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{Abstract & START Commentary} {Full Article}

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- A mathematical modelling study estimating age-stratified deaths and disability-adjusted life-years (DALYs) averted due to vaccination against 10 pathogens (hepatitis B virus, Haemophilus influenzae type B, human papillomavirus, Japanese encephalitis, measles, Neisseria meningitidis serogroup A, Streptococcus pneumoniae, rotavirus, rubella, and yellow fever) in 98 LMICs by calendar year and by annual birth cohort, 2000-2030.

6 Immunogenicity and safety of a novel ten-valent pneumococcal conjugate vaccine in healthy infants in The Gambia: a phase 3, randomised, double-blind, non-inferiority trial.

{Abstract & START Commentary} {Full Article}

- A phase 3, randomized, double-blind non-inferiority trial, using a per-protocol analysis to compare the ten-valent pneumococcal conjugate vaccine developed by Serum Institute of India (SIIPL-PCV) to the pneumococcal polysaccharide protein D-conjugate vaccine (PHiD-CV), in the Gambia between 2017-2018.

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{Abstract & START Commentary} {Full Article}

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8 Vaccination coverage and adherence to a dengue vaccination program in the state of Paraná, Brazil.

{Abstract & START Commentary} {Full Article}

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10 Diphtheria in Metro Manila, the Philippines 2006-2017: A Clinical, Molecular, and Spatial Characterization.

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- A retrospective cohort study, analyzing the clinical, microbiological, and epidemiological features of patients admitted to Manila's National Infectious Disease hospital with a diagnosis of diphtheria from January 2006 to February 2017.

Appendix

Details of Articles

1. Determinants of vaccination dropout among children 12-23 months age in north Gondar zone, northwest Ethiopia, 2019.

Chanie M, Ewunetie G, Molla A, Muche A.

PLoS One. 2021 Feb 12;16(2):e0246018.
PubMed ID: 33556103

ABSTRACT

BACKGROUND: Vaccination is a proven tool in preventing and eradicating childhood infectious diseases. Each year, vaccination averts an estimated 2-3 million deaths from vaccine preventable diseases. Even though immunization coverage is increasing globally, many children in developing countries still dropout vaccination. The objective of this study was to identify determinants of vaccination dropout among children age 12-23 months in North Gondar, North west Ethiopia.

METHODS: Community based unmatched case-control study was conducted in north Gondar from March 1-27, 2019 among 366 children age 12-23 months (92 cases and 274 controls). Multistage sampling was used for reaching to the community. Data were collected from mothers who had 12-23 months age children using a pretested structured face to face interview. Data were entered using Epi info v. 7 and exported to SPSS v. 20 for analysis. On multivariable logistic regression variables with P-value <0.05 at 95% CI were considered statistically significant.

RESULT: Counseling for mothers about vaccination (AOR = 7.2, 95% CI: (2.93-17.5)); fear of vaccine side effects (AOR = 3.5, 95% CI: (1.56-8.12)); PNC attended (AOR = 3.6, 95% CI: (1.52-8.39)) and mothers not received tetanus toxoid vaccination (AOR = 2.4, 95% CI: (1.03-5.35)) were found risk factors of vaccination dropout.

CONCLUSION: Counseling on vaccination, fear of vaccine side effects, PNC attended and mothers' tetanus toxoid vaccination status during ANC visit were found risk factors. Management bodies and health workers need to consider "reaching every community" approach, Counsel every mother at any opportunity, and provide TT vaccination for all pregnant mothers helps to reduce vaccination dropout among children.

WEB: 10.1371/journal.pone.0246018
IMPACT FACTOR: 2.740
CITED HALF-LIFE: 5.6

START COMMENTARY

In this community based unmatched case control study, Chanie *et al.* identify determinants of vaccination dropout among children age 12–23 months in North Gondar in March 2019. Mothers/ caregivers of children were selected using a multi-stage sampling technique. Vaccination dropout was measured by asking yes/no questions about each of the three Pentavalent vaccines doses during in-person interviews. Multivariable logistic regression was used to identify significant predictors of vaccination dropout (p-value < 0.05). A total of 90 cases (i.e., children 12–23 months who did not complete their vaccination before their first birthday) and 269 controls (with 98% response rate) participated in the study. The main reasons for vaccination dropout included not knowing continuation phases of vaccination (31.5%), forgetting appointments (16.7%), and child sickness (5.6%). Risk factors of vaccination dropout included lack of counseling about vaccination (AOR = 7.2, 95% CI: 2.93-17.5), not attending postnatal care visits (AOR = 3.6, 95% CI: 1.52-8.39), fear of vaccine side effects (AOR = 3.5, 95% CI: 1.56-8.12), and no maternal tetanus toxoid vaccination (AOR = 2.4, 95% CI: 1.03-5.35). Limitations of the study include potential recall bias and misclassification of vaccination status among mothers/caregivers due to self-report. The findings from this study underscore the importance of health facility counseling for mothers and caregivers on the health benefits and safety of completing child vaccination.

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2. Knowledge, attitudes, and practices of seasonal influenza vaccination in healthcare workers, Honduras.

Madewell Z, Chacón-Fuentes R, Jara J, Mejía-Santos H, Molina I, Alvis-Estrada J, et al.

PLoS One. 2021 Feb 14;16(2):e0246379.
PubMed ID: 33539428

ABSTRACT

BACKGROUND: Seasonal influenza is a highly contagious vaccine-preventable disease that may cause high morbidity and mortality in susceptible populations. Healthcare workers are a priority group for seasonal influenza vaccination to protect them from contracting influenza and prevent nosocomial transmission to patients. This study aimed to evaluate knowledge, attitudes, and practices (KAP) of seasonal influenza vaccination among healthcare workers in Honduras.

METHOD: From August 24 to October 21, 2018, we conducted a cross-sectional KAP survey regarding seasonal influenza vaccination to a random sample of healthcare workers who attended patients in hospitals of the Ministry of Health of Honduras (SESAL) and Honduran Social Security Institute (IHSS). We reported frequency distributions of demographics, vaccination KAP, sources of information, and reasons for non-vaccination. We used principal components factor analysis to create knowledge and attitude scores. We used linear regression to analyze associations between demographics and sources of information about the influenza vaccine, and knowledge and attitude scores. We used logistic regression to analyze associations between demographics, sources of information, knowledge scores, and attitude scores, and influenza vaccination.

RESULT: We surveyed 947 healthcare workers who attended patients in 13 SESAL hospitals and two IHSS hospitals. Only 4.6% of participants knew the seasonal influenza vaccine was composed of inactivated viruses, 94.7% believed vaccination causes flu-like symptoms, and 52.0% were vaccinated for influenza in 2018. Knowledge scores were lower for nursing assistants and other healthcare professionals compared to doctors, and higher for healthcare workers who attended a healthcare facility training (P-values≤0.030). Attitude scores were higher for healthcare workers who attended ≥11 patients per day having ≤10 patients per day as reference, self-reported influenza vaccination in previous year, and cited trainings and informal information at the healthcare facility as sources of information for influenza vaccination (P-values≤0.030). Factors associated with self-reported vaccination were self-reported influenza vaccination in previous year (aOR: 7.61; 95% CI:

5.24-11.04), attitude score (aOR: 1.14; 95% CI: 1.07-1.21), and worked in a SESAL hospital (aOR: 1.73; 95% CI: 1.12-2.68) having IHSS as reference.

CONCLUSION: Although influenza vaccination is required by law in Honduras and available for free in public health centers, coverage of healthcare workers in 2018 was half that reported in 2017. Lower coverage may be attributed to misconceptions of vaccination side effects.

WEB: 10.1371/journal.pone.0246379
IMPACT FACTOR: 2.740
CITED HALF-LIFE: 5.6

START COMMENTARY

Madewell *et al.* conducted a cross-sectional knowledge, attitudes, and practices (KAP) survey on seasonal influenza vaccination among healthcare workers with direct patient contact in Honduras in 2018. Separate probabilistic, two-stage, stratified and conglomerate sampling was used to select a random sample of healthcare workers (doctors, nurses, and other healthcare workers) from 13 Ministry of Health of Honduras (SESAL) and two Honduran Social Security Institute (IHSS) hospitals. Principal components factor analysis was utilized to create a knowledge score based on seven variables and an attitude score based on nine variables. Frequency distributions and 95% confidence intervals (CI) were reported for knowledge and attitudes of influenza virus, transmission, and vaccination; sources of information about influenza vaccination; clinical manifestations seven days after vaccination; and reasons for non-vaccination. Of 947 healthcare workers surveyed, 945 knew their vaccination status, of whom 491 self-reported being vaccinated for seasonal influenza (52.0%; 95% CI: 48.8–55.1%). Factors associated with vaccination included previous influenza vaccination (aOR: 7.61; 95% CI: 5.24-11.04), working in a SESAL hospital (aOR: 1.73; 95% CI: 1.12-2.68), and every one unit increase in attitude score (aOR: 1.14; 95% CI: 1.07-1.21). To note, vaccine coverage estimates found in this study (ranging from 24.7–87.9% across hospitals) were much lower than the 100% coverage reported by PAHO for all healthcare workers (including those without direct patient contact) in Honduras in 2017. Among those who were not vaccinated for seasonal influenza (n = 454), 45.6% (95% CI: 41.0–50.2%) cited access limitations (e.g., time constraints, not being offered vaccine) and 41.6% (95% CI: 37.1–46.2%) cited fear of adverse effects as reasons for non-vaccination. Limitations of this study include the potential for social desirability bias and recall bias due to self-report, response bias if vaccinated healthcare workers were more inclined to participate in the study, which could likely lead to an overestimate of vaccine coverage meaning that the true vaccine coverage could be even lower. Additionally, this study may have limited generalizability beyond hospital health care workers. This is the first KAP study of seasonal influenza vaccination among healthcare workers in Central America and thus adds valuable evidence to inform strategies to increase coverage.

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3. The importance of supplementary immunisation activities to prevent measles outbreaks during the COVID-19 pandemic in Kenya.

Mburu C, Ojal J, Chebet R, Akech D, Karia B, Tuju J, et al.

BMC Med. 2021 Feb 11;19(1):35.
PubMed ID: 33531015

ABSTRACT

BACKGROUND: The COVID-19 pandemic has disrupted routine measles immunisation and supplementary immunisation activities (SIAs) in most countries including Kenya. We assessed the risk of measles outbreaks during the pandemic in Kenya as a case study for the African Region.

METHODS: Combining measles serological data, local contact patterns, and vaccination coverage into a cohort model, we predicted the age-adjusted population immunity in Kenya and estimated the probability of outbreaks when contact-reducing COVID-19 interventions are lifted. We considered various scenarios for reduced measles vaccination coverage from April 2020.

RESULTS: In February 2020, when a scheduled SIA was postponed, population immunity was close to the herd immunity threshold and the probability of a large outbreak was 34% (8-54). As the COVID-19 contact restrictions are nearly fully eased, from December 2020, the probability of a large measles outbreak will increase to 38% (19-54), 46% (30-59), and 54% (43-64) assuming a 15%, 50%, and 100% reduction in measles vaccination coverage. By December 2021, this risk increases further to 43% (25-56), 54% (43-63), and 67% (59-72) for the same coverage scenarios respectively. However, the increased risk of a measles outbreak following the lifting of all restrictions can be overcome by conducting a SIA with ≥ 95% coverage in under-fives.

CONCLUSION: While contact restrictions sufficient for SAR-CoV-2 control temporarily reduce measles transmissibility and the risk of an outbreak from a measles immunity gap, this risk rises rapidly once these restrictions are lifted. Implementing delayed SIAs will be critical for prevention of measles outbreaks given the roll-back of contact restrictions in Kenya.

WEB: 10.1186/s12916-021-01906-9
IMPACT FACTOR: 6.782
CITED HALF-LIFE: 5.2

START COMMENTARY

Mburu *et al.* built a mathematical cohort model combining measles serological data, age-specific contact patterns, and national vaccination coverage estimates to understand the potential impact of reduced measles vaccination coverage due to COVID-19 on the risk of measles outbreaks. Using data from Kenya as a case study, the authors projected the impact of suspended supplementary immunization activities (SIAs) under four routine vaccination scenarios: 1) coverage remained the same (79% MCV1 and 45% MCV2), 2) coverage reduced by 15% for both MCV1 and MCV2, 3) coverage reduced by 50% for both MCV1 and MCV2, 4) routine vaccination suspended. In February 2020, at the time of the planned national SIA, the authors estimated that 90% (95% CI: 85–92%) of the population were immune, equivalent to a 34% (95% CI: 8–54%) probability of a large outbreak. By December 2020, the probability of a large measles outbreak was estimated to be 38% (95% CI: 19–54%), 46% (95% CI: 30–59%), and 54% (95% CI: 43–64%), assuming a 15%, 50%, or 100% reduction in routine measles vaccination coverage, respectively. By December 2021, this risk was estimated to increase to 43% (95% CI: 25–56%), 54% (95% CI: 43–63%), and 67% (95% CI: 59–72%), respectively. Serological data estimates and the mixing matrix came specifically from Kilifi, Kenya and thus may not be fully representative of the country or more urban areas. Additionally, there is some uncertainty around the actual reduction in transmission due to variability in compliance with physical distancing measures in place. This study emphasizes the importance of maintaining high routine measles immunization coverage during the COVID-19 pandemic and supports the need to conduct a SIA with ≥ 95% coverage among children less than five years old before or immediately after all COVID-19-related restrictions on physical contact are lifted in Kenya. This model may be useful to inform planned immunization activities in other measles-endemic settings in rural Africa.

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4. Effect of intensive training in improving older women's knowledge and support for infant vaccination in Nigerian urban slums: a before-and-after intervention study.

Balogun F, Bamidele O, Bamgboye E.

BMC Public Health. 2021 Feb 06;21(1):266.

PubMed ID: 33530963

ABSTRACT

BACKGROUND: One of the strategies for improving vaccination uptake is to make communities understand the importance of immunization and this is expected to drive the demand for vaccines. Building the capacity of older women who supervise child care in Africa may improve infant vaccination in underserved communities. This study determined the impact of training of older women on their knowledge and support for infant vaccination in selected urban slum communities in Ibadan, Nigeria.

METHODS: This was a before-and-after study that enrolled women aged ≥35 years. They were trained with a manual and short video using participatory learning methods over an 8 month period. The content of their training includes importance of immunization timeliness and completion, how vaccines work and how to be advocates and supporters of infant vaccination. Their knowledge and support for infant vaccination at baseline were compared with post training values using Student's t test and Chi square test with the level of significance set at 5%.

RESULTS: There were 109 women with mean age 55.8 ± 11.6. they had a mean of 5.7 ± 2.1 training sessions. At the end of the training, their knowledge about infant vaccination and the support they give to it increased from 4.8 ± 3.8 to 10.7 ± 0.6, and 3.1 ± 3.5 to 8.1 ± 1.7 respectively. Those with good knowledge about infant vaccination increased significantly from 37(33.9%) to 82(82.8%), while those with good support for the same increased from 31(28.4%) to 85(85.9%). Women who were ≤ 64 years significantly had improved knowledge after the training compared to the older ones. Those with post secondary education had better knowledge and greater support for infant vaccination at baseline. However, there was no difference in the knowledge and support for infant vaccination among the women across the different educational levels after the training.

CONCLUSIONS: Participatory learning improved the knowledge about, and support for infant vaccination among older women supervising child care in these urban slum communities. Similar training may be extended to comparable settings in order to improve demand for infant vaccination.

WEB: 10.1186/s12889-021-10310-0
IMPACT FACTOR: 2.521
CITED HALF-LIFE: 6.0

START COMMENTARY

Balogun *et al.* examine the impact of an eight-month infant vaccination training intervention on changes in the mean knowledge and support scores among older women caregivers aged 35+ years living in seven urban slum communities in Ibadan, Nigeria. Study participants were recruited through a convenience sample, using pregnant women attending antenatal clinic visits from selected slums to refer potential older caregivers. The participatory training program consisted of eight 90-120 minute sessions conducted once a month, covering content related to infant immunization uptake (e.g., how vaccines work, common myths, importance of timeliness and completion, and how to overcome barriers and be an advocate). Semi-structured questionnaires administered before and after the intervention were used to categorize good (≥ 75th percentile) or poor (<75th percentile) knowledge or support scores. Bivariate analysis with Students' t tests and Chi square tests were used to determine differences in and factors associated with knowledge and support scores pre- and post-intervention ($\alpha = 0.05$). Among 109 participants with a mean age of 55.8 (± 11.6) years, 50.0% had secondary school education and 56.0% had five or more of their own biological children. The mean number of trainings attended was 5.7 (± 2.1) out of the eight-part series. From pre- to post-intervention, there was a significant increase in mean knowledge (+5.9 points, 95% CI: 5.2–6.7) and mean support score (+4.9 points, 95% CI: 4.1–5.7) ($p < 0.01$). Good knowledge increased from 33.9% to 82.8%, while good support increased from 28.4% to 85.9%. Participants aged 35-44 years old had the largest increase in good knowledge (26.7% to 92.9%), while those aged 65+ years old had the smallest increase (33.9% to 82.8%). Limitations of this study include potential for social desirability bias, impact of external factors beyond training, as well as lack of data on actual changes in immunization uptake. Generalizability may also be limited due to convenience sampling. As the culture of older women supervising infant care is widespread in Nigeria and many other countries, this intervention may be useful to adapt to other urban slum settings.

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5. Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study.

Li X, Mukandavire C, Cucunubá Z, Echeverria Londono S, Abbas K, Clapham H, et al.
Lancet. 2021 Feb 21;397(10272):398-408.
PubMed ID: 33516338336102l0

ABSTRACT

BACKGROUND: The past two decades have seen expansion of childhood vaccination programmes in low-income and middle-income countries (LMICs). We quantify the health impact of these programmes by estimating the deaths and disability-adjusted life-years (DALYs) averted by vaccination against ten pathogens in 98 LMICs between 2000 and 2030.

METHODS: 16 independent research groups provided model-based disease burden estimates under a range of vaccination coverage scenarios for ten pathogens: hepatitis B virus, Haemophilus influenzae type B, human papillomavirus, Japanese encephalitis, measles, Neisseria meningitidis serogroup A, Streptococcus pneumoniae, rotavirus, rubella, and yellow fever. Using standardised demographic data and vaccine coverage, the impact of vaccination programmes was determined by comparing model estimates from a no-vaccination counterfactual scenario with those from a reported and projected vaccination scenario. We present deaths and DALYs averted between 2000 and 2030 by calendar year and by annual birth cohort.

FINDINGS: We estimate that vaccination of the ten selected pathogens will have averted 69 million (95% credible interval 52-88) deaths between 2000 and 2030, of which 37 million (30-48) were averted between 2000 and 2019. From 2000 to 2019, this represents a 45% (36-58) reduction in deaths compared with the counterfactual scenario of no vaccination. Most of this impact is concentrated in a reduction in mortality among children younger than 5 years (57% reduction [52-66]), most notably from measles. Over the lifetime of birth cohorts born between 2000 and 2030, we predict that 120 million (93-150) deaths will be averted by vaccination, of which 58 million (39-76) are due to measles vaccination and 38 million (25-52) are due to hepatitis B vaccination. We estimate that increases in vaccine coverage and introductions of additional vaccines will result in a 72% (59-81) reduction in lifetime mortality in the 2019 birth cohort.

INTERPRETATION: Increases in vaccine coverage and the introduction of new vaccines into LMICs have had a major impact in reducing mortality. These public health gains are predicted to increase in coming decades if progress in increasing coverage is sustained.

FUNDING: Gavi, the Vaccine Alliance and the Bill & Melinda Gates Foundation.

WEB: 10.1016/S0140-6736(20)32657-X
IMPACT FACTOR: 60.390
CITED HALF-LIFE: 8.6

START COMMENTARY

In this high-impact modelling study, Li *et al.* estimate age-stratified deaths and disability-adjusted life-years (DALYs) averted due to vaccination against ten pathogens in 98 low- and middle-income countries (LMICs) by calendar year and annual birth cohort from 2000-2030. Generated by 16 independent research groups within the Vaccine Impact Modelling Consortium, two mathematical models were used for each pathogen (with the exception of yellow fever and hepatitis B virus which had one and three models, respectively). Each model represents the impact of vaccine coverage and efficacy on national-level disease burden (and in some cases disease transmission dynamics) compared to no vaccination. Credible intervals (CrIs) were derived by combining probabilistic distributions of estimated impact from available models for each pathogen. No discounting or weighting was applied in the calculation of DALYs. Between 2000 and 2030, 69 million (95% CrI: 52–88) deaths were estimated to be averted, of which 37 million (95% CrI: 30–48) were averted between 2000 and 2019. Of the ten pathogens, vaccination against measles has the largest impact, with 56 million (95% CrI: 39–74) deaths averted by calendar year from 2000 to 2030. Considering deaths averted by birth cohorts born between 2000 and 2030, the authors predict 120 million (95% CrI: 93-150) deaths averted by vaccination, of which 58 million (95% CrI: 39-76) and 38 million (95% CrI: 25-52) are due to measles and hepatitis B vaccination, respectively. Estimates indicate that increasing human papillomavirus (HPV) vaccine coverage in girls will avert more deaths per person vaccinated than any other immunization activity, whereas increasing pneumococcal conjugate vaccine (PCV) coverage will give the largest reductions in mortality among children under five years old. This study estimates the health impact of immunization on the largest scale to date, with an emphasis on standardizing model inputs (vaccine coverage and demography) and outputs (mortality and DALYs averted), and in assessing structural uncertainty. The results show where future vaccine investments can lead to the greatest impact and highlight the importance of increasing vaccine coverage to sustain gains in reducing infectious disease-related mortality across LMICs.

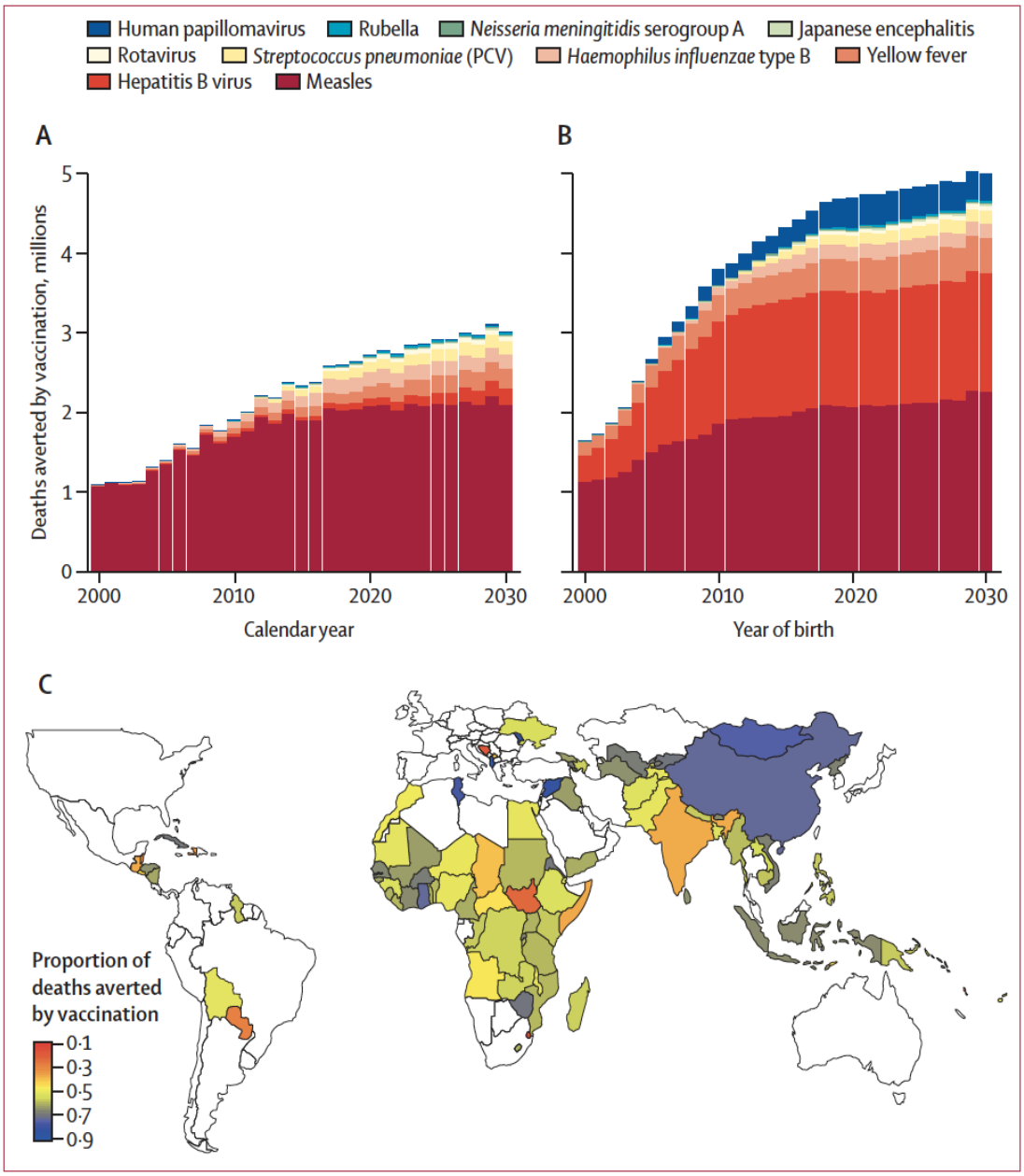

Figure Estimates of deaths averted by vaccination against 10 pathogens in 98 LMICs (a) by calendar year (summing across all ages) (b) by year of birth (summing across lifetime) (c) by country, across 2000–19 birth cohorts (proportion of lifetime deaths). Figure 3 in manuscript.

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6. Immunogenicity and safety of a novel ten-valent pneumococcal conjugate vaccine in healthy infants in The Gambia: a phase 3, randomised, double-blind, non-inferiority trial.

Clarke E, Bashorun A, Adigweme I, Badjie Hydara M, Umesi A, Futa A, et al.

Lancet Infect Dis. 2021 Jan 31.

PubMed ID: 33516293

ABSTRACT

BACKGROUND: An affordable pneumococcal conjugate vaccine (PCV) is needed to ensure sustainable access in low-income and middle-income countries. This trial examined the immunogenicity and safety of a novel ten-valent PCV (SIIPL-PCV) containing serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F compared with the pneumococcal polysaccharide protein D-conjugate vaccine (PHiD-CV; Synflorix; GlaxoSmithKline; Brentford, UK).

METHODS: In this single-centre, randomised, double-blind, phase 3, non-inferiority trial in The Gambia, healthy, PCV-naive infants aged 6-8 weeks were enrolled and assigned using permuted block randomisation to receive one of three lots of SIIPL-PCV or to PHiD-CV in a ratio of 2:2:2:3. Parents and all staff assessing study outcomes were masked to group assignment. Vaccines (0·5 mL SIIPL-PCV or 0·5 mL PHiD-CV) were administered at ages 6, 10, and 14 weeks by intramuscular injection. Primary immunogenicity outcomes, measured at age 18 weeks, were serotype-specific IgG geometric mean concentrations (GMCs) and seroresponse rates (IgG ≥ 0·35 µg/mL). Lot-to-lot equivalence (objective 1) was shown if the upper and lower bounds of the two-sided 95% CI around the GMC ratio for each pairwise lot-to-lot comparison was between the 0·5 and 2·0 equivalence margins for all ten serotypes. The immunogenicity of SIIPL-PCV was defined as being non-inferior to that of PHiD-CV (objective 2) if, for at least seven of the ten serotypes in SIIPL-PCV, the lower bound of the 97·5% CI for the GMC ratio was greater than 0·5, or the lower bound of the 97·5% CI for differences in seroresponse rate was greater than -10%. The GMC and seroresponse rates to serotypes 6A and 19A, which are not in PHiD-CV, were compared with those of the serotype in PHiD-CV that had the lowest seroresponse rate. Non-inferiority of the immune responses to antigens in the co-administered Expanded Programme on Immunization (EPI) vaccines (objective 3) was declared if the lower bound of the 95% CI for the difference between SIIPL-PCV and PHiD-CV in seroresponse rates, or GMC ratios for pertussis antigens, was greater than -10% (or 0·5 for pertussis antigens) for all vaccine antigens. Safety data were assessed according to

treatment received at the first visit in infants who received at least one dose of study vaccine and for whom at least some post-vaccination safety data were available. The primary immunogenicity analysis was in the per-protocol immunogenicity population, which included infants who received all study vaccines and had immunogenicity measurements after vaccination and no major protocol deviations. This trial is registered at ClinicalTrials.gov (NCT03197376).

FINDINGS: Between June 21, 2017, and Jan 29, 2018, 2250 infants were enrolled and randomly assigned to receive SIIPL-PCV (n=1503; 502 to lot 1, 501 to lot 2, and 500 to lot 3) or PHiD-CV (n=747). 1458 (97·0%) infants assigned to SIIPL-PCV and 724 (96·9%) assigned to PHiD-CV were included in the per-protocol primary immunogenicity analysis. Lot-to-lot equivalence was shown, with the lowest lower bound of the 95% CI for the GMC ratio being 0·52 (for serotype 6B in lot 2 vs lot 3) and the highest upper bound being 1·69 (for serotype 6B in lot 1 vs lot 2). SIIPL-PCV was non-inferior to PHiD-CV in terms of immunogenicity: the lower bound of the 97·5% CI for the GMC ratio was greater than 0·5 (the lowest being 0·67 for serotype 19F) and the lower bound of the 97·5% CI for the difference in seroresponse rate was greater than -10% (the lowest being -2·2% for serotype 6B) for all ten serotypes in SIIPL-PCV. The lowest seroresponse rate after PHiD-CV was to serotype 6B (76·7% [95% CI 73·4-79·7]). This serotype was therefore used for the comparisons with serotype 6A and 19A in SIIPL-PCV. Non-inferiority of immune responses to the EPI vaccines after co-administration with SIIPL-PCV compared with after co-administration with PHiD-CV was shown for all vaccine antigens included in the primary series. The lowest lower bound of the 95% CI for the difference in seroresponse rates was -7·1% for rotavirus antibody and for the GMC ratio for pertussis antigens was 0·62 for anti-pertussis toxoid. 1131 (75·2%) of 1503 infants in the SIIPL-PCV group and 572 (76·6%) of 747 in the PHiD-CV group had at least one unsolicited adverse event. 36 (2·4%) participants in the SIIPL-PCV group and 18 (2·4%) in the PHiD-CV group had a serious adverse event; none were considered related to vaccination. In infants who were selected to have solicited adverse events recorded, injection-site induration after primary vaccinations occurred in 27 (4·9%) of 751 infants who received SIIPL-PCV versus 34 (9·4%) of 364 who received PHiD-CV (p=0·0032). There were no other notable differences in the safety profiles of the two vaccines. One infant in the SIIPL-PCV group and two in the PHiD-CV group died during the study. The deaths were not considered to be related to study vaccination or study participation.

INTERPRETATION: The immunogenicity of SIIPL-PCV was non-inferior to that of PHiD-CV, for which efficacy and effectiveness data against pneumococcal disease are available. The vaccine is safe and can be co-administered with routine EPI vaccines. The data generated in this trial have supported the licensure and pre-qualification of SIIPL-PCV, making the vaccine available for introduction into national immunisation programmes. Generating post-implementation data confirming vaccine impact remains important.

FUNDING: Bill & Melinda Gates Foundation.

WEB: 10.1016/S1473-3099(20)30735-0
IMPACT FACTOR: 24.446
CITED HALF-LIFE: 4.7

START COMMENTARY

In this double-blind, phase 3, randomized trial conducted in the Gambia in 2017 to 2018, Clarke *et al.* found the ten-valent pneumococcal conjugate vaccine developed by Serum Institute of India (SIIPL-PCV) to be non-inferior to the pneumococcal polysaccharide protein D-conjugate vaccine (PHiD-CV). Using a per-protocol analysis, primary outcomes included lot-to-lot equivalence, PCV immunogenicity, and Expanded Programme on Immunization (EPI) vaccine immunogenicity. Among 2,250 PCV-naive infants aged 6-8 weeks enrolled, 1,503 (66.8%) were randomly assigned to receive one of the three lots of SIIPL-PCV using permuted block randomization of 2:2:2:3. Based on pneumococcal serotype-specific IgG geometric mean concentrations (GMCs) assessed at the post-primary visit, the prespecified lot-to-lot equivalence criteria was met for all pairwise lot-to-lot comparisons, for all ten serotypes. Seroresponse rates at the post-primary visit ranged from 99.7% (95% CI: 99.3–99.9%) for serotype 1 to 78.7% (95% CI: 76.5–80.7%) for serotype 6B after SIIPL-PCV, and from 99.0% (95% CI: 98.0–99.6%) for serotype 1 to 76.7% (95% CI: 73.4–79.7%) for serotype 6B after PHiD-CV. Seroresponse rates to tetanus, diphtheria, hepatitis B, Hib, and polio were high irrespective of whether the vaccines were co-administered with SIIPL-PCV or PHiD-CV. The study also found robust response to a 9-month booster dose of SIIPL-PCV, as well as high functional opsonophagocytic activity antibody titres after primary vaccinations and booster. A limitation of using PHiD-CV as the comparator vaccine in this study is the consequent absence of matched responses for serotypes 6A and 19A in SIIPL-PCV. Results from this trial supported the licensure and WHO prequalification of SIIPL-PCV and suggest the vaccine can have an impact on pneumococcal disease globally, especially in low- and middle-income countries.

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7. Uganda's increasing dependence on development partner's support for immunization - a five year resource tracking study (2012 - 2016).

Kamya C, Abewe C, Waiswa P, Asiimwe G, Namugaya F, Opio C, et al.

BMC Public Health. 2021 Jan 23;21(1):160.

PubMed ID: 33468094

ABSTRACT

BACKGROUND: In Uganda, there are persistent weaknesses in obtaining accurate, reliable and complete data on local and external investments in immunization to guide planning, financing, and resource mobilization. This study aimed to measure and describe the financial envelope for immunization from 2012 to 2016 and analyze expenditures at sub-national level.

METHODS: The Systems of Health Accounts (SHA) 2011 methodology was used to quantify and map the resource envelope for immunization. Data was collected at national and sub-national levels from public and external sources of immunization. Data were coded, categorized and disaggregated by expenditure on immunization activities using the SHA 2011.

RESULTS: Over the five-year period, funding for immunization increased fourfold from US$ 20.4 million in 2012 to US$ 85.6 million in 2016. The Ugandan government was the main contributor (55%) to immunization resources from 2012 to 2014 however, Gavi, the Vaccine Alliance contributed the majority (59%) of the resources to immunization in 2015 and 2016. Majority (66%) of the funds were managed by the National Medical Stores. Over the five-year period, 80% of the funds allocated to immunization activities were spent on facility based routine immunization (expenditure on human resources and outreaches). At sub-national level, districts allocated 15% of their total annual resources to immunization to support supervision of lower health facilities and distribution of vaccines. Health facilities spent 5.5% of their total annual resources on immunization to support outreaches.

CONCLUSION: Development partner support has aided the improvement of vaccine coverage and increased access to vaccines however, there is an increasing dependence on this support for a critical national program raising sustainability concerns alongside other challenges like being off-budget and unpredictable. To ensure financial sustainability, there is need to operationalize the immunization fund, advocate and mobilize additional resources for immunization from the

Government of Uganda and the private sector, increase the reliability of resources for immunization as well as leverage on health financing reforms like the National Health Insurance.

WEB: 10.1186/s12889-021-10178-0
IMPACT FACTOR: 2.521
CITED HALF-LIFE: 6.0

START COMMENTARY

In this retrospective resource tracking study in Uganda, Kamya *et al.* use Systems of Health Accounts (SHA) 2011 methodology to 1) measure and describe the resource envelope for immunization activities at the national level from 2012-2016, and 2) conduct an expenditure analysis of the immunization resources received and utilized at sub-national level from 2015-2016. Information was collected from a combination of face-to-face key informant interviews using structured data collection tools, and review of documents provided by respondents. Immunization stakeholders included individuals from public entities, development partners, international non-governmental organizations, and districts and health facilities. The study found a fourfold increase in the resource envelope for immunization, from US$ 20.4 million in 2012 to US$ 85.6 million in 2016, mainly attributed to new vaccine introduction and the lift of the ban of Gavi funding to Uganda in 2012. While the Ugandan government was the main contributor (55%) to immunization resources from 2012 to 2014, Gavi, the Vaccine Alliance contributed the majority (59%) of the resources to immunization from 2015 to 2016. To ensure financial sustainability of the Ugandan immunization program, findings from this study emphasize the need to operationalize the immunization fund in the immunization act, advocate and mobilize additional resources for immunization from the ministry of health and private sector, increase the reliability of resources for immunization, as well as leverage on health financing reforms (e.g., National Health Insurance). This study highlights the need to ring-fence resources for immunization at the district and health facility level and calls for continuous tracking of resources for immunization moving forward.

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8. Vaccination coverage and adherence to a dengue vaccination program in the state of Paraná, Brazil.

Preto C, Maron de Mello A, Cesário Pereira Maluf E, Teixeira Krainski E, Graeff G, de Sousa G, et al.

Vaccine. 2021 Jan 15;39(4):711-719.
PubMed ID: 33386178

ABSTRACT

The success of vaccination programs depends on the level of acceptance of the vaccine to achieve high vaccine coverage rates (VCR). Vaccine hesitancy is a challenge, especially concerning new vaccines. Dengue vaccine, Dengvaxia®, was licensed in Brazil in 2015 and implemented, in a pioneering publicly-funded initiative in the state of Paraná, between 2016 and 2018. The vaccination program took place in five phases in the 30 municipalities most affected by dengue in the state, targeting individuals from nine to 44 years-old in two cities and from 15 to 27 years-old in the other 28 municipalities, totaling a target population of 500,000 individuals. A cross-sectional descriptive study was carried out to assess VCR and adherence to the dengue vaccine in this program. VCR, dropout ratio (DR), and compliance with the vaccination schedule (CVS) were analyzed by sex, age group, and municipality size. A total of 302,603 individuals (60.5%) received ≥ 1 dose, 44.2% received ≥ 2 doses, and 28.6% 3 doses. The DR was 52.8%. Among individuals who started vaccination, 40.6% achieved CVS. The highest VCR, highest CVS, and lowest DR occurred in the age group from 9 to 14 years old and from 28 to 44 years old and in smaller municipalities. A greater proportion of men started vaccination (male 64.0%; female 57.1%) however, the DR was higher in men (male 55.4%; female 49.9%), and a higher percentage of women completed the vaccination schedule according to the recommendations (CVS male 37.8%; female 43.6%). Differences were noted in the CVS according to the initial phase of the program (first phase 50.8%; second phase 18.8%). The heterogeneity in vaccine uptake and compliance according to sex, age, and municipality size suggests the need for differentiated strategies to address challenges with new and multiple-dose vaccines.

WEB: 10.1016/j.vaccine.2020.12.030
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

In this descriptive, cross-sectional study, Preto *et al.* describe dengue vaccine coverage, dropout, and compliance with a three-dose, 160-day dose interval, vaccine schedule in the state of Paraná, Brazil between August 2016 and December 2018. These outcomes were compared by age, sex, and municipalities grouped by population size, using chi-2 tests and 95% confidence intervals (95% CI) with two-sided p-values <0.05 deemed statistically significant. Among the target population of 500,000 individuals,16.3%, 15.7%, and 28.6% received only one, only two, or three-doses, respectively, leading to a total of 302,603 individuals (60.5%) who received any dengue vaccination. While a greater proportion of men (64.0%) initiated vaccination compared to women (57.1%), compliance with the full vaccination schedule was significantly higher among women (43.6% women vs. 37.8% men, p<0.01). Those aged 9-14 and 28-44 years-old had the highest degree of coverage (49.9% and 48.8%), compliance (55.6% and 48.8%), and lowest dropout (33.2% and 45.3%) compared to those in age groups between 15-27 years-old. Dengue vaccine coverage was 73.2% (95% CI: 72.4–73.9%) and 21.5% (95% CI: 21.3–21.6%) in municipalities with <10,000 and ≥50,000 inhabitants, respectively. Results showed a progressive decrease in vaccine coverage and compliance with the increase in municipality size. Limitations of this study include differences in the immunization record quality between municipalities, as well as inaccuracy in target population calculations that led to coverage over 100% in some small municipalities. This novel study on mass dengue vaccination highlights heterogeneity among the population and potential need for differentiated implementation strategies to improve vaccination outcomes.

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9. An inventory-location optimization model for equitable influenza vaccine distribution in developing countries during the COVID-19 pandemic.

Rastegar M, Tavana M, Meraj A, Mina H.

Vaccine. 2021 Jan 13;39(3):495-504.
PubMed ID: 33342632

ABSTRACT

The addition of other respiratory illnesses such as flu could cripple the healthcare system during the coronavirus disease 2019 (COVID-19) pandemic. An annual seasonal influenza vaccine is the best way to help protect against flu. Fears of coronavirus have intensified the shortage of influenza shots in developing countries that hope to vaccinate many populations to reduce stress on their health services. We present an inventory-location mixed-integer linear programming model for equitable influenza vaccine distribution in developing countries during the pandemic. The proposed model utilizes an equitable objective function to distribute vaccines to critical healthcare providers and first responders, elderly, pregnant women, and those with underlying health conditions. We present a case study in a developing country to exhibit efficacy and demonstrate the optimization model's applicability.

WEB: 10.1016/j.vaccine.2020.12.022
IMPACT FACTOR: 3.143
CITED HALF-LIFE: 7.3

START COMMENTARY

Rastegar *et al.* develop a mixed-integer linear programming (MILP) model for equitable influenza vaccine distribution accounting for inventory-location problems and using a customizable objective function. The objective function aims to distribute vaccines equitably by maximizing the minimum delivery-to-demand ratio per group in each province and each time-period. In the country case study of Iran, the authors apply this vaccine distribution model to inform strategy for how to cope with the influenza vaccine shortage amidst the COVID-19 pandemic. The Iranian population was divided into eight groups according to Iran Ministry of Health and Medical Education (MOHME) priorities based on age, pre-existing medical conditions, pregnancy, and healthcare-related jobs. The optimal

solution identified selected Tehran as a distribution center considering a total budget of $270,000,000 and purchasing 15,398,713 doses of the vaccines. Details of the number of doses distributed to each province across four time periods are presented, with each group allocated an equitable number of vaccine doses according to their coverage rate. For example, the authors demonstrate the scenario where 121,686, 479,059, and 121,801 vaccine doses shipped from the Tehran distribution center to the East Azarbaijan warehouse in time-periods 1, 2, and 4, respectively (no vaccine doses shipped in time-period 3 as demand was covered by time-period 2 shipment). Group 1 (Infants and toddlers aged six to 35 months) and Group 3 (Adults aged 65+ years with pre-existing medical conditions), were allocated 199,841 and 17,602 doses, respectively. Limitations of this study include exclusion of vehicle routing and number of vaccination centers.

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10. Diphtheria in Metro Manila, the Philippines 2006-2017: A Clinical, Molecular, and Spatial Characterization.

Saito N, Dimapilis V, Fujii H, Suzuki M, Telan E, Umipig D, et al.

Clin Infect Dis. 2021 Jan 29;72(1):61-68.
PubMed ID: 32160282

ABSTRACT

BACKGROUND: Diphtheria is a vaccine-preventable disease that persists as a global health problem. An understanding of the pattern of disease is lacking in low- and middle-income countries such as the Philippines.

METHODS: We conducted a retrospective review of the clinical, microbiological, and epidemiological features of patients admitted with a clinical diagnosis of diphtheria to an infectious disease referral hospital in Metro Manila, the Philippines, between 2006 and 2017. Cases were mapped and the distribution was compared with population density. Corynebacterium diphtheriae isolates from between 2015 and 2017 were examined by multilocus sequence typing (MLST).

RESULTS: We studied 267 patients (range:12-54 cases/year) admitted between 2006 and 2017. The case fatality rate (CFR) was 43.8% (95% confidence interval, 37.8-50.0%). A higher number of cases and CFR was observed among children <10 years. Mortality was associated with a delayed admission to hospital and a lack of diphtheria antitoxin. Between 2015 and 2017 there were 42 laboratory-confirmed cases. We identified 6 multilocus sequence types (STs). ST-302 was the most common (17/34, 48.6%), followed by ST67 (7/34, 20%) and ST458 (5/34, 14%). Case mapping showed a wide distribution of diphtheria patients in Metro Manila. Higher case numbers were found in densely populated areas but with no apparent clustering of ST types.

CONCLUSIONS: Our analysis indicates that diphtheria remains endemic in Metro Manila and that the infection is frequently fatal in young children. Improved vaccine coverage and a sustainable supply of diphtheria antitoxin should be prioritized.

WEB: 10.1093/cid/ciaa005
IMPACT FACTOR: 8.313
CITED HALF-LIFE: 8.3

START COMMENTARY

In this retrospective cohort study, Saito *et al.* analyze the clinical, microbiological, and epidemiological features of patients with clinically diagnosed diphtheria admitted to San Lazaro Hospital (SLH) in Manila, Philippines from January 2006 to February 2017. To identify diphtheria hotspot areas, case maps were developed using kernel density analysis. An unadjusted logistic regression model was used to calculate risk ratios of the effect of various exposures on fatal outcomes. A total of 267 patients (mean: 24 cases/year; range: 12−54 cases/year) with diphtheria were admitted to SLH, of whom 117 (43.8%) died in the hospital. The majority (86.5%) of cases were children under 15 years old, with the case fatality rate (CFR) highest among children younger than five years (60.2%; 95% CI: 48.9−70.8%). Twenty (47.6%) of the 42 patients with laboratory-confirmed diphtheria reported having received three primary doses of DPT vaccine; no significant difference in the CFR was found between subjects with and without a vaccination history three DPT doses. There was a significantly lower CFR among patients given diphtheria antitoxin (DAT) as part of their clinical management compared with patients not given DAT due to limited availability (47.7%, vs. 27.5%, $p < 0.01$) and among patients attending the hospital within four days after onset of symptom compared to those admitted five or more days (28%, 95% CI: 12.1−49.4% vs. 64.7%, 38.3−85.8%; $p = 0.03$). Those living outside Metro Manila (33.3%) had significantly higher CFRs compared with patients living in Metro Manila (64.3% vs 32.1%, $p = 0.049$). Case mapping showed a wide distribution of patients with diphtheria, with many identified in highly populated areas. Sequence types (ST) from 34 isolates were scattered around the city, with no apparent clustering of STs. The most common ST type was ST-302 (n = 17; 48.6%). Limitations of this study include potential recall bias due to self-reported vaccination status, and likely underestimation of the burden of diphtheria as the data may not reflect the true number of cases across the city (as mild cases may not be referred to SLH). Diphtheria persists as a public health problem in Manila and renewed efforts to improve DPT vaccine coverage are needed. This study's findings support consideration of a booster dose of DPT for children under five years old, further education and awareness for early detection and treatment of diphtheria, and ensuring a sustainable supply of DAT is available.

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Appendix

The literature search for the March 2021 Vaccine Delivery Research Digest was conducted on February 16, 2021. We searched English language articles indexed by the US National Library of Medicine and published between January 15, 2021 and February 14, 2021. The search resulted in 376 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]) (“2021/01/15”[PDAT] : “2021/02/14”[PDAT]))