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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/.

MCV coverage by source of information (vaccination card, mother's report and either source). Lastly, we calculated VAS coverage by administrative region and child's age at interview. From the original DHS programme databases, we extracted data and created working databases to perform our statistical analyses using Stata v.10 software (StataCorp LP, College Station, Texas, USA). The "rcentile" package (www.imperial.ac.uk/nhli/r.newson/stata.htm) was used to calculate robust confidence intervals for percentiles, allowing for clustered sampling and weighting.

3. Results

3.1. Median age at vaccination

In Kenya, Ghana, and Senegal, the recommended age at DTP1 vaccination was 42 days and the actual median estimates were 48, 56, and 59 days, respectively; DTP2 was scheduled at 70 days and was given at median ages of 82, 92, and 98 days, respectively; and DTP3 was recommended at 98 days, and median ages were 115, 128, and 137 days, respectively (Table 1). In Burkina Faso, where DTP doses were to be received at 56, 84, and 112 days, estimated median ages for DTP doses were 66, 101, and 137 days, while in Tanzania, where DTP doses were scheduled at 28, 56 and 84 days, median ages at vaccination were 44, 83, and 123 days. In all five countries, measles vaccination was mostly given within the recommended age of 9 months (i.e., before the 10th month of age), with the median age at MCV injection ranging from 274 to 305 days. Where YFV was listed in the DHS Programme databases (Burkina Faso, Kenya, and Senegal), the median age at injection was consistent with the recommended age of 9 months.

Within countries, substantial variation in age of DTP vaccination was seen but not for MCV (Appendix Tables A1 to A5). The highest variations were described for DTP3, with differences between the reference date of vaccination and the actual injection varying by 53 days between regions, both in Ghana (from 23 days difference in Brong-Ahafo to 76 days in the Northern region), and in Kenya (from 7 days in Central to 60 days in North Eastern regions).

3.2. Deviations from recommended schedules

We estimated the difference in days before and after the reference dates for DTP1, DTP2, DTP3, and MCV (Table 2). Among vaccinees receiving their DTP dose after the reference day, depending on the country, the median time interval ranged from 12 to 22 days for DTP1, from 17 to 33 days for DTP2, and from 23 to 45 days for DTP3. For all doses, the shortest median time interval was always observed in Kenya, while the highest was observed in Senegal (Table 2). A quarter of the children received DTP1 injection nine days or less after the reference date, DTP2 two weeks or less after the reference date, and DTP3 3 weeks or less after the reference date. In Senegal, where time intervals were the greatest, 75% DPT1 coverage was achieved at 47 days after the reference date; for DTP2 and DTP3, 75% coverage was attained at 67 and 96 days, respectively. In all countries, median time intervals were approximately twice as long for DTP3 as for DTP1. For vaccinees receiving DTP vaccination before the reference date, median early deliveries were similar for all doses in all countries (7 days for DTP1 in Senegal and for DTP3 in Ghana and Kenya, and up to 12 days for DTP3 in Senegal).

For MCV, among the 34% of children vaccinated after age 9 months (i.e., after day 304 of life), half had time intervals of two months or more (61 ± 3 days in Burkina Faso, Ghana and Tanzania; 76 days in Kenya and Senegal). The 75th percentile delays were 99 days in Burkina Faso and up to 170 days in Kenya. Unlike with DTP, Kenya had the longest median delay for MCV. For vaccinees receiving MCV early, 75% were vaccinated when they were age 8 months.

Table 1
Estimates of age at vaccination for DTP1, DTP2, DTP3, measles and yellow fever vaccines in the five study countries.

	Burkina Faso 2010	Ghana 2008	Kenya 2008–09	Senegal 2010–11	Tanzania
DTP1 vaccination					
Reference date	*56 days*	*42 days*	*42 days*	*42 days*	*28 days*
Children with DTP1 done	12,027	2494	5034	10,132	6878
Children with accurate age at vaccination for DTP1	4430	1842	3076	1702	5207
Mean age (St. Err.)	75.27 (0.83)	68.79 (1.74)	65.34 (2.38)	75.16 (2.16)	60.86 (na)
Median age (IQR)	66 [60–79]	56 [45–72]	48 [43–65]	59 [46–80]	44 [34–64]
DTP2 vaccination					
Reference date	*84 days*	*70 days*	*70 days*	*70 days*	*56 days*
Children with DTP2 done	11,571	2346	4706	9498	6521
Children with accurate age at vaccination for DTP2	4227	1772	2932	1574	4958
Mean age (St. Err.)	113.03 (1.01)	110.72 (2.23)	101.51 (2.53)	119.23 (2.99)	106.08 (na)
Median age (IQR)	101 [92–119]	92 [79–116]	82 [73–105]	98 [80–129]	83 [67–113]
DTP3 vaccination					
Reference date	*112 days*	*98 days*	*98 days*	*98 days*	*84 days*
Children with DTP3 done	10,861	2098	4121	8572	6088
Children with accurate age at vaccination for DTP3	4034	1677	2679	1444	4660
Mean age (St. Err.)	153.62 (1.34)	152.96 (2.45)	139.41 (2.82)	170.30 (4.21)	152.25 (na)
Median age (IQR)	137 [124–162]	128 [112–161]	115 [104–145]	137 [114–186]	123 [101–166]
Measles vaccination					
Reference date	*9 months = 274–304 days*				
Children with MCV done	9845	2042	3964	8348	5404
Children with accurate age at vaccination for MCV	3445	1446	2124	1160	3910
Mean age (St. Err.)	299.47 (1.79)	316.02 (3.1)	317.89 (4.68)	327.57 (6.61)	320.12 (na)
Median age (IQR)	284 [273–304]	294 [276–321]	287 [275–318]	288 [274–330]	295 [280–325]
Yellow fever vaccination					
Reference date	*9 months = 274–304 days*				
Children with YF done	6922	na	na	8161	na
Children with accurate age at vaccination for YF	3450	na	182	1144	na
Mean age (St. Err.)	300.04 (1.78)	na	334.12 (na)	333.9 (6.83)	na
Median age (IQR)	284 [273–304]	na	290 [252–347]	290 [276–331]	na

Data are calculated from the latest available DHS programme databases. Reference dates for vaccination are in *italics*.

Table 2
Duration between reference day of vaccination and actual injection, before and after the reference date: 25th, 50th and 75th percentile duration, by country.

Vaccines	Delays percentiles and IQR	Burkina Faso Time to the vaccination (in days)			Ghana Time to the vaccination (in days)			Kenya Time to the vaccination (in days)			Senegal Time to the vaccination (in days)			Tanzania Time to the vaccination (in days)		
			Before reference date	After reference date		Before reference date	After reference date		Before reference date	After reference date		Before reference date	After reference date		Before reference date	After reference date
DTP1	*Reference date*	*56 days*			*42 days*			*42 days*			*42 days*			*28 days*		
	(Nt); (Nb); (Na)	(4430)	(648)	(3709)	(1842)	(216)	(1554)	(3076)	(555)	(2281)	(1702)	(223)	(1459)	(5207)	(261)	(4893)
	25th		19	6		20	9		17	4		18	8		19	9
	50th		11	13		8	19		7	12		9	22		9	20
	75th		6	26		3	36		3	31		3	47		3	38
	IQR		*13*	*20*		*17*	*27*		*14*	*27*		*15*	*39*		*16*	*29*
DTP2	*Reference date*	*84 days*			*70 days*			*70 days*			*70 days*			*56 days*		
	(Nt); (Nb); (Na)	(4227)	(438)	(3748)	(1772)	(147)	(1589)	(2932)	(409)	(2399)	(1574)	(120)	(1439)	(4958)	(151)	(4787)
	25th		17	10		16	14		19	6		22	15		18	15
	50th		10	19		9	26		8	17		10	33		10	30
	75th		5	37		4	51		3	41		5	67		3	57
	IQR		*12*	*27*		*12*	*37*		*16*	*35*		*17*	*52*		*15*	*42*
DTP3	*Reference date*	*112 days*			*98 days*			*98 days*			*98 days*			*84 days*		
	(Nt); (Nb); (Na)	(4034)	(302)	(3701)	(1677)	(89)	(1562)	(2679)	(289)	(2317)	(1444)	(78)	(1352)	(4660)	(95)	(4558)
	25th		15	14		16	18		17	9		20	22		21	21
	50th		11	27		7	35		7	23		12	45		11	41
	75th		5	51		3	72		4	54		4	96		4	80
	IQR		*10*	*37*		*13*	*54*		*13*	*45*		*16*	*74*		*17*	*59*
Measles	*Reference date*	*9 months = 274–304 days*			*9 months = 274–304 days*			*9 months = 274–304 days*			*9 months = 274–304 days*			*9 months = 274–304 days*		
	(Nt); (Nb); (Na)	(3445)	(873)	(843)	(1446)	(296)	(546)	(2126)	(514)	(683)	(1160)	(254)	(433)	(3910)	(534)	(1546)
	25th		20	40		31	42		34	44		30	45		26	44
	50th		8	58		15	62		16	76		11	76		12	64
	75th		4	99		6	128		5	170		5	156		4	111
	IQR		*16*	*59*		*25*	*86*		*29*	*126*		*25*	*111*		*22*	*67*

Reference days and percentile difference from recommended date, are in days. The total number of vaccinees for a specific dose (Nt), the number of vaccinees vaccinated before (Nb) and after (Na) the reference date are indicated.

3.3. Coverage by age among vaccinees

Using DHS data, and based on both vaccination cards and mother's report, we found that the proportion of 12–23 month old children vaccinated with DTP1 and DTP2 at any time before the survey was over 90%. In the same population, DTP3 coverage ranged from 83% in Senegal to nearly 90% in Burkina Faso. MCV coverage ranged from 82% in Senegal to 90% in Ghana (Table A6 in Appendix).

Among vaccinated children for whom a precise date of vaccination is available, the percent of children who had received DTP vaccine by the recommended date for each dose was relatively

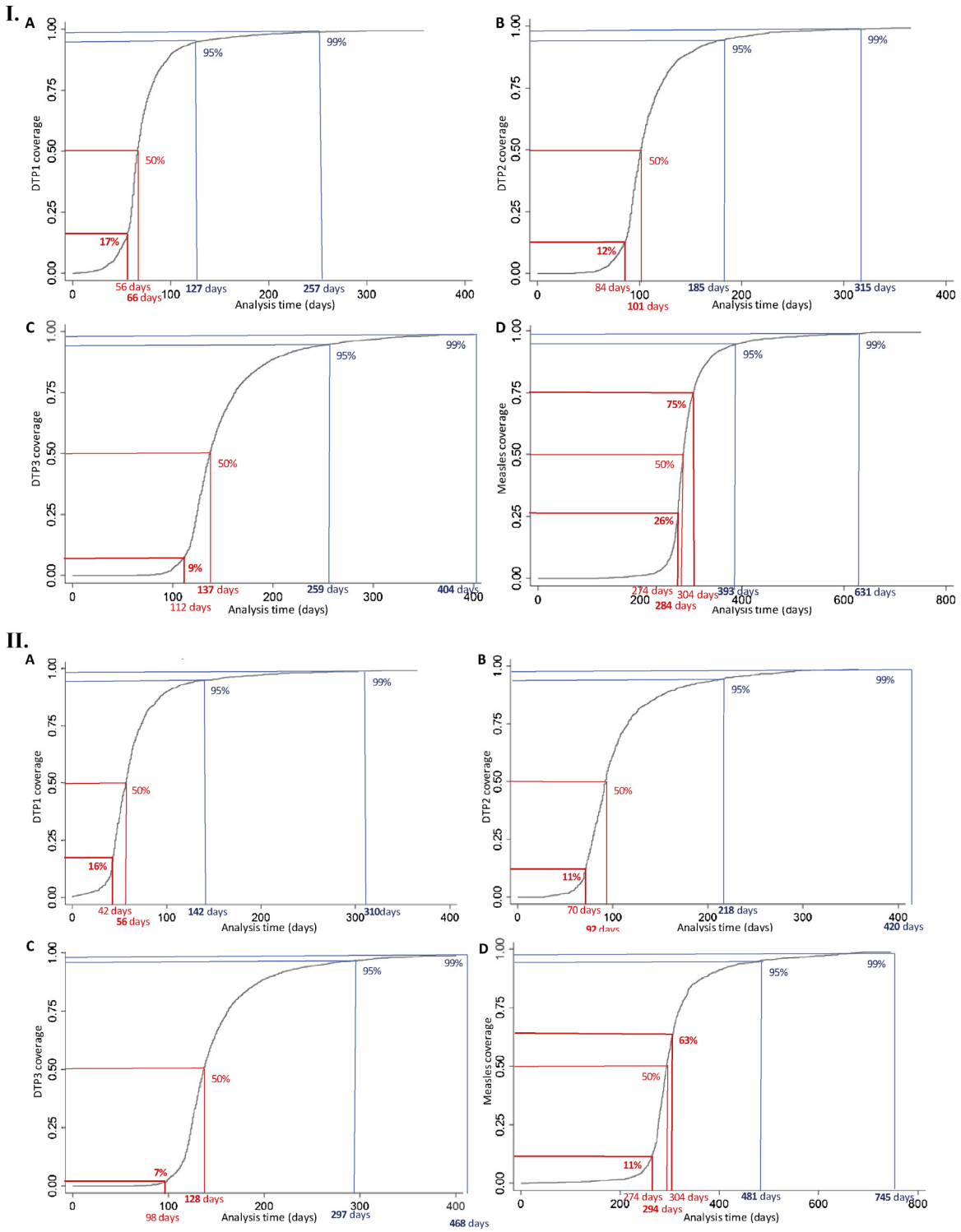

Fig. 1. Inverse Kaplan–Meyer estimate for DTP and measles vaccination coverage: (A) DTP1; (B) DTP2; (C) DTP3; (D) MCV. Footnote: In bold red, percent of vaccinees receiving vaccine by the recommended age (for MCV, two lines represents the lowest and highest boundaries of the 10th month), and in red, age at which 50% of vaccinees are vaccinated. In blue, age at which 95% and 99% of vaccinees received vaccination. Coverage are given for (I) Burkina Faso; (II) Ghana; (III) Kenya; (IV) Senegal and (V) Tanzania. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

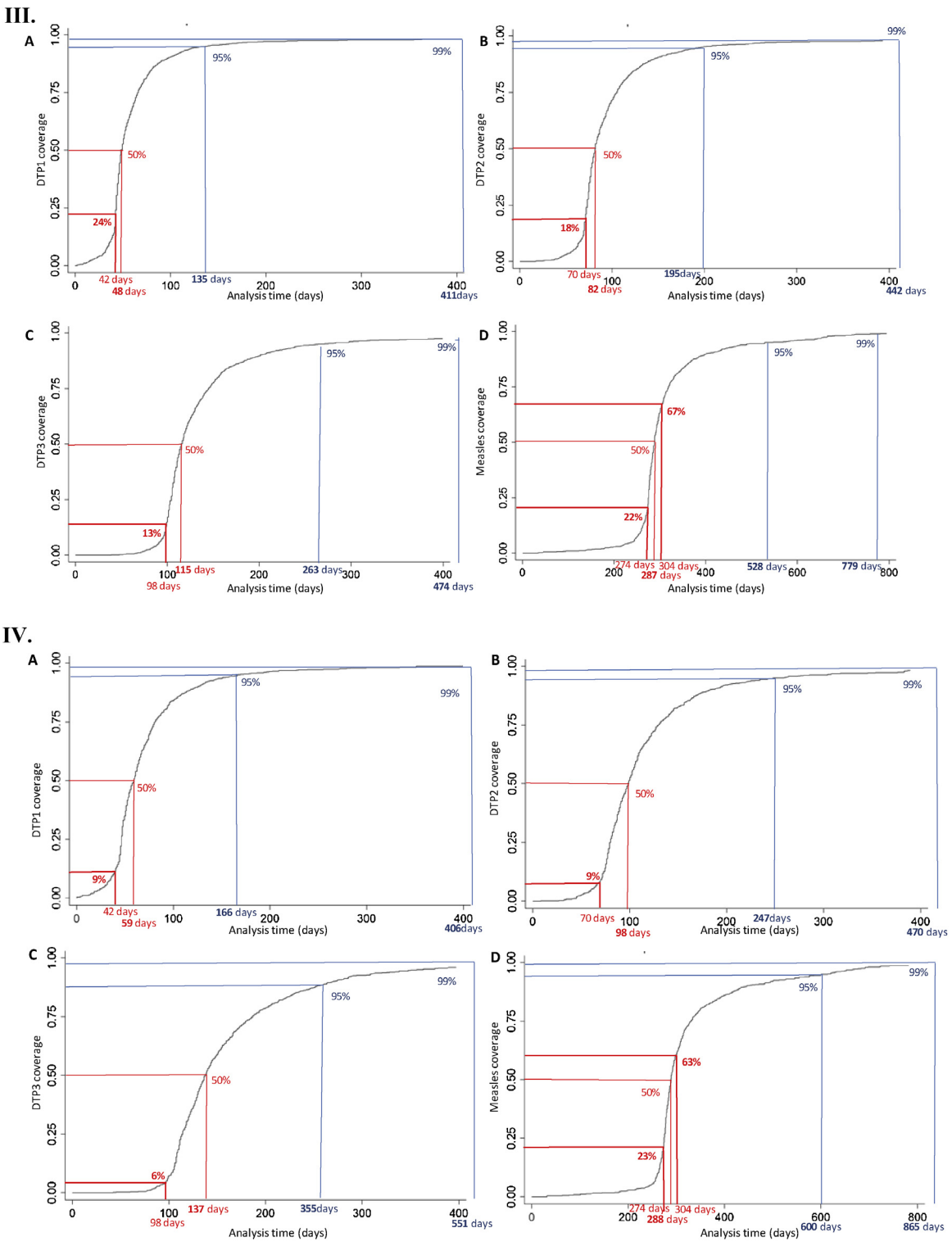

Fig. 1. (*Continued*).

low and varied by country (Fig. 1I–V): from 6.5%, 3.5%, and 2.3% in Tanzania, to 24%, 18%, and 13% in Kenya, for DTP1-3, respectively. By the end of the 10th month, over 60% of vaccinees had received MCV (from 61% in Tanzania to 75% in Burkina Faso). The median age in days at which 95% of vaccinees had received the four different study vaccines was highest in Senegal at 166, 247, 355 and 600 days for DTP1-3 and MCV, respectively; while the earliest was reached in Burkina Faso, at 127, 185, 259, and 393 days for DTP1-3 and MCV, respectively.

3.4. Vitamin A administration

VAS coverage was described in the study countries using the latest DHS data (Table 3). The lowest coverage was observed in Kenya

Table 3
Vitamin A supplement intake coverage, by children age group at interview.

Demographic & Health Survey	Vitamin A supplement intake coverage Children age group at interview (in months)						Total
	6–9	10–11	12–23	24–35	36–47	48–59	
Burkina Faso 2010	61.6 (1015)	72.7 (473)	66.7 (2822)	64.5 (2729)	61.3 (2821)	57.9 (2613)	63.0 (12,473)
Ghana 2008	72.3 (191)	74.6 (111)	67.0 (552)	52.8 (496)	49.3 (506)	43.9 (559)	55.8 (2414)
Kenya 2008–09	46.7 (419)	60.9 (187)	40.9 (1096)	25.9 (1132)	21.8 (1071)	20.4 (1041)	30.3 (4946)
Senegal 2010–11	66.4 (690)	75.4 (409)	81.2 (2199)	80.0 (2195)	77.9 (2234)	78.7 (1963)	78.4 (9689)
Tanzania 2010	42.4 (499)	65.0 (302)	67.4 (1576)	60.5 (145)	60.9 (1567)	59.2 (143)	60.8 (6824)

Percentage and number of children aged 6–59 months who received vitamin A supplements in the six months preceding the surveys. DHS Programme STAT compiler, http://www.statcompiler.com – March 24, 2015.

2009 with 30.3% of children under age five years supplemented during the 6 months preceding the survey; and the highest described in Senegal 2010–2011 with 78.4% coverage. In all countries, children less than 2 years old were more likely to have received VAS. In Burkina Faso, Ghana and Kenya, children were the most likely to have received VAS within the first year of life, with 72.7%, 74.6% and 60.9%, respectively. In Senegal and Tanzania, the highest VAS coverage was reported for the 6–23 month age group (12–23 months at interview), with 81.3% and 67.4% coverage, respectively. Large variations in VAS coverage were observed within each study country, depending on region and type of residence of the children, with the highest difference described in Tanzania (nearly 70% difference between Shinyanga and Iringa), and Burkina Faso (54% difference between Sahel and Centre Sud) (Table A7 to A11 in Appendix).

4. Discussion

In our study population, we showed high vaccine coverage among infants and young children in five sub-Saharan African low-income countries. We showed a global trend towards administration of DTP3 and measles vaccination beyond the recommended age. A similar pattern has been described for other sub-Saharan settings, including Kenya, South Africa, Uganda, Malawi, Nigeria, Tanzania, and The Gambia [13–15,28–31]. While the data derive from different areas and use different methods, as a whole, and in combination with our study, they indicate a long-standing issue with timely infant vaccination in sub-Saharan Africa. The degree to which this low compliance to schedules occurs has varied within and between countries [6,10]. Our results also showed regional disparities of vaccination timeliness, with Ghana and Kenya displaying the largest variations.

Several factors might explain the variation observed, such as increasing distance to the clinic, immunization administration outside a health facility [30,32–35], and low health worker density [36]. Rural areas, often with limited health services, may have populations who are less compliant to schedules than urban populations. For example in Ghana, rural areas [16] had longer delays from recommended schedules than urban areas [35]. Even within a rural area, such as rural Malawi, more remote settings with no access to vaccination teams had poorer compliance [32]. Childhood vaccination is often conducted via outreach by public health nurses where all children in a village receive their dose on the same day, possibly leading to age-inappropriate vaccinations. However, the generalization of increased risk in rural areas is not universal. Rural children in Burkina Faso had timelier receipt of vaccination than urban children, probably due to greater access to mobile vaccination teams [17]. Compliance to schedules may also be less among children of lower socioeconomic status and born to less educated mothers, as has been shown in Senegal [37], Ghana [16], Burkina Faso [17], Malawi [30], Uganda [34], Tanzania [14], and South Africa [28]. Another significant known predictor of timely vaccine coverage is seasonality, with delays observed during the rainy season [13,32]. In addition, it was reported that delays in previous vaccinations increased the likelihood of further delays in later vaccinations [15,31].

In theory, new interventions, such as use of malaria vaccine outside of routine infant DTP schedules, could take advantage of other interventions such as VAS. However, we found that VAS coverage is relatively low, higher in urban zones, and with large variations within and between countries. To result in a measurable impact on child survival at the population level, at least 80% of children in this age group should receive VAS twice a year [38], with an optimal interval between two VAS doses of four to six months [39]. Even after several years of implementation, VAS programmes still depend on opportunistic contacts (measles vaccination, National Immunization Days for polio eradication, multi-antigens catch-up campaigns), or on National Child Health Days as key delivery mechanisms. Incorporation of additional routine interventions into the VAS encounter thus will require additional investment including increased human resources and sustainable financing. In addition, this will require a commitment by countries to incorporating immunization into routine encounters outside of infancy.

Our study had limitations. Only children with a vaccination card available were included and they do not represent all children within the surveyed communities, as these children may be more likely to have received timely vaccination. We also did not assess reasons why vaccinations were delayed. This information could improve performance of vaccination programmes, helping them to focus on sub-populations with increased risk of low compliance.

Our study leads to several recommendations. As with vaccination coverage, levels of poor compliance to vaccination schedules likely will vary by time and place, and monitoring of vaccination schedule should be incorporated into routine programme management. Specific community-based contextual information should be investigated to explain low levels of timely vaccination, since this can assist with identifying profiles for at-risk populations, and thus facilitate social messaging and other targeted interventions. Any interventions should consider previous findings showing that restricting the age for vaccination may decrease coverage by increasing missed opportunities for vaccination [40]; this is particularly true since achieving full vaccination, even if delayed, is likely to be of more public health value than timely but incomplete vaccination receipt. Emphasis on vaccine timeliness may have the unintended consequence of increasing the number of doses given too early, which could manifest as vaccines given at an age when immune responses are less (especially the first dose) or with an interval too short to optimize the booster effect. Lastly, our findings have implications for using existing intervention schedules for new vaccines, particularly during impact evaluations. Specifically, in addition to coverage, actual age of vaccination should be monitored to interpret results related to measured

vaccine-preventable disease burden, vaccine effectiveness, and vaccine safety.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.10.107.

References

[1] Wkly Epidemiol Rec 2008;83(49):441–8.
[2] Murray CJ, Shengelia B, Gupta N, Moussavi S, Tandon A, Thieren M. Validity of reported vaccination coverage in 45 countries. Lancet 2003;362:1022–7.
[3] Burton A, Monasch R, Lautenbach B, Gacic-Dobo M, Neill M, Karimov R, et al. WHO and UNICEF estimates of national infant immunization coverage: methods and processes. Bull World Health Organ 2009;87:535–41.
[4] Akmatov MK, Kretzschmar M, Krämer A, Mikolajczyk RT. Timeliness of vaccination and its effects on fraction of vaccinated population. Vaccine 2008;26:3805–11, http://dx.doi.org/10.1016/j.vaccine.2008.05.031 [Epub 2008 June].
[5] Fadnes LT, Nankabirwa V, Sommerfelt H, Tylleskär T, TumwineF J.K., Engebretsen IM. Is vaccination coverage a good indicator of age-appropriate vaccination? A prospective study from Uganda. Vaccine 2011;29:3564–70, http://dx.doi.org/10.1016/j.vaccine.2011.02.093.
[6] Akmatov MK, Mikolajczyk RT. Timeliness of childhood vaccinations in 31 low and middle-income countries. J Epidemiol Community Health 2012;66:e14, http://dx.doi.org/10.1136/jech.2010.124651.
[7] Laubereau B, Hermann M, Schmitt HJ, Weil J, vonKries R. Detection of delayed vaccinations: a new approach to visualize vaccine uptake. Epidemiol Infect 2002;128:185–92.
[8] Luman ET, Barker LE, McCauley MM, Drews-Botsch C. Timeliness of childhood immunizations: a state-specific analysis. Am J Public Health 2005;95:1367–74.
[9] Dombkowski KJ, Lantz PM, Freed GL. The need for surveillance of delay in age-appropriate immunization. Am J Prev Med 2002;23:36–40.
[10] Clark A, Sanderson C. Timing of children's vaccination in 45 low-income and middle-income countries: an analysis of survey data. Lancet 2009;373:1543–9, http://dx.doi.org/10.1016/S0140-6736(09)60317-2.
[11] Bicaba A, Haddad S, Kabore M, Taminy E, Feletto M, Fournier P. Monitoring the performance of the Expanded Program on Immunization: the case of Burkina Faso. BMC Int Health Hum Rights 2009;9:S12, http://dx.doi.org/10.1186/1472-698X-9-S1-S12.
[12] Olusanya BO. Pattern and determinants of BCG immunization delays in a sub-Saharan African community. Health Res Policy Syst 2010;8:1, http://dx.doi.org/10.1186/1478-4505-8-1.
[13] Moïsi JC, Kabuka J, Mitingi D, Levine OS, Scott JA. Spatial and sociodemographic predictors of time-to-immunization in a rural area in Kenya: is equity attainable? Vaccine 2010;28:5725–30, http://dx.doi.org/10.1016/j.vaccine.2010.06.011.
[14] Le Polain de Waroux O, Schellenberg JR, Manzi F, Mrisho M, Shirima K, Mshinda H, et al. Timeliness and completeness of vaccination and risk factors for low and late vaccine uptake in young children living in rural southern Tanzania. Int Health 2013;5:139–47, http://dx.doi.org/10.1093/inthealth/iht006.
[15] Scott S, Odutola A, Mackenzie G, Fulford T, Afolabi MO, Lowe Jallow Y, et al. Coverage and timing of children's vaccination: an evaluation of the expanded programme on immunisation in The Gambia. PLOS ONE 2014;9:e107280, http://dx.doi.org/10.1371/journal.pone.0107280.
[16] Gram L, Soremekun S, ten Asbroek A, Manu A, O'Leary M, Hill Z, et al. Socio-economic determinants and inequities in coverage and timeliness of early childhood immunisation in rural Ghana. Trop Med Int Health 2014;19:802–11, http://dx.doi.org/10.1111/tmi.12324.
[17] Schoeps A, Ouédraogo N, Kagoné M, Sié A, Müller O, Becher H. Socio-demographic determinants of timely adherence to BCG, Penta3, measles, and complete vaccination schedule in Burkina Faso. Vaccine 2013;32:96–102, http://dx.doi.org/10.1016/j.vaccine.2013.10.063.
[18] Akmatov MK, Kimani-Murage E, Pessler F, Guzman CA, Krause G, Kreienbrock L, et al. Evaluation of invalid vaccine doses in 31 countries of the WHO African Region. Vaccine 2015;33:892–901, http://dx.doi.org/10.1016/j.vaccine.2014.10.089.
[19] Grant CC, Roberts M, Scragg R, Stewart J, Lennon D, Kivell D, et al. Delayed immunisation and risk of pertussis in infants: unmatched case–control study. BMJ 2003;326:852–3.
[20] vonKries R, Böhm O, Windfuhr A. *Haemophilus influenzae* b-vaccination: the urgency for timely vaccination. Eur J Pediatr 1997;156:282–7.
[21] Rothman KJ, Young-Xu Y, Arellano F. Age dependence of the relation between reassortant rotavirus vaccine (RotaShield) and intussusception. J Infect Dis 2006;193:898.
[22] The RTS,S Clinical Trials Partnership. Efficacy and safety of the RTS S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. PLOS Med 2014;11:e1001685, http://dx.doi.org/10.1371/journal.pmed.1001685.
[23] World Health Organization, http://apps.who.int/iris/bitstream/10665/44664/1/9789241501767_eng.pdf?ua=1 (lastly accessed 12.03.15) Guideline: Vitamin A supplementation in infants and children 6–59 months of age. Geneva: World Health Organization; 2011.
[24] Corsi DJ, Neuman M, Finlay JE, Subramanian SV. Demographic and health surveys: a profile. Int J Epidemiol 2012;41:1602–13, http://dx.doi.org/10.1093/ije/dys184.
[25] ICF International. Demographic and Health Survey. Sampling and household listing manual. Calverton, Maryland, USA: MEASURE DHS; 2012.
[26] Dayan GH, Shaw KM, Baughman AL, Orellana LC, Forlenza R, Ellis A, et al. Assessment of delay in age-appropriate vaccination using survival analysis. Am J Epidemiol 2006;163:561–70.
[27] ICF International. The DHS program STATcompiler; 2012. http://www.statcompiler.com (lastly accessed 12.03.15).
[28] Fadnes LT, Jackson D, Engebretsen IM, Zembe W, Sanders D, Sommerfelt H, et al. Vaccination coverage and timeliness in three South African areas: a prospective study. BMC Public Health 2011;11:404, http://dx.doi.org/10.1186/1471-2458-11-404.
[29] Fadnes LT, Nankabirwa V, Sommerfelt H, Tylleskär T, Tumwine JK, Engebretsen IM. Is vaccination coverage a good indicator of age-appropriate vaccination? A prospective study from Uganda. Vaccine 2011;29:3564–70, http://dx.doi.org/10.1016/j.vaccine.2011.02.093 [Epub 2011 Mar 12].
[30] Jahn A, Floyd S, Mwinuka V, Mwafilaso J, Mwagomba D, Mkisi RE, et al. Ascertainment of childhood vaccination histories in northern Malawi. Trop Med Int Health 2008;13:129–38, http://dx.doi.org/10.1111/j.1365-3156.2007.01982.x.
[31] Sadoh AE, Eregie CO. Timeliness and completion rate of immunization among Nigerian children attending a clinic-based immunization service. J Health Popul Nutr 2009;27:391–5.
[32] Vaahtera M, Kulmala T, Maleta K, Cullinan T, Salin ML, Ashorn P. Childhood immunization in rural Malawi: time of administration and predictors of non-compliance. Ann Trop Paediatr 2000;20:305–12.
[33] Ndiritu M, Cowgill KD, Ismail A, Chiphatsi S, Kamau T, Fegan G, et al. Immunization coverage and risk factors for failure to immunize within the Expanded Programme on Immunization in Kenya after introduction of new *Haemophilus influenzae* type b and hepatitis b virus antigens. BMC Public Health 2006;6:132.
[34] Babirye JN, Engebretsen IM, Makumbi F, Fadnes LT, Wamani H, Tylleskar T, et al. Timeliness of childhood vaccinations in Kampala Uganda: a community-based cross-sectional study. PLoS ONE 2012;7:e35432, http://dx.doi.org/10.1371/journal.pone.0035432.
[35] Laryea DO, AbbeyquayeParbie E, Frimpong E. Timeliness of childhood vaccine uptake among children attending a tertiary health service facility-based immunisation clinic in Ghana. BMC Public Health 2014;14:90, http://dx.doi.org/10.1186/1471-2458-14-90.

[36] Anand S, Bärnighausen T. Health workers and vaccination coverage in developing countries: an econometric analysis. Lancet 2007;369:1277–85.
[37] Ndiaye NM, Ndiaye P, Diédhiou A, Guèye AS, Tal-Dia A. Factors related to failure to complete immunization of children aged 10–23 months in Ndoulo (Senegal). Sante 2009;19:9–13, http://dx.doi.org/10.1684/san.2009.0139 [article in French].
[38] Imdad A, Herzer K, Mayo-Wilson E, Yakoob MY, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age. Cochrane Database Syst Rev 2010;(12):CD008525, http://dx.doi.org/10.1002/14651858.CD008524.pub2.
[39] Ross DA. Recommendations for vitamin A supplementation. J Nutr 2002;132:2902S–6S.
[40] Fisker AB, Hornshøj L, Rodrigues A, Balde I, Fernandes M, Benn CS, et al. Effects of the introduction of new vaccines in Guinea-Bissau on vaccine coverage, vaccine timelines, and child survival: an observational study. Lancet Glob Health 2014;2:e478–87, http://dx.doi.org/10.1016/S2214-109X(14)70274-8 [Epub 2014 Jul 23].