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From current vaccine recommendations to everyday practices: An analysis in five sub-Saharan African countries

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ABSTRACT

Background: Estimates of WHO and UNICEF vaccination coverage may provide little insight into the extent to which vaccinations are administered on time. Yet, lack of adherence to the recommended age to receive a specific vaccination may have detrimental health consequences. For example, delays in receiving vaccination will prolong the risk of lack of protection, often when disease risk is highest, such as during early infancy. We estimated the reported age at vaccination, and vaccine coverage at different ages in children from five sub-Saharan African countries.

Methods: We analyzed data from the latest Demographic and Health Programme databases available for Burkina Faso 2010 (n = 15,044 observations), Ghana 2008 (n = 2992), Kenya 2008–9 (n = 6079), Senegal 2010–11 (n = 12,326), and Tanzania 2010 (n = 8023). We assessed, amongst vaccinees, the exact age when vaccine was administered for the three infant doses of pentavalent vaccine (DTP) and the first dose of measles-containing-vaccine (MCV), as well as the proportion of children immunized with these antigens by a certain age. Vitamin A supplementation (VAS) coverage was evaluated as a potential contact visit for vaccine introduction.

Results: For all DTP doses, the median intervals between recommended and actual ages of receiving vaccination ranged from 12, 17 and 23 days in Kenya, to 22, 33 and 45 days in Senegal. MCV was mostly given during the recommended age of 9 months. In each country, there was a large discrepancy in the median age at DTP vaccination between regions. VAS coverage in young children ranged from 30.3% in Kenya to 78.4% in Senegal, with large variations observed between areas within each study country.

Conclusion: In the context of new vaccine introduction, age of children at vaccination should be monitored to interpret data on vaccine-preventable disease burden, vaccine effectiveness, and vaccine safety, and to adapt targeted interventions and messages.

1. Introduction

As a result of the strengthening of the Expanded Programme on Immunization (EPI) starting four decades ago, and more recently with the support of Gavi, the Vaccine Alliance (formerly the Global Alliance for Vaccines and Immunization), global child deaths from vaccine-preventable diseases have dramatically decreased in Africa. In addition to the large impact of measles vaccination on child survival [1], these advances are also due to the introduction of five new vaccines to national vaccination plans (i.e., vaccines against *Haemophilus influenzae type b*, hepatitis B virus, pneumococcus, rotavirus, and meningococcus A), and to the reinforcement of vaccine implementation strategies and monitoring, driven by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF). The possible introduction of a vaccine against malaria in the coming years may further improve child health and survival in malaria endemic areas.

In the context of vaccine evaluation, the design of effectiveness, post-introduction impact, and safety studies depends on vaccination coverage and timeliness data. Vaccination coverage rates are often estimated based on programmatic data (i.e., by dividing the number of doses distributed or administered by the estimated

Abbreviations: DHS, Demographic and Health Surveys; DTP, diphtheria, pertussis, and tetanus; DTwP, diphtheria, tetanus, and whole-cell pertussis; EPI, Expanded Programme on Immunization; hepB, hepatitis B; Hib, *Haemophilus influenzae* type B; IQR, interquartile range; MCV, measles-containing vaccine; PCV, pneumococcal conjugate vaccine; UNICEF, United Nations Children's Fund; VAS, vitamin A supplementation; WHO, World Health Organization; YFV, yellow fever vaccination.

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target population sizes). The resulting estimations may be unreliable where the target population size is poorly known [2], or when only the distributed doses are reported. To mitigate this issue, WHO-UNICEF currently emphasizes the need for more precise estimates combining various sources of information: reports by national authorities, survey data, and views of local country experts [3]. In addition to precisely defining coverage, age at vaccination is important to assess the performance of a vaccination programme, and previous studies document that high coverage does not necessarily imply timely vaccination [4,5]. Substantial childhood vaccinations delays were described in low-to-middle [6], and high income countries [7–9]. African children may also experience a gap between recommended and actual vaccine schedules [10]. Published analyses have revealed that adherence to recommended schedules varies substantially within and between African countries [6,10–14], a finding confirmed by recent manuscripts [15–18].

Delays in receipt of specific doses or completing a childhood vaccination series could benefit an individual child by inducing a stronger immune response, ensuring a prolonged duration of protection. However, regardless of completion of the full schedule, children with delayed vaccination, experience longer periods of increased susceptibility to the vaccine preventable disease, as reported for pertussis [19] or *Haemophilus influenza type b* (Hib) invasive disease [20]. In addition, delay at vaccination may raise safety concerns depending on the age related risk of adverse events, as exemplified by the *RotaShield*™ (Wyeth-Ayerst, Philadelphia, PA, USA) vaccination against rotavirus, that was associated with an increased intussusceptions risk among children age greater than 12 weeks [21]. Policy decision makers recommend schedules by trying to balance duration of immunity with period of risk assuming that children will receive vaccine at the recommended age.

In sub-Saharan Africa, recent vaccines such as rotavirus vaccine (RotaTeq™ and Rotarix™), pneumococcal conjugate vaccine (PCV) (Prevnar-13™ and Synflorix™), and serogroup A meningococcal conjugate vaccine (MenAfriVac™) were designed to protect infants and young children when administered between 6 weeks and 2 years of age, depending on the vaccine. The RTS,S/AS01 malaria vaccine candidate may be integrated into the national vaccine programme of sub-Saharan African countries, either with a primary series of three doses concurrent with diphtheria, tetanus, and pertussis (DTP) containing vaccines during early infancy or starting in children between 5 and 17 months of age [22].

In this article, we estimated the reported age at vaccination, and vaccine coverage at different ages in children from the first five sub-Saharan African countries where the RTS,S/AS01 candidate malaria vaccine may be introduced, namely Burkina Faso, Ghana, Kenya, Senegal and Tanzania. These countries have been identified as early adopters because they represent a broad spectrum of malaria endemicity and each has the capacity to perform vaccine safety evaluations. To evaluate the potential deviation from the age recommended for vaccination within the EPI schedule, we analyzed age at vaccination and administration of the three primary doses of DTP combined with hepatitis B (hepB) and Hib conjugate vaccine (abbreviated as DTP1, DTP2 and DTP3), as well as measles-containing vaccine (MCV).

An earlier analysis provided data on immunization delays globally during 1996–2005 [10]. Our study advances beyond this by including more recent data, a critical issue given the large investments made in improving immunization services, including in Africa. Additionally, we considered sub-national delays in immunization, since immunization service delivery may vary considerably within African countries. Lastly, current international recommendations call for children age 6–59 months living in high risk areas to receive a single dose of yellow fever vaccination (YFV) introduced into routine immunization programmes, and one dose of Vitamin A supplementation (VAS) in children from 6 to 11 months and every 4–6 months in children 12–59 months of age [23]. Consequently, we also investigated timeliness for YFV visits, and coverage for VAS contacts, as they may serve as contacts for new vaccine interventions.

2. Methods

We used publically available data from the programme Demographic and Health Surveys (DHS),[1] which generates data from nationally representative household surveys [24]. The standard DHS have large sample sizes and use a two-stage sampling design, with a first selection of primary clusters from a list of enumeration areas, followed by a second random selection of households from each cluster [25]. Eligible women of reproductive age are interviewed using an individual standard questionnaire and asked to show the health cards of their children born in the 5 years before the survey to document the date each vaccine dose was administered. When no card is presented, the mother is asked to recall vaccinations dates. An analysis of retrospective data was conducted from the latest standard DHS surveys databases available for the five study countries: Burkina Faso 2010, Ghana 2008, Kenya 2008–9, Senegal 2010–11 and Tanzania 2010. For each country, the numbers of children aged 0–5 years born from sub-sampled women, were 15,044, 2992, 6079, 12,326 and 8023, respectively. We limited our analysis to children who had complete (day, month, year) birth and vaccination dates recorded on a vaccination card.

For each vaccination dose (DTP1, DTP2, DTP3, MCV, and YFV when data were available), we estimated the mean, median and interquartile ranges (IQRs) for age at vaccination in each study country. WHO does not have a universal, biologically defined schedule for DTP immunization, but rather provides recommendation on appropriate ranges. Consequently, we created a reference standard based on each country's national programmatic standards. For DTP1, DTP2, and DTP3 vaccinations, this included: days 56, 84 and 112 in Burkina Faso; days 42, 70 and 98 in Ghana, Kenya and Senegal; and days 28, 56 and 84 in Tanzania. For MCV-related calculations, we used when the child was age 9 months (i.e., the 10th month of life or 274–304 days as a reference. We calculated the time interval between the observed age at vaccination and the reference date recommended for vaccination. The ages for vaccination were converted to days based on 30.4375 days per month. In each country, medians and percentile (25th and 75th) durations before and after the reference dates were determined for each vaccine dose, and the numbers and proportions of children vaccinated outside the reference dates were calculated.

For analysis, we used the sampling weights provided in each DHS dataset to extrapolate sample data to the entire population of each country. To adjust for clusters and strata, the survey design applied considered the following variables: sample weight, primary sampling unit, type of place of residence (urban/rural) and region. For vaccination dose uptake estimation, we used the Kaplan Meyer survival analysis method to describe time-to-event data [7,26]. Children with missing dates of vaccination were excluded from individual analyses. For children with valid dates for birth and vaccination, we calculated coverage at age-appropriate time points, and ages at which 95% and 99% of vaccinated children received their injection.

We used the DHS Programme STATcompiler tool version1.5.2 [27] to generate descriptive data within various stratification categories. We calculated age at DTP and measles vaccination by administrative region within each country. We calculated DTP and

[1] For more information on the DHS programme, see http://dhsprogram.com/.