VACCINE DELIVERY RESEARCH DIGEST

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REPORT TO THE BILL & MELINDA GATES FOUNDATION

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1. **Mapping diphtheria-pertussis-tetanus vaccine coverage in Africa, 2000-2016: a spatial and temporal modelling study**

PubMed ID: 30961907

**ABSTRACT**

**BACKGROUND:**
Routine childhood vaccination is among the most cost-effective, successful public health interventions available. Amid substantial investments to expand vaccine delivery throughout Africa and strengthen administrative reporting systems, most countries still require robust measures of local routine vaccine coverage and changes in geographical inequalities over time.

**METHODS:**
This analysis drew from 183 surveys done between 2000 and 2016, including data from 881,268 children in 49 African countries. We used a Bayesian geostatistical model calibrated to results from the Global Burden of Diseases, Injuries, and Risk Factors Study 2017, to produce annual estimates with high-spatial resolution (5 × 5 km) of diphtheria-pertussis-tetanus (DPT) vaccine coverage and dropout for children aged 12-23 months in 52 African countries from 2000 to 2016.

**FINDINGS:**
Estimated third-dose (DPT3) coverage increased in 72.3% (95% uncertainty interval [UI] 64.6-80.3) of second-level administrative units in Africa from 2000 to 2016, but substantial geographical inequalities in DPT coverage remained across and within African countries. In 2016, DPT3 coverage at the second administrative (ie, district) level varied by more than 25% in 29 of 52 countries, with only two (Morocco and Rwanda) of 52 countries meeting the Global Vaccine Action Plan target of 80% DPT3 coverage or higher in all second-level administrative units with high confidence (posterior probability ≥95%). Large areas of low DPT3 coverage (≤50%) were identified in the Sahel, Somalia, eastern Ethiopia, and in Angola. Low first-dose (DPT1) coverage (≤50%) and high relative dropout (≥30%) together drove low DPT3 coverage across the Sahel, Somalia, eastern Ethiopia, Guinea, and Angola.

**INTERPRETATION:**
Despite substantial progress in Africa, marked national and subnational inequalities in DPT coverage persist throughout the continent. These results can help identify areas of low coverage and vaccine
delivery system vulnerabilities and can ultimately support more precise targeting of resources to improve vaccine coverage and health outcomes for African children.

**WEB:** 10.1016/S0140-6736(19)30226-0

**IMPACT FACTOR:** 53.25

**CITED HALF-LIFE:** 9.20

## START COMMENTARY

In this spatial modeling study, Mosser et al. used a two-step modeling process that first modeled diphtheria-pertussis-tetanus (DPT) vaccine coverage with spatial covariates and then incorporated residual spatial and temporal correlation using a Bayesian geostatistical model. Mosser et al. mapped DPT1 and DPT3 coverage and DPT1-3 dropout across 52 African countries from 2000 to 2016 by 5 x 5 km units and by second administrative units. The authors found improvement in DPT1 and DPT3 coverage over time, but subnational variation in coverage as depicted in Figures 1, 2, 3, and 4. To the authors' knowledge, this is the first study to assess DPT coverage in Africa across time and space at such a high resolution. A limitation of this study is potential recall bias as vaccination status was obtained via maternal recall when vaccination cards were not available. Another limitation was the use of administrative level estimates for 5 x 5 km unit estimates when more granular geographic information was not available. This study uses data of children 12 to 59 months of age to retrospectively estimate coverage levels among children 12 to 23 months, which does not account for potential higher likelihood of vaccination status misclassification among older age cohorts or effects of migration and differential mortality. Additionally, data were not available for all countries and years, so estimates may be biased if covariates do not adequately estimate coverage for those countries and years. The results of this study, in conjunction with additional data (e.g., cost-effectiveness and local burden), can inform local vaccination program.

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2. **Mapping vaccination coverage to explore the effects of delivery mechanisms and inform vaccination strategies**


PubMed ID: 30967543

**ABSTRACT**

The success of vaccination programs depends largely on the mechanisms used in vaccine delivery. National immunization programs offer childhood vaccines through fixed and outreach services within the health system and often, additional supplementary immunization activities (SIAs) are undertaken to fill gaps and boost coverage. Here, we map predicted coverage at 1 x 1 km spatial resolution in five low- and middle-income countries to identify areas that are under-vaccinated via each delivery method using Demographic and Health Surveys data. We compare estimates of the coverage of the third dose of diphtheria-tetanus-pertussis-containing vaccine (DTP3), which is typically delivered through routine immunization (RI), with those of measles-containing vaccine (MCV) for which SIAs are also undertaken. We find that SIAs have boosted MCV coverage in some places, but not in others, particularly where RI had been deficient, as depicted by DTP coverage. The modelling approaches outlined here can help to guide geographical prioritization and strategy design.

**WEB:** [10.1038/s41467-019-09611-1](https://doi.org/10.1038/s41467-019-09611-1)

**IMPACT FACTOR:** 12.35

**CITED HALF-LIFE:** 1.90

**START COMMENTARY**

Utazi et al. estimated diphtheria-tetanus-pertussis (DTP) and measles vaccination coverage by 1 x 1 km units using the most recent Demographic and Health Surveys for Mozambique (2011), Nigeria (2013), Cambodia (2014), the Democratic Republic of Congo (DRC; 2014), and Ethiopia (2016). For context, refer to supplementary table 8 for a summary of measles supplementary immunization activities occurring over the survey periods. Figure 4 shows the difference in DTP and measles vaccination coverage for the five countries, with overall higher measles coverage especially in DRC and pockets of higher DTP coverage especially in Cambodia and Mozambique. Mapping these differences shed light on the performance of routine immunization programs and supplementary immunization activities and can inform strategic local vaccination efforts. Limitations of the study include potential bias from using maternal recall to establish vaccination status when vaccination
cards were not available as well as higher likelihood of bias among older age cohorts since data for children under 5 years of age were used to estimate coverage of DTP. Furthermore, the study does not capture impact of vaccination campaigns that occur after survey assessment. Authors also note that including additional covariates, such as ethnicity, vaccine refusal, and stockouts, would further improve the predictability of their models.

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3. **Targeting and vaccine durability are key for population-level impact and cost-effectiveness of a pox-protein HIV vaccine regimen in South Africa**


PubMed ID: 30890385

**ABSTRACT**

**BACKGROUND:**
RV144 is to date the only HIV vaccine trial to demonstrate efficacy, albeit rapidly waning over time. The HVTN 702 trial is currently evaluating in South Africa a similar vaccine formulation to that of RV144 for subtype C HIV with additional boosters (pox-protein regimen). Using a detailed stochastic individual-based network model of disease transmission calibrated to the HIV epidemic, we investigate population-level impact and maximum cost of an HIV vaccine to remain cost-effective.

**METHODS:**
Consistent with the original pox-protein regimen, we model a primary series of five vaccinations meeting the goal of 50% cumulative efficacy 24 months after the first dose and include two-yearly boosters that maintain durable efficacy over 10 years. We simulate vaccination programs in South Africa starting in 2027 under various vaccine targeting and HIV treatment and prevention assumptions.

**RESULTS:**
Our analysis shows that this partially effective vaccine could prevent, at catch-up vaccination with 60% coverage, up to 941,000 (15.6%) new infections between 2027 and 2047 assuming current trends of antiretroviral treatment. An impact of up to 697,000 (11.5%) infections prevented could be achieved by targeting age cohorts of highest incidence. Economic evaluation indicates that, if treatment scale-up was achieved, vaccination could be cost-effective at a total cost of less than $385 and $62 per 10-year series (cost-effectiveness thresholds of $5,691 and $750).

**CONCLUSIONS:**
While a partially effective, rapidly waning vaccine could help to prevent HIV infections, it will not eliminate HIV as a public health priority in sub-Saharan Africa. Vaccination is expected to be most effective under targeted delivery to age groups of highest HIV incidence. Awaiting results of trial, the introduction of vaccination should go in parallel with continued innovation in HIV prevention, including studies to determine the costs of delivery and feasibility and further research into products with greater efficacy and durability.
Selinger et al. conduct a stochastic agent-based model study to estimate population-level health impacts and cost-effectiveness of an HIV vaccine in a South African population. HIV vaccine efficacy estimate inputs were based on results of RV144. Authors used a modified EMOD-HIV v2.5 model and defined cost-effective as 1x the 2015 GDP per capita in South Africa as well as 750 US$ per DALY averted. Authors found that the highest health impact would be achieved if 18-year-old women and 23-year-old men were vaccinated. Figure 3 and Table 2 summarize differences in health and economic impact based on various immunization scenarios, including vaccination under “Fast Track with PrEP” and “Status Quo without PrEP.” Limitations of this study include uncertainty in the model inputs related to RV144, which is still under study, and limited economic evaluation (e.g., incorporating off-set costs). Furthermore, more complex behavioral factors, such as risk compensation, were not modeled.
4. **Measles and rubella serosurvey identifies rubella immunity gap in young adults of childbearing age in Zambia: The added value of nesting a serological survey within a post-campaign coverage evaluation survey**

PubMed ID: 30905529

**ABSTRACT**

**BACKGROUND:**
Serological surveys can potentially complement vaccine coverage surveys, such as post-vaccination campaign coverage evaluation surveys (PCES), by providing direct information on population immunity within and outside the target age range of the mass vaccination campaign. We estimate age-specific population immunity to measles and rubella viruses in Southern Province, Zambia, and assess the value of adding serological data to vaccination coverage estimates by nesting a serological survey within a PCES.

**METHODS:**
Dried blood spots (DBS) from fingerprick blood were collected from all individuals ages nine months or older in households participating in the PCES and tested for measles and rubella virus-specific immunoglobulin G (IgG) by enzyme immunoassay (Siemens Enzygnost, Marburg, Germany).

**RESULTS:**
Overall seroprevalence was 95.5% (95% CI: 92.8, 97.2) for measles virus-specific IgG and 97.7% (95% CI: 96.0, 98.7) for rubella virus-specific IgG. Rubella seroprevalence was 98.4% (95% CI: 95.9, 99.4) among children eligible for the MR vaccination campaign, significantly higher than the reported measles-rubella (MR) vaccination campaign coverage of 89.8% (p = 0.003), and higher than the 91.3% rubella seroprevalence for adolescents and adults 16-30 years of age (p = 0.049).

**CONCLUSION:**
Seroprevalence to measles and rubella viruses in children younger than 16 years of age was significantly higher than expected from vaccination coverage estimates, likely reflecting exposure to wild-type viruses and underreporting of vaccination. The serosurvey revealed rubella immunity gaps among women 16-30 years of age, precisely the age group in which protection from rubella is most important to prevent congenital rubella syndrome. Nesting serological surveys within existing surveys can leverage resources and infrastructure while providing complementary information important to immunization programs.
START COMMENTARY

The sampling strategy for both the post-vaccination campaign coverage evaluation survey (PCES) and the serosurvey was a probabilistic two-stage cluster survey with a ward as the primary sampling unit. Five hundred ninety blood samples were included in the study. Authors found high seropositivity for both measles and rubella following the national catch-up measles and rubella vaccination campaign targeting children 9 months to less than 16 years old (see Figure 3 and Table 2). Seroprevalence was higher than reported vaccination coverage estimates, which authors attribute to exposure to wildtype rubella and measles viruses as well as underreporting of measles vaccination as vaccinations received during national measles vaccination campaigns since 2000 were not captured on vaccination cards. This study is subject to potential selection and misclassification bias. Some clusters and households refused to participate in the study. Enzyme immunoassays do not measure functional, protective antibodies, though the impact of the test would suggest the estimates were conservative.

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5. **Modeling the economic impact of different vial-opening thresholds for measles-containing vaccines**


PubMed ID: 30914223

**ABSTRACT**

**INTRODUCTION:**
The lack of specific policies on how many children must be present at a vaccinating location before a healthcare worker can open a measles-containing vaccine (MCV) - i.e. the vial-opening threshold - has led to inconsistent practices, which can have wide-ranging systems effects.

**METHODS:**
Using HERMES-generated simulation models of the routine immunization supply chains of Benin, Mozambique and Niger, we evaluated the impact of different vial-opening thresholds (none, 30% of doses must be used, 60%) and MCV presentations (10-dose, 5-dose) on each supply chain. We linked these outputs to a clinical- and economic-outcomes model which translated the change in vaccine availability to associated infections, medical costs, and DALYs. We calculated the economic impact of each policy from the health system perspective.

**RESULTS:**
The vial-opening threshold that maximizes vaccine availability while minimizing costs varies between individual countries. In Benin (median session size = 5), implementing a 30% vial-opening threshold and tailoring distribution of 10-dose and 5-dose MCVs to clinics based on session size is the most cost-effective policy, preventing 671 DALYs ($471/DALY averted) compared to baseline (no threshold, 10-dose MCVs). In Niger (median MCV session size = 9), setting a 60% vial-opening threshold and tailoring MCV presentations is the most cost-effective policy, preventing 2897 DALYs ($16.05/ DALY averted). In Mozambique (median session size = 3), setting a 30% vial-opening threshold using 10-dose MCVs is the only beneficial policy compared to baseline, preventing 3081 DALYs ($85.98/DALY averted). Across all three countries, however, a 30% vial-opening threshold using 10-dose MCVs everywhere is the only MCV threshold that consistently benefits each system compared to baseline.

**CONCLUSION:**
While the ideal vial-opening threshold policy for MCV varies by supply chain, implementing a 30% vial-opening threshold for 10-dose MCVs benefits each system by improving overall vaccine availability and reducing associated medical costs and DALYs compared to no threshold.
Wedlock et al. used the Highly Extensible Resource for Modeling Supply Chains (HERMES) modeling software to assess the impact of three measles-containing vaccine (MCV) vial-opening threshold policies—no threshold, 30% of doses must be used, or 60% of doses must be used. Vaccine use, availability and wastage by country and scenario are summarized in Table 2. Table 3 summarizes the incremental cost-effectiveness ratios for the MCV vial-opening threshold policies. Limitations to this study include not reporting confidence intervals or uncertainty of the results as well as dated supply chain model inputs (e.g., Benin in 2012, Mozambique in 2014 and Niger in 2011). Authors suggest considering potential impacts of various vial-opening thresholds in context of cold chain constraints.
6. Seasonal gaps in measles vaccination coverage in Madagascar

Mensah K, Heraud JM, Takahashi S, Winter AK, Metcalf CJE, Wesolowski A.
PubMed ID: 30940486

ABSTRACT

INTRODUCTION:
Measles elimination depends on the successful deployment of measles containing vaccine. Vaccination programs often depend on a combination of routine and non-routine services, including supplementary immunization activities (SIAs) and vaccination weeks (VWs), that both aim to vaccinate all eligible children regardless of vaccination history or natural infection. Madagascar has used a combination of these activities to improve measles coverage. However, ongoing massive measles outbreak suggests that the country was in a "honeymoon" period and that coverage achieved needs to be re-evaluated. Although healthcare access is expected to vary seasonally in low resources settings, little evidence exists to quantify temporal fluctuations in routine vaccination, and interactions with other immunization activities.

METHODS:
We used three data sources: national administrative data on measles vaccine delivery from 2013 to 2016, digitized vaccination cards from 49 health centers in 6 health districts, and a survey of health workers. Data were analyzed using linear regressions, analysis of variance, and t-tests.

FINDINGS:
From 2013 to 2016, the footprint of SIAs and VWs is apparent, with more doses distributed during the relevant timeframes. Routine vaccination decreases in subsequent months, suggesting that additional activities may be interfering with routine services. The majority of missed vaccination opportunities occur during the rainy season. Health facility organization and shortage of vaccine contributed to vaccination gaps. Children born in June were the least likely to be vaccinated on time.

DISCUSSION:
Evidence that routine vaccination coverage varies over the year and is diminished by other activities suggests that maintaining routine vaccination during SIAs and VWs is a key direction for strengthening immunization programs, ensuring population immunity and avoiding future outbreaks.

WEB: 10.1016/j.vaccine.2019.02.069
IMPACT FACTOR: 3.29
CITED HALF-LIFE: 5.50
START COMMENTARY

In this study assessing vaccination coverage of measles in Madagascar, Mensah et al. show high coverage levels (>100%) for most regions in Table 1. However, in Table 2, the proportion of children with vaccination cards who are unvaccinated is relatively high (47%). Authors attribute the mismatch to the inability to identify and parse out additional vaccine doses, monthly aggregated vaccine data, and missing data from vaccinations performed outside of a healthcare facility. Misclassification of vaccination strategy responsible for a vaccination is possible since vaccination strategy was determined by time. Authors also noted large spatial heterogeneity that may subject their analysis to other seasonal and vaccine administration influences.

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7. **Defining & assessing the quality, usability, and utilization of immunization data**

Bloland P, MacNeil A.


PubMed ID: 30947703

**ABSTRACT**

**BACKGROUND:**
High quality data are needed for decision-making at all levels of the public health system, from guiding public health activities at the local level, to informing national policy development, to monitoring the impact of global initiatives. Although a number of approaches have been developed to evaluate the underlying quality of routinely collected vaccination administrative data, there remains a lack of consensus around how data quality is best defined or measured.

**DISCUSSION:**
We present a definitional framework that is intended to disentangle many of the elements that have confused discussions of vaccination data quality to date. The framework describes immunization data in terms of three key characteristics: data quality, data usability, and data utilization. The framework also offers concrete suggestions for a specific set of indicators that could be used to better understand immunization those key characteristics, including Trueness, Concordance, Relevancy, Efficiency, Completeness, Timeliness, Integrity, Consistency, and Utilization.

**CONCLUSION:**
Being deliberate about the choice of indicators; being clear on their definitions, limitations, and methods of measurement; and describing how those indicators work together to give a more comprehensive and practical understanding of immunization data quality, usability, and use, should yield more informed, and therefore better, programmatic decision-making.

**WEB:** [10.1186/s12889-019-6709-1](10.1186/s12889-019-6709-1)

**IMPACT FACTOR:** 2.42

**CITED HALF-LIFE:** 3.90

**START COMMENTARY**

Bloland and MacNeil present a well-organized definitional framework for describing and measuring immunization data quality. Authors note that “good agreement between sources does not necessarily guarantee high quality data,” a common measure among data quality studies. They highlight the importance of assessing Trueness, which is defined as “a measure of the degree of agreement between a given measurement and the actual (true) value” as well as factoring in work
force and programmatic considerations into data quality measures. Authors close with a reminder that the pursuit of quality data should be done with the intention to improve health outcomes.

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8. **An agent-based model of dengue virus transmission shows how uncertainty about breakthrough infections influences vaccination impact projections**


PubMed ID: 30893294

**ABSTRACT**

Prophylactic vaccination is a powerful tool for reducing the burden of infectious diseases, due to a combination of direct protection of vaccinees and indirect protection of others via herd immunity. Computational models play an important role in devising strategies for vaccination by making projections of its impacts on public health. Such projections are subject to uncertainty about numerous factors, however. For example, many vaccine efficacy trials focus on measuring protection against disease rather than protection against infection, leaving the extent of breakthrough infections (i.e., disease ameliorated but infection unimpeded) among vaccinees unknown. Our goal in this study was to quantify the extent to which uncertainty about breakthrough infections results in uncertainty about vaccination impact, with a focus on vaccines for dengue. To realistically account for the many forms of heterogeneity in dengue virus (DENV) transmission, which could have implications for the dynamics of indirect protection, we used a stochastic, agent-based model for DENV transmission informed by more than a decade of empirical studies in the city of Iquitos, Peru. Following 20 years of routine vaccination of nine-year-old children at 80% coverage, projections of the proportion of disease episodes averted varied by a factor of 1.76 (95% CI: 1.54-2.06) across the range of uncertainty about breakthrough infections. This was equivalent to the range of vaccination impact projected across a range of uncertainty about vaccine efficacy of 0.268 (95% CI: 0.210-0.329). Until uncertainty about breakthrough infections can be addressed empirically, our results demonstrate the importance of accounting for it in models of vaccination impact.

**WEB:** [10.1371/journal.pcbi.1006710](10.1371/journal.pcbi.1006710)

**IMPACT FACTOR:** 3.96

**CITED HALF-LIFE:** 4.30

**START COMMENTARY**

In this agent-based model, Perkins et al. finds uncertainty in the Dengue vaccine and breakthrough infections. Authors note that their study is intended to inform future modeling studies of the
uncertainty of vaccine efficacy data inputs and caution any inference beyond the confines of the study. The authors comment that other important factors also influence population protection, including vaccination coverage and contact structure.
9. **Effect of household relocation on child vaccination and health service utilisation in Dhaka, Bangladesh: a cross-sectional community survey**

Horng L, Kakoly NS, Abedin J, Luby SP.


PubMed ID: 30878989

**ABSTRACT**

**OBJECTIVE:**
To explore the relationship between household relocation and use of vaccination and health services for severe acute respiratory illness (ARI) among children in Dhaka, Bangladesh.

**DESIGN:**
Analysis of cross-sectional community survey data from a prior study examining the impact of Haemophilus influenzae type b vaccine introduction in 2009 on meningitis incidence in Bangladesh.

**SETTING:**
Communities surrounding two large paediatric hospitals in Dhaka, Bangladesh.

**PARTICIPANTS:**
Households with children under 5 years old who either recently relocated ≤12 months or who were residentially stable living >24 months in their current residence (total n = 10,020) were selected for this study.

**PRIMARY OUTCOME MEASURES:**
Full vaccination coverage among children aged 9-59 months and visits to a qualified medical provider for severe ARI among children under 5 years old.

**RESULTS:**
Using vaccination cards with maternal recall, full vaccination was 80% among recently relocated children (n = 3795) and 85% among residentially stable children (n = 4713; \(\chi^2 = 37.2, p < 0.001\)). Among children with ARI in the prior year, 69% of recently relocated children (n = 695) had visited a qualified medical provider compared with 82% of residentially stable children (n = 763; \(\chi^2 = 31.9, p < 0.001\)). After adjusting for demographic and socioeconomic characteristics, recently relocated children were less likely to be fully vaccinated (prevalence ratio [PR] 0.97; 95% CI 0.95 to 0.99; p = 0.016) and to have visited a qualified medical provider for ARI (PR 0.88; 95% CI 0.84 to 0.93; p < 0.001).

**CONCLUSIONS:**
Children in recently relocated households in Dhaka, Bangladesh, have decreased use of vaccination and qualified health services for severe ARI.
In this secondary analysis of the Hib impact study, Horng et al. found an association between child relocation and vaccination and health services for acute respiratory infection. Authors note that the study may not be generalizable to urban areas. Key information regarding distances moved or frequency of moving was not obtained. The analysis did not include cost of services, which is a known barrier. This study highlights the need to address healthcare needs of relocated children populations.

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10. **Prioritizing the scale-up of interventions for malaria control and elimination**

Winskill P, Walker PG, Cibulskis RE, Ghani AC.


PubMed ID: 30961603

**ABSTRACT**

**BACKGROUND:**
A core set of intervention and treatment options are recommended by the World Health Organization for use against falciparum malaria. These are treatment, long-lasting insecticide-treated bed nets, indoor residual spraying, and chemoprevention options. Both domestic and foreign aid funding for these tools is limited. When faced with budget restrictions, the introduction and scale-up of intervention and treatment options must be prioritized.

**METHODS:**
Estimates of the cost and impact of different interventions were combined with a mathematical model of malaria transmission to estimate the most cost-effective prioritization of interventions. The incremental cost effectiveness ratio was used to select between scaling coverage of current interventions or the introduction of an additional intervention tool.

**RESULTS:**
Prevention, in the form of vector control, is highly cost effective and scale-up is prioritized in all scenarios. Prevention reduces malaria burden and therefore allows treatment to be implemented in a more cost-effective manner by reducing the strain on the health system. The chemoprevention measures (seasonal malaria chemoprevention and intermittent preventive treatment in infants) are additional tools that, provided sufficient funding, are implemented alongside treatment scale-up. Future tools, such as RTS,S vaccine, have impact in areas of higher transmission but were introduced later than core interventions.

**CONCLUSIONS:**
In a programme that is budget restricted, it is essential that investment in available tools be effectively prioritized to maximize impact for a given investment. The cornerstones of malaria control: vector control and treatment, remain vital, but questions of when to scale and when to introduce other interventions must be rigorously assessed. This quantitative analysis considers the scale-up or core interventions to inform decision making in this area.


**IMPACT FACTOR:** 2.85

**CITED HALF-LIFE:** 4.00
START COMMENTARY

Figure 4 shows cost-effectiveness of LLINs, treatment, and RTS,S. Authors note that surveillance, monitoring and evaluation activities were not included in this analysis, which could be included in future study, as well as the impact of drug resistance and other key drivers related to cost.

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Appendix

The literature search for the May 2019 Vaccine Delivery Research Digest was conducted on April 25, 2019. We searched English language articles indexed by the US National Library of Medicine and published between March 15, 2019 and April 14, 2019. The search resulted in 213 items.

Search Terms