisation; primary immunisation schedules were evaluated; immunogenicity, safety data and/or cost were reported. We calculated risk differences (RD). Studies were included in meta-analysis if: a pre-defined immune correlate of protection was assessed; WHO-recommend schedules and antigen doses were used in the control group; the same schedule was applied to both ID and control groups (PROSPERO registration no. CRD42020151725).

RESULTS: The primary search yielded 5,873 articles, of which 156 articles were included; covering 12 vaccines. Non-inferiority of immunogenicity with 20-60% of antigen used with ID vaccines was demonstrated for influenza (H1N1: RD -0·01; 95% CI -0·02, 0·01; I2 = 55%, H2N3: RD 0·00; 95% CI -0·01, 0·01; I2 = 0%, B: RD -0·00; 95% CI -0·02, 0·01; I2 = 72%), rabies (RD 0·00; 95% CI -0·02, 0·02; I2 = 0%), and hepatitis B vaccines (RD -0·01; 95% CI -0·04, 0·02; I2 = 20%). Clinical trials on the remaining vaccines yielded promising results, but are scarce.

CONCLUSIONS: There is potential for inoculum/antigen dose-reduction by using ID immunisation as compared to standard routes of administration for some vaccines (e.g. influenza, rabies). When suitable, vaccine trials should include an ID arm.

WEB: 10.1016/j.tmaid.2020.101868

IMPACT FACTOR: 4.589

CITED HALF-LIFE: 4.0

START COMMENTARY

In this systematic review and meta-analysis, Schnyder *et al.* compile and compare all studies on fractionated intradermal (ID) doses as an alternative to standard intramuscular (IM) and subcutaneous (SC) immunization. Authors highlight that dose-sparing intradermal immunization could potentially increase vaccine supplies and reduce costs globally, which may be particularly timely and relevant for ongoing and future vaccine development and delivery (e.g. the SARS-CoV-2 vaccine, which would have to be scaled up rapidly to 60-70% of the world's population). Schnyder *et al.* focused on assessing if the literature review supports the concept that ID immunization can induce antibody responses equivalent to IM and SC immunization, if differences in dose of ID vaccines affect the antibody response, whether ID can be a safe alternative to IM and SC, and if ID is cost-saving compared to IM and SC. Most of the included studies (N=156) focused on influenza (n=51), hepatitis B (HBV) (n=43) and rabies (n=37) vaccines. Non-inferiority of immunogenicity with reduced doses was demonstrated for influenza, rabies, and HBV. However, for other vaccine such as inactivated polio vaccine (IPV) and measles, the evidence on non-inferiority of immunogenicity was mixed. For other vaccines, studies were scarce limiting the ability to make conclusions. Schnyder *et al* presented safety outcomes of ID immunization and costs of HBV and rabies vaccines. One key limitation which may affect the conclusions include that studies were published over a long period (from 1949 to 2019) in which ID delivery devices have evolved dramatically. A key strength of this study include the strict adherence to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, which was shown in the transparent and detailed supplementary materials, which include the search appendix (*Supplementary Table 1*); the Cochrane Risk-of-Bias Tool results (*Supplementary Table 2*); Data extraction of included studies (*Supplementary Table 3*); and a critical appraisal of the included studies (*Supplementary Table 4 and 5*).

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2. Population impact and effectiveness of sequential 13-valent pneumococcal conjugate and monovalent rotavirus vaccine introduction on infant mortality: prospective birth cohort studies from Malawi

King C, Bar-Zeev N, Phiri T et al.

BMJ Glob Health. 2020 Sep;5(9):e002669.

PubMed ID: 32912855

ABSTRACT

BACKGROUND: Pneumococcal conjugate vaccine (PCV) and rotavirus vaccine (RV) are key tools for reducing common causes of infant mortality. However, measurement of population-level mortality impact is lacking from sub-Saharan Africa. We evaluated mortality impact and vaccine effectiveness (VE) of PCV13 introduced in November 2011, with subsequent RV1 roll-out in October 2012, in Malawi.

METHODS: We conducted two independent community-based birth cohort studies. Study 1, in northern Malawi (40000population), evaluated population impact using change-point analysis and negative-binomial regression of non-traumatic 14-51-week infant mortality pre-introduction (1 January 2004 to 31 September 2011) and post-introduction (1 October 2011 to 1 July 2019), and against three-dose coverage. Study 2, in central Malawi (465 000 population), was recruited from 24 November 2011 to 1 June 2015. In the absence of pre-introduction data, individual three-dose versus zero-dose VE was estimated using individual-level Cox survival models. In both cohorts, infants were followed with household visits to ascertain vaccination, socioeconomic and survival status. Verbal autopsies were conducted for deaths.

RESULTS: Study 1 included 20 291 live births and 216 infant deaths. Mortality decreased by 28.6% (95% CI: 15.3 to 39.8) post-PCV13 introduction. A change-point was identified in November 2012. Study 2 registered 50 731 live births, with 454 deaths. Infant mortality decreased from 17 to 10/1000 live births during the study period. Adjusted VE was 44.6% overall (95% CI: 23.0 to 59.1) and 48.3% (95% CI: -5.9 to 74.1) against combined acute respiratory infection, meningitis and sepsis-associated mortality.

CONCLUSION: These data provide population-level evidence of infant mortality reduction following sequential PCV13 and RV1 introduction into an established immunisation programme in Malawi. These data support increasing coverage of vaccine programmes in high-burden settings.

WEB: 10.1136/bmjgh-2020-002669
IMPACT FACTOR: 4.280
CITED HALF-LIFE: 5.1

START COMMENTARY

In this prospective birth cohort, King *et al.* present the effectiveness and impact on population-level infant mortality of sequential 13-valent pneumococcal conjugate (PCV13) and monovalent rotavirus vaccine (RV1) introduction. King *et al.* report significant declines in vaccine age-eligible infant mortality two birth cohorts in Malawi, one in the northern region (Study 1) and other in the central region (Study 2), which support continued investment and scale-up of vaccines to prevent pneumonia and diarrhea in high infant mortality settings.

One key strength of this article is the inclusion of a change-point model with the full time series for Study 1, which helps to disentangle infant mortality reductions attributed to PCV13 and RV1 introduction from general declining trends. This study design, location, and population may imply greater generalizability to other settings in sub-Saharan Africa.

A limitation of note is that there may be some selection bias and misclassification relating to vaccination status and follow up. For example, health passports (which include immunization information) observation was not consistent across deceased and surviving infants in both studies. For Study 1, 67% of deceased and 92% of surviving infants' passports were observed, compared to 26% and 90%, respectively, in Study 2 which could introduce lower documented vaccine status among the deceased as these reports rely on the caregiver's recall. However, authors addressed this potential bias by observing and finding comparable vaccination rates in deceased infants with and without a health passport (*online supplementary Table 1.2)*.

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3. Effectiveness of the 10-valent pneumococcal conjugate vaccine against radiographic pneumonia among children in rural Bangladesh: A case-control study

McCollum ED, Ahmed S, Roy AD, et al.

Vaccine. 2020 Sep 29;38(42):6508-6516.
PubMed ID: 32873404

ABSTRACT

BACKGROUND: Pneumococcal conjugate vaccine (PCV) effectiveness against radiographic pneumonia in South Asia is unknown. Bangladesh introduced PCV10 in 2015 using a three dose primary series (3 + 0). We sought to measure PCV10 effectiveness for two or more vaccine doses on radiographic pneumonia among vaccine-eligible children in rural Bangladesh.

METHODS: We conducted a matched case-control study over two years from 2015 to 2017 using clinic and community controls in three subdistricts of Sylhet, Bangladesh. Cases were vaccine eligible 3-35 month olds at Upazila Health Complex outpatient clinics with World Health Organization-defined radiographic primary endpoint pneumonia (radiographic pneumonia). Clinic controls were matched to cases within a one week time window by age, sex, and clinic and had an illness unlikely to be Streptococcus pneumoniae; community controls were healthy and similarly matched within a one week time window by age and sex, and distance from the clinic. We estimated adjusted vaccine effectiveness (aVE) using conditional logistic regression.

RESULTS: We matched 1262 cases with 2707 clinic and 2461 community controls. Overall, aVE using clinic controls was 21.4% (95% confidence interval, -0.2%, 38.4%) for ⩾2 PCV10 doses and among 3-11 month olds was 47.3% (10.5%, 69.0%) for three doses. aVE increased with higher numbers of doses in clinic control sets (p = 0.007). In contrast, aVE using community controls was 7.6% (95% confidence interval, -22.2%, 30.0%) for ⩾2 doses. We found vaccine introduction in the study area faster and less variable than expected with 75% coverage on average, which reduced power. Information bias may also have affected community controls.

CONCLUSIONS: Clinic control analyses show PCV10 prevented radiographic pneumonia in Bangladesh, especially among younger children receiving three doses. While both analyses were underpowered, community control enrollment - compared to clinic controls - was more difficult in a complex, pluralistic healthcare system. Future studies in comparable settings may consider alternative study designs.

WEB: 10.1016/j.vaccine.2020.08.035
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

This case-control study conducted by McCollum *et al.* is impactful as it presents the effectiveness of pneumococcal conjugate vaccine (PCV) in Bangladesh, which has a very high burden of pneumococcal pneumonia cases (i.e. 10% of the world's pneumococcal pneumonia mortality burden of under-five year old children). In adjusted models, there was statistically significant vaccine effectiveness when comparing age-eligible cases who received 3 doses of vaccine versus matched clinic controls, but not with community controls. Authors hypothesize that this could be a result of higher than anticipated vaccine coverage (which impacted study power) and information bias which may have misclassified children with prior radiographic pneumonia as community controls. This study contributes to the literature, as it is consistent with other case-control studies of PCV effectiveness in low- and middle-income countries (LMICs), and further supports PCV introduction in Bangladesh and Southeast Asia.

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4. Inferring antenatal care visit timing in low- and middle-income countries: Methods to inform potential maternal vaccine coverage

Baral R, Fleming J, Khan S, et al.

PLoS One. 2020 Aug 20;15(8):e0237718.

PubMed ID: 32817688

ABSTRACT

BACKGROUND: The timing of antenatal care (ANC) visits directly affect health intervention coverage and impact, especially for those interventions requiring strict gestational age windows for administration, such as maternal respiratory syncytial virus (RSV) vaccine. Existing nationally representative population-based surveys do not record the timing of ANC visits beyond the first, limiting the availability of reliable data around timing of subsequent ANC visits in most low- and middle-income countries (LMICs). Here, we describe a model that estimates the timing of ANC visits by gestational age using publicly available multi-country survey data.

METHODS AND FINDINGS: We used the Demographic and Health Surveys (DHS) data from 69 LMICs. We used several factors to estimate the timing of subsequent ANC visits by gestation age: the timing of the first ANC visit (ANC1) in a given pregnancy, derived from the DHS; the country's reported average ANC coverage at each ANC visit (ANC1 through the fourth ANC visit [ANC4]); and the World Health Organization's guidance on recommended ANC visit. We then used the timing of ANC visit by gestation age to predict the coverage of a potential maternal RSV vaccine administered at 24-36 weeks of gestation. We calculated the maternal immunization coverage by summing the number of eligible women vaccinated at any ANC visit divided by the total number of pregnant women. We find, in general, countries with higher ANC1 coverage were predicted to have higher vaccination coverage. In 82% of countries, the modeled vaccine coverage is less than ANC4 coverage.

CONCLUSIONS: The methods illustrated in this paper have implications on the precision of estimating impact and programmatic feasibility of time-critical interventions, especially for pregnant women. The methods can be easily adapted to vaccine demand forecasts models, vaccine impact assessments, and cost-effectiveness analyses and can be adapted to other maternal interventions that have administration timing restrictions.

WEB: 10.1371/journal.pone.0237718

IMPACT FACTOR: 2.740

CITED HALF-LIFE: 5.6

START COMMENTARY

Baral *et al.* use Demographic and Health Surveys (DHS) from 69 LMICs to demonstrate a method of estimating the timing of antenatal (ANC) visits by gestational age to predict coverage of a potential maternal respiratory syncytial virus (RSV) vaccine that would be administered between 24-36 weeks of gestation. This article fills a critical gap in the literature regarding antenatal timing in LMICs, which is critical information for vaccines that have restricted gestational windows for administration in order to be effective. Further, it is particularly timely given that RSV vaccines are currently in development allowing this study to contribute to other analyses assessing effectiveness and cost-effectiveness of maternal RSV vaccination. The authors found that the first ANC visit (ANC1) occurred later in pregnancy for women in the sub-Saharan region compared to other regions, with only 14% of ANC1 attendance occurring within the first three months of pregnancy. This finding is important given that interventions that rely on strict gestational windows depend on the timing of the first and subsequent ANC visits and the availability and acceptability of services during these visits. Baral *et al.* noted wide variation in the average timing of ANC visits by country, which is highlighted in *Supplementary 2 Appendix: ANC1 timing by gestation month across countries*. The authors predict RSV maternal immunization at 24-36 weeks of gestation by multiplying the number of unvaccinated women attending an ANC visit between 24 and 36 weeks of gestation by service availability and acceptance. Predicted vaccine coverage ranged from <20% in Afghanistan to >90% in Armenia. One limitation of note is that the surveys were not conducted in the same year across countries, but rather, relied on the most recent DHS data available. Though most of the included DHS datasets (n=56, >80%) were from after 2010, some estimates may be outdated and underestimated given recent improvements in ANC attendance and vaccine coverage globally. Despite this limitation, this article demonstrates a method for calculating ANC visit timing which is relevant for informing the planning and implementation of interventions that need to be administered during specific gestational windows.

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5. Assessment of missed opportunities for vaccination in Kenyan health facilities, 2016

Li AJ, Tabu C, Shendale S, et al.

PLoS One. 2020 Aug 20;15(8):e0237913.
PubMed ID: 32817630

ABSTRACT

BACKGROUND: In November 2016, the Kenya National Vaccines and Immunization Programme conducted an assessment of missed opportunities for vaccination (MOV) using the World Health Organization (WHO) MOV methodology. A MOV includes any contact with health services during which an eligible individual does not receive all the vaccine doses for which he or she is eligible.
METHODS: The MOV assessment in Kenya was conducted in 10 geographically diverse counties, comprising exit interviews with caregivers and knowledge, attitudes, and practices (KAP) surveys with health workers. On the survey dates, which covered a 4-day period in November 2016, all health workers and caregivers visiting the selected health facilities with children <24 months of age were eligible to participate. Health facilities (n = 4 per county) were purposively selected by size, location, ownership, and performance. We calculated the proportion of MOV among children eligible for vaccination and with documented vaccination histories (i.e., from a home-based record or health facility register), and stratified MOV by age and reason for visit. Timeliness of vaccine doses was also calculated.
RESULTS: We conducted 677 age-eligible children exit interviews and 376 health worker KAP surveys. Of the 558 children with documented vaccination histories, 33% were visiting the health facility for a vaccination visit and 67% were for other reasons. A MOV was seen in 75% (244/324) of children eligible for vaccination with documented vaccination histories, with 57% (186/324) receiving no vaccinations. This included 55% of children visiting for a vaccination visit and 93% visiting for non-vaccination visits. Timeliness for multi-dose vaccine series doses decreased with subsequent doses. Among health workers, 25% (74/291) were unable to correctly identify the national vaccination schedule for vaccines administered during the first year of life. Among health workers who reported administering vaccines as part of their daily work, 39% (55/142) reported that they did not always have the materials they needed for patients seeking immunization services, such as vaccines, syringes, and vaccination recording documents.
CONCLUSIONS: The MOV assessment in Kenya highlighted areas of improvement that could reduce MOV. The results suggest several interventions including standardizing health worker practices, implementing an orientation package for all health workers, and developing a stock management module to reduce stock-outs of vaccines and vaccination-related supplies. To improve

vaccination coverage and equity in all counties in Kenya, interventions to reduce MOV should be considered as part of an overall immunization service improvement plan.

WEB: 10.1371/journal.pone.0237913
IMPACT FACTOR: 2.740
CITED HALF-LIFE: 5.6

START COMMENTARY

Li *et al.* present a cross-sectional study assessing missed opportunities for vaccination (MOV) which are defined as any contact between an individual, who is eligible for vaccination, and health services, which does not result in receiving all of the vaccine doses that the individual is eligible for. This study was conducted as part of a MOV assessment to understand the reasons for under-vaccination and determine priority interventions. This study found that of 324 children <24 months that were eligible for at least one vaccine dose, only 25% were vaccinated with all of the eligible vaccine doses, indicating a very high MOV prevalence. Authors stratified by reason for visit and found that nearly all (93%) of children who visited the health facility for reasons besides vaccination, and over half (55%) of children]who visited the health facility for a vaccine-related issue remained incompletely vaccinated.

The study found that training on vaccination and vaccine-preventable disease was lacking, with only 41% of staff ever receiving such training. Among health workers that do administer vaccines as part of their work, many reported missing required materials for immunizations including the vaccines, syringes, and immunization booklets. These findings regarding high MOV, low health worker training and knowledge on vaccines and a lack of supplies are critical to address to help Kenya, and other countries, reach their immunization targets. An important strength of this study is the recruitment of all health workers, regardless of their involvement with routine immunization, which provides a comprehensive overview of all potential opportunities for vaccination. One limitation of this study is the purposive sampling of counties and facilities. The team considered logistics and ease of accessibility in choosing health clinics, which may limit the generalizability of findings to health clinics that are remote and difficult to reach.

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6. The potential role of pneumococcal conjugate vaccine in reducing acute respiratory inflammation in community-acquired pneumococcal pneumonia

Shen CF, Wang SM, Chi H, et al.

J Biomed Sci. 2020 Aug 19;27(1):88.

PubMed ID: 32814590

ABSTRACT

BACKGROUND: Pneumococcal conjugate vaccine (PCV) reduces both invasive pneumococcal disease (IPD) and other pneumococcal infections worldwide. We investigated the impact of stepwise implementation of childhood PCV programs on the prevalence of pneumococcal pneumonia, severity of acute inflammation, and associations between breakthrough pneumonia and pneumococcal serotypes in Taiwan.

METHODS: In total, 983 children diagnosed with community-acquired pneumococcal pneumonia were enrolled between January 2010 and December 2015.

RESULTS: Proportions of pneumococcal vaccinations increased each year in age-stratified groups with PCV7 (32.2%) as the majority, followed by PCV13 (12.2%). The proportion of pneumococcal pneumonia decreased each year in age-stratified groups, especially in 2-5 year group. Serotype 19A is the leading serotype either in vaccinated (6.4%) or unvaccinated patients (5.2%). In particular, vaccinated patients had significantly higher lowest WBC, lower neutrophils, lower lymphocytes and lower CRP values than non-vaccinated patients ($p < 0.05$). After stratifying patients by breakthrough infection, those with breakthrough pneumococcal infection with vaccine coverage serotypes had more severe pneumonia disease ($p < 0.05$).

CONCLUSION: Systematic childhood pneumococcal vaccination reduced the prevalence of community-acquired pneumococcal pneumonia, especially in 2-5 year group. Serotype 19A was the major serotype for all vaccine types in patients with pneumococcal pneumonia and severity of acute inflammatory response was reduced in vaccinated patients.

WEB: 10.1186/s12929-020-00680-9

IMPACT FACTOR: 5.762

CITED HALF-LIFE: 5.7

START COMMENTARY

In this prospective cohort study, Ching-Fen *et al.* report on the stepwise implementation of pneumococcal conjugate vaccine (PCV) with a focus on the reduction in the prevalence, severity of

acute inflammation, and serotypes associated with breakthrough pneumococcal pneumonia in Taiwan. The authors found that the implementation of the PCV immunization reduced the prevalence of pneumococcal pneumonia in the community, and that the severity of inflammation was reduced in vaccinated patients, compared to unvaccinated patients. This article is impactful as it is the first to report attenuated inflammation in breakthrough pneumococcal pneumonia infection, which supports the implementation of PCV immunization despite the risks of vaccine failure. One key of this study include the data source, which was a nationwide Taiwanese surveillance of childhood community-acquired pneumonia from January 2010 to January 2016 that included both definitive and probable cases. One limitation of this study was that serotype was only determined in some (n=81) of the total definitive cases (n=133) and not for any of the probable cases (n=850) which may limit the ability to conclude which serotypes are responsible for disease.

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7. A systematic review of studies that measure parental vaccine attitudes and beliefs in childhood vaccination

Dyda A, King C, Dey A, et al.

BMC Public Health. 2020 Aug 17;20(1):1253.

PubMed ID: 32807124

ABSTRACT

BACKGROUND: Acceptance of vaccines is an important predictor of vaccine uptake. This has public health implications as those who are not vaccinated are at a higher risk of infection from vaccine preventable diseases. We aimed to examine how parental attitudes and beliefs towards childhood vaccination were measured in questionnaires through a systematic review of the literature.

METHODS: We systematically reviewed the literature to identify primary research studies using tools to measure vaccine attitudes and beliefs, published between January 2012 and May 2018. Studies were included if they involved a quantitative survey of the attitudes and beliefs of parents about vaccinations recommended for children. We undertook a synthesis of the results with a focus on evaluating the tools used to measure hesitancy.

RESULTS: A total of 116 studies met the inclusion criteria, 99 used a cross sectional study design, 5 used a case control study design, 4 used a pre-post study design and 8 used mixed methods study designs. Sample sizes of included studies ranged from 49 to 12,259. The most commonly used tool was the Parent Attitudes about Childhood Vaccines (PACV) Survey (n = 7). The most common theoretical framework used was the Health Belief Model (n = 25). Questions eliciting vaccination attitudes and beliefs varied widely.

CONCLUSIONS: There was heterogeneity in the types of questionnaires used in studies investigating attitudes and beliefs about vaccination in parents. Methods to measure parental attitudes and beliefs about vaccination could be improved with validated and standardised yet flexible instruments. The use of a standard set of questions should be encouraged in this area of study.

WEB: 10.1186/s12889-020-09327-8

IMPACT FACTOR: 2.521

CITED HALF-LIFE: 6.0

START COMMENTARY

Dyda *et al.* present a systematic review of parental vaccine acceptance, which is a critical factor to understanding to increase vaccine uptake and coverage globally. The authors found that most

studies assess attitudes and beliefs about childhood vaccination generally (n=57 studies) whereas others asked about influenza (n=35) and others (n=24) about specific vaccines. More than half (n=63) of studies reported one aspect of validation of questionnaires. Some studies relied on the Health Belief Model (n=25) and Theory of Planned Behavior (n=5). However, many studies did not use validated or previously developed questionnaires, or explicitly discuss theoretical frameworks to inform the design of questionnaires. The lack of consistent and validated instruments to measure attitudes and beliefs across studies made comparisons of findings challenging for the researchers. This article is impactful as it highlights gaps in understanding vaccine acceptance. Most studies were conducted in high income countries (HIC) including 36 in the US, 9 in Canada, and 8 in the UK, indicating that there is a limited understanding of parental attitudes and beliefs about childhood vaccination in LMICs. Further, authors highlight that though there are many studies on parental acceptance (N=116) across many countries (N=36), the heterogeneity of results, and the lack of standard validated questions makes drawing conclusions across settings impossible. There is an evident need for studies with improved instruments to help understand the parental attitudes and beliefs to increase vaccine uptake and coverage.

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8. The effects of switching from 10 to 5-dose vials of MR vaccine on vaccination coverage and wastage: A mixed-method study in Zambia

Krudwig K, Knittel B, Karim A, et al.

Vaccine. 2020 Aug 18;38(37):5905-5913.
PubMed ID: 32703746

ABSTRACT

INTRODUCTION: Vaccines procured for low-income countries are often packaged in multi-dose vials to reduce program costs. To avoid wastage, health workers may refrain from opening a vial if few children attend an immunization session, possibly leading to lower coverage. Lowering the number of doses in a vial may increase coverage and reduce wastage.

METHODS: We used a mixed methods approach to measure the effects of switching from conventional 10-dose measles containing vaccine (MCV) vials to 5-dose MCV vials on coverage and open vial wastage in 14 districts purposely selected from two provinces in Zambia. The districts were paired based on the number of health facilities and the average size of the health facility catchment population. One district from each pair was randomly allocated to receive 5-dose vials while the other continued with the conventional vials. We applied propensity score matched difference-in-difference analysis to estimate intervention effects on coverage using pre-intervention household survey and post-intervention household survey after 11 months of the intervention. The intervention effects on wastage rates were estimated from multivariate analysis of the administrative data. Key informant interviews were conducted to better understand health workers' behavior and preferences at baseline, midline and endline, and analyzed using thematic analysis techniques.

RESULTS: MCV coverage rates increased across both arms for both doses. A five percentage-point intervention effect was detected for MCV1 and 3.5 percentage-point effect for MCV2. The MCV wastage rate was 47% lower in facilities using 5-dose vials (16.2%) versus 10-dose vials (30.5%). Healthcare workers reported being more willing to open a 5-dose vial than a 10-dose vial for one child, as they were less concerned about wastage.

DISCUSSION: Switching 10-dose MCV vials to 5-dose vials improved coverage, decreased wastage, and improved willingness to open a vial. These findings can contribute to strategies for reducing missed opportunities for vaccination.

WEB: 10.1016/j.vaccine.2020.07.012
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

Krudwig *et al.* present the results of a mixed-methods study assessing vaccine coverage and wastage in 14 paired districts across two provinces in Zambia. This study is impactful as it addresses a key challenge of vaccine wastage in LMICs, in which health workers may hesitate to open multi-dose vials of vaccines. Multi-dose vials of vaccines are procured in LMICs to reduce costs, distribution, and cold chain requirements, which can be challenging in LMICs. However, with multi-dose vaccines, there are concerns regarding wastage as the vials must be discarded soon after opening or reconstitution. Though national guidance recommends opening a vial for every eligible child, health workers still must decide if it is worth opening a new vial or if they should delay an immunization for an eligible child to avoid vaccine wastage, which is a major concern. In this study, Krudwig *et al.* address this problem by reporting the results of a difference-in-difference study assessing 10-dose vs. 5-dose vials of measles and rubella (MR) on first and second dose of measles-containing vaccine (MCV) coverage, drop-outs, wastage, session size and frequency, and healthcare worker behavior. The study found promising results related to coverage and reduced drop out for the 5-dose vial compared to the 10-dose vial when considering vaccine cards and caregiver's review. Further, there were significant impacts on wastage because of switching to 5-dose vials. Lastly, health workers reported concerns about wastage and stock availability, which was alleviated by the introduction of the 5-dose vial. One key limitation of note is that masking of the intervention was not possible, and frequent communication with the control facilities may have resulted in better performance in the from of higher vaccine coverage and reduced drop-outs and wastage, which may have affected the results of the study. In conclusion, this study provides evidence on the role of reduced dose vials to reduce wastage and missed opportunities for vaccination in LMICs.

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9. Viral Emerging Diseases: Challenges in Developing Vaccination Strategies

Trovato M, Sartorius R, D'Apice L, Manco R, et al.

Front Immunol. 2020 Sep 3;11:2130.
PubMed ID: 33013898

ABSTRACT

In the last decades, a number of infectious viruses have emerged from wildlife or re-emerged, generating serious threats to the global health and to the economy worldwide. Ebola and Marburg hemorrhagic fevers, Lassa fever, Dengue fever, Yellow fever, West Nile fever, Zika, and Chikungunya vector-borne diseases, Swine flu, Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and the recent Coronavirus disease 2019 (COVID-19) are examples of zoonoses that have spread throughout the globe with such a significant impact on public health that the scientific community has been called for a rapid intervention in preventing and treating emerging infections. Vaccination is probably the most effective tool in helping the immune system to activate protective responses against pathogens, reducing morbidity and mortality, as proven by historical records. Under health emergency conditions, new and alternative approaches in vaccine design and development are imperative for a rapid and massive vaccination coverage, to manage a disease outbreak and curtail the epidemic spread. This review gives an update on the current vaccination strategies for some of the emerging/re-emerging viruses, and discusses challenges and hurdles to overcome for developing efficacious vaccines against future pathogens.

WEB: 10.3389/fimmu.2020.02130
IMPACT FACTOR: 5.085
CITED HALF-LIFE: 2.6

START COMMENTARY

In this commentary, Trovato *et al.* present an overview of emerging viral infectious diseases including the name of the disease, virus, family/genus, reservoir/spill over hosts, and transmission methods (*Table 1).* In addition to describing the emerging viral infectious diseases and their history, the authors present vaccine platforms that have been established to quickly act and curtail outbreaks. Details on current vaccine candidates, in clinical trials are presented in *Table 2*. This article is impactful as it provides an up-to-date view of vaccine candidates and a focus on coronaviruses, which is particularly relevant given the current COVID-19 pandemic. This article can inform the rapid response and vaccine development for the emergence of high-risk viral infectious disease in the future. Trovata *et al.* also highlight the need to fill gaps in our understanding of

epidemiology (i.e. understanding reservoirs/spill-over hosts and transmission) to improve the timeliness, safety and effectiveness of vaccines being developed during epidemics and pandemics.

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10. Vaccination With Moderate Coverage Eradicates Oncogenic Human Papillomaviruses If a Gender-Neutral Strategy Is Applied

Vänskä S, Luostarinen T, Baussano I, et al.

J Infect Dis. 2020 Aug 17;222(6):948-956.
PubMed ID: 32161969

ABSTRACT

BACKGROUND: Human papillomavirus (HPV) vaccination of girls with very high (>90%) coverage has the potential to eradicate oncogenic HPVs, but such high coverage is hard to achieve. However, the herd effect (HE) depends both on the HPV type and the vaccination strategy.
METHODS: We randomized 33 Finnish communities into gender-neutral HPV16/18 vaccination, girls-only HPV16/18 vaccination, and hepatitis B virus vaccination arms. In 2007–2010, 11 662 of 20 513 of 40 852 of 39 420 resident boys/girls from 1992 to 1995 birth cohorts consented. In 2010–2014, cervicovaginal samples from vaccinated and unvaccinated girls at age 18.5 years were typed for HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59/66/68. Vaccine efficacy for vaccinated girls, HE for unvaccinated girls, and the protective effectiveness (PE) for all girls were estimated. We extended the community-randomized trial results about vaccination strategy with mathematical modeling to assess HPV eradication.
RESULTS: The HE and PE estimates in the 1995 birth cohort for HPV18/31/33 were significant in the gender-neutral arm and 150% and 40% stronger than in the girls-only arm. Concordantly, HPV18/31/33 eradication was already predicted in adolescents/young adults in 20 years with 75% coverage of gender-neutral vaccination. With the 75% coverage, eventual HPV16 eradication was also predicted, but only with the gender-neutral strategy.
CONCLUSION: Gender-neutral vaccination is superior for eradication of oncogenic HPVs.
WEB: 10.1093/infdis/jiaa099
IMPACT FACTOR: 5.022
CITED HALF-LIFE: 9.8

START COMMENTARY

Vänskä *et al.* conducted a community-randomized trial to compare the impact of a girls-only vs. a gender-neutral vaccination strategy on HPV prevalence in an HPV vaccination-naïve adolescent population in Finland. This large-scale study achieved vaccination coverage of 47-49% among females and 23% among males. This article reports that the randomized trial results and associated

modeling show that moderate HPV vaccine coverage can rapidly eradicate high risk human papillomaviruses (hrHPVs) with a gender-neutral strategy. Modeling results show that strains 18, 31, and 33 can be eradicated within 20 years, and even persistent and widely circulated HPV16 can be eradicated within 30 years given 75% coverage of existing hrHPV vaccines and a gender-neutral strategy. This finding is critical as many HPV vaccination strategies focus on girls-only and cannot eradicate HPV even with moderate to high coverage (50-75%), indicating that immunization strategies should be reconsidered. Though this article highlights the potential of a gender-neutral vaccination to eradicate oncogenic HPVs, it takes place in Finland, which is a HIC with a strong health system. Therefore, these findings may not be generalizable to other settings.

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Appendix

The literature search for the October 2020 Vaccine Delivery Research Digest was conducted on September 22nd, 2020. We searched English language articles indexed by the US National Library of Medicine and published between August 15, 2020 and September 14, 2020. The search resulted in 324 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]) ("2020/8/15"[PDAT] : "2020/09/14"[PDAT]))