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Vaccine Delay and Its Association With Undervaccination in Children in Sub-Saharan Africa

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Introduction: Improving the timeliness and completion of vaccination is the key to reducing under-5 childhood mortality. This study examines the prevalence of delayed vaccination for doses administered at birth and age 6 weeks, 10 weeks, 14 weeks, and 9 months and its association with undervaccination among infants in Sub-Saharan Africa.

Methods: Pooling data across 33 Sub-Saharan Africa countries, vaccination timing and series completion were assessed for children aged 12−35 months who were included in the immunization module of the Demographic and Health Surveys conducted between 2010 and 2019. Survey design −adjusted logistic regression modeled the likelihood of not fully completing the basic immunization schedule associated with dose-specific delays in vaccination. Data were obtained and analyzed in May 2020.

Results: Among children with complete date records (n=70,006), the proportion of children vaccinated with delays by ≥1 month was high: 25.9% for Bacille Calmette-Guerin (at birth); 49.1% for the third dose of pentavalent combination vaccine (at 14 weeks); and 63.9% for the first dose of measles vaccines (at 9 months). Late vaccination was more common for children born to mothers with lower levels of educational attainment (p<0.001) and wealth (p<0.001). Controlling for place, time, and sociodemographics, vaccination delays at any dose were significantly associated with not completing the immunization schedule by 12 months (Bacille Calmette-Guerin: AOR=1.93, [95% CI=1.83, 2.02]; pentavalent 3: AOR=1.50 [95% CI=1.35, 1.64]; measles: AOR=3.76 [95% CI=3.37, 4.15]).

Conclusions: Timely initiation of vaccination could contribute to higher rates of immunization schedule completion, improving the reach and impact of vaccination programs on child health outcomes in Sub-Saharan Africa.

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INTRODUCTION

Considerable progress has been made in reducing under-5 mortality, which globally has declined by 53% from 1990 to 2015.[1] Despite this success, progress in Sub-Saharan Africa (SSA) has been slower: only 8 of 43 countries in the region met or exceeded the Millennium Development Goals related to childhood survival by 2015.[2] Consequently, it is estimated that nearly two thirds of SSA countries will need to accelerate improvement to achieve the updated goal of reducing under-5 mortality to <25 deaths per 1,000 live births in every country by 2030 in line with the Sustainable Development Goals.[1]

Inequities in vaccination are a major contributor to disparities in childhood health and survival.[3,4] This is evidenced in SSA, where some of the highest rates of childhood mortality globally (>100 per 1,000 live births) coincide with less than one third of countries reporting immunization schedule completion in infants by >60%.[5] The low rates of age-appropriate vaccination directly threaten the progress made in the control and elimination of vaccine-preventable diseases (VPDs) that contributes importantly to improving childhood survival.[6,7] The WHO Expanded Programme on Immunization recommends that young children in most countries globally receive 1 dose of Bacille Calmette-Guerin (BCG) at birth; 3 doses of oral polio vaccine (polio) and 3 doses of the pentavalent combination vaccine (Penta) (i.e., diphtheria-tetanus-pertussis, hepatitis B, *Haemophilus influenzae* type b) at age 6 weeks, 10 weeks, and 14 weeks; and 1 dose of measles-containing vaccine (measles) at age 9 months.[8] These recommendations are adapted to address the specific epidemiologic profile at the country level, but all countries in SSA at a minimum use this basic series, and some may additionally offer newer childhood vaccines. To achieve effective control of VPDs, high rates of both timely receipt and completion of the basic schedule are needed. In acknowledgment of this, the WHO's Immunization Agenda 2030, which has put forth aspirational goals for national immunization programs in line with the Sustainable Development Goal agenda, underscores the importance of both receiving vaccination altogether but also ensuring that access to on-time vaccination is available to target the age-specific vulnerabilities children have for each VPD covered in the schedule.[9]

Previous studies on timeliness and completion of childhood vaccination in SSA have focused on underlying determinants, including spatial and sociodemographic factors associated with low uptake or poor adherence to age-specific vaccination recommendations.[10–15] However, no studies have evaluated the association between delayed vaccination and failure to complete the basic series by 12 months outside of high-income countries.[16,17] Delayed vaccination poses public health risks both in terms of disease acquisition for the individual as well as transmission in the community as children remain susceptible to and reservoirs for VPDs for unnecessarily prolonged periods.[18,19] In real time, the level and duration of the risk associated with delayed vaccination are unknown because the visibility of vaccination timing is limited when relying on administrative data.[7] Across countries, vaccination coverage is estimated by aggregating reported administrative data on the total doses administered for each vaccine in the target population of surviving infants, estimated from census data, over a defined period.[20] These aggregate measures of coverage mask age-specific vulnerabilities and potentially obscure the patterns of clustered risk that program managers and policymakers could address with a more granular view of adherence to age-specific vaccination recommendations.[7] Importantly, although a less commonly explored implication, vaccination delays may also increase the likelihood of missing subsequent doses and even dropping out of the schedule before concluding the full series of vaccines in the first year of life, as is recommended. Understanding the extent to which vaccine delays occur across the schedule and defining the role that delayed vaccination plays in completing all recommended vaccines could help inform strategies that reduce bottlenecks to achieving full coverage of the childhood vaccination schedule, ultimately improving the effectiveness of vaccination and its impact on childhood survival. Using data from the Demographic Health Survey (DHS) conducted in 33 SSA countries, this study seeks to (1) estimate the prevalence of delayed vaccination at specific vaccination encounters in the schedule and (2) explore the association between delays in dose-specific vaccination and the completion of the basic immunization schedule.

METHODS

Study Population

Established in 1984, the DHS program collects nationally representative data on health and demographics using standardized survey designs across the participating countries.[21] This widely used cross-sectional data source has been described in depth elsewhere.[22] All publicly accessible DHS surveys in SSA conducted between 2010 and 2019 were identified for this study, totaling 47 surveys from 33 countries (available as of June 2020 at www.dhsprogram.com/data/available-datasets.cfm). The sample was restricted to the most recent survey conducted per country (Appendix Table 1, available online).

The DHS uses a multistage, unequal probability sampling scheme to identify a nationally representative sample of households.[22] At the first stage, household clusters are selected on the basis of probability proportional to the population area size from each rural or urban strata, defined by the host country. Then, after

creating a complete listing of households within the cluster, approximately 30 households are randomly sampled. All women aged 15–49 years who reside in the selected households are invited to participate in the survey.[23]

Vaccination data are collected for living children who were born in the 3–5 years before the interview.[24] Data from children aged 12–35 months at the time of the interview were used in this study because this age group consistently participated in the vaccination module across the countries selected for inclusion. Owing to the potential of correlated vaccination patterns among siblings, the sample was restricted to the youngest child in instances where multiple children from the same family were age eligible (excluding 3.2% of the age-eligible sample).

Mothers are asked to report on their children's status of receipt for each recommended vaccine in the national immunization schedule. To verify, interviewers review family health cards or children's immunization records, when available, to confirm the date of vaccination.[25] Dates recorded on the vaccination card were used to assess timeliness and series completion. Children who did not have a card available at the time of the interview or who had a card without a record of complete or plausible vaccination dates were excluded from analysis.

Measures

The primary outcome of interest was the completion of the recommended immunization schedule in the first year of life. All analyses used complete vaccination series status as the reference level. Incomplete vaccination schedules were defined as lacking any dose in the 8 basic dose series, which includes BCG at birth, 3 doses each of Penta and polio at age 6, 10, and 14 weeks, and 1 dose of measles at age 9 months. Dose-specific vaccination timeliness was explored by creating a 3-way categorization that reflects adherence or nonadherence to the age-specific recommendations for each dose.[9] Doses administered were defined as on time; delayed, as a first instance (of delayed vaccination in the schedule); or delayed, with previous instances (of delay at previous vaccination encounters). Any dose that was recorded as having been administered ≥4 after the recommended age was considered delayed. Age (in days) at vaccination was used as the cut off for on-time versus delayed vaccination, and the history of delayed vaccination for any previous dose was used to assign children to delayed, with previous instances (Table 1).

Age in days at vaccination was calculated by subtracting the child's birthdate from the vaccination date recorded on a child's immunization card. Where month or year of birth were missing, other available dates in the survey were cross-referenced to define plausibility bounds. For cases in which the day of birth was missing but the date of BCG vaccination was complete (n=14,243), age at vaccination was imputed by drawing from the distribution of known values for age at BCG vaccination, and then, birthdate was back calculated by subtracting the imputed age in days from the date at BCG vaccination.

Known predictors of vaccination timeliness and completion were also explored and used as covariates in the analysis. Birth setting was defined as institutional delivery in a public sector setting, institutional delivery in a private sector setting, non-institutional delivery with the presence of skilled healthcare attendant, non-institutional delivery with a traditional birth attendant, or non-institutional delivery with no assistance. Child's rank in the birth order, adjusting for multiple births, was also considered. Missed opportunity for coadministration was assessed using a dichotomous variable for each of the 3 instances where Penta and polio coadministration should occur. Maternal educational attainment, parental marital status, household wealth, and residence location were assessed using the categorical definitions used by DHS.[26]

Statistical Analysis

Delayed vaccination across levels of child characteristics was assessed, and the significance of differences was evaluated. Using multinomial logistic regression, predictors were evaluated for categories of dose-specific delayed vaccination: (1) delayed, first instance versus on-time vaccination and (2) delayed, previous instance versus on-time vaccination. Then, the primary association of interest was explored, separately evaluating the association between delayed receipt of BCG, Penta1, Penta2, Penta3, and measles and schedule completion in a set of logistic regression models that included children conditional on having received the vaccine. ORs, average marginal effects, and predicted probabilities of the outcome were estimated for first instance of delayed vaccination and repeated delays in vaccination versus on-time receipt. Average marginal effects and predicted probabilities of the outcome allow for making appropriate comparisons across models owing to the failure to assume that unobserved heterogeneity is the same across model samples conditional on having received a vaccine, such as children who receive BCG differ from children who receive doses later in the schedule. Covariates that were identified as significantly associated with vaccination delays were retained for controls in the adjusted models exploring the associations between dose-specific delays and schedule completion. Necessitating a control for time and place in the multicountry models, indicator dummy variables for each country and continuous variables for year and child's age at the interview were used. As a sensitivity analysis, country-stratified models were used to evaluate the heterogeneity in effects across countries in the sample. All analyses used country-specific sampling weights and

Table 1. Age-Specific Recommendations for the Basic Immunization Schedule Endorsed by WHO

Age at administration	Vaccines	Minimum acceptable age (days)	Delays initiated (age in days)
Birth	BCG, OPV0[a]	0	≥28
6 (8) weeks	Penta1, OPV1	42 (56)	>70 (84)
10 (12/16) weeks	Penta2, OPV2	Age in days at previous dose + 28	>98 (112/140)
14 (16/24) weeks	Penta3, OPV3	Age in days at previous dose + 28	>126 (140/196)
9 months	Measles	252	>280

Note: A total of 4 countries in the sample use the schedules denoted in parentheses.
[a]Dose 0 refers to a dose at birth.
BCG, Bacille Calmette-Guerin; OPV, oral polio vaccine; Penta, pentavalent combination vaccine.

survey design strata variables to account for the complex sample design. Unweighted case frequencies and weighted proportions are reported. All analyses were conducted in Stata, version 16.1.

RESULTS

A total of 136,745 children aged 12–35 months were surveyed in the most recent DHS waves during 2010–2019 across the 33 included countries. After selecting the youngest child from households with multiple age-eligible children, the availability of vaccination records in 132,405 children was assessed. Across country surveys, the median proportion of age-eligible children who had a vaccination card available during the interview was 58% (IQR=46%–63%). In total, 61,399 age-eligible children were excluded (Table 2) owing either to having no vaccination

Table 2. Characteristics of Children Aged 12–35 Months According to Data Availability for Assessing Vaccination Status

Characteristics	Card verification (*n*=78,746)		Maternal recall, % (*n*=53,659)	Overall, % (*n*=132,405)
	Complete dates, %	Incomplete dates, %		
Child's age, *n*	70,006	8,740	53,659	132,405
12–23 months	50	50	50	50
24–35 months	50	50	50	50
Child's sex, *n*	70,006	8,740	53,659	132,405
Male	57	55	45	52
Female	43	45	55	48
Birth order, *n*	70,006	8,740	53,659	132,405
First	23	22	22	23
75% second to third	37	36	34	36
Fourth to fifth	29	29	30	29
Sixth+	11	13	14	12
Birth setting, *n*	69,180	8,616	53,049	130,845
Institutional, public	66	61	50	59
Institutional, private	9	8	8	9
Home, skilled attendant	2	3	3	2
Home, traditional attendant	21	25	34	26
Home, no attendant	3	3	5	4
Vaccination status, according to card or recall, *n*	70,006	8,740	53,659	132,405
Fully vaccinated	21	26	78	43
Not fully vaccinated	79	74	22	57
Maternal age, years (at child's birth), *n*	70,006	8,740	53,659	132,405
Under 19	15	17	18	16
20–29	52	52	52	52
30–39	29	28	26	28
40–49	4	4	4	4
Maternal education, *n*	69,995	8,739	53,655	132,389
None	36	37	44	39
Primary	34	35	29	32
Secondary	27	25	24	25
Higher	3	3	3	3
Household wealth quintile, *n*	70,006	8,389	53,659	132,405
Poorest	20	22	25	22
Poorer	21	22	22	22
Middle	21	21	19	20
Richer	20	19	18	19
Richest	18	16	15	17
Place of residence, *n*	70,006	8,389	53,659	132,405
Urban	34	34	33	34
Rural	66	66	67	66

Note: Only children with complete dates were included in the analytic sample.

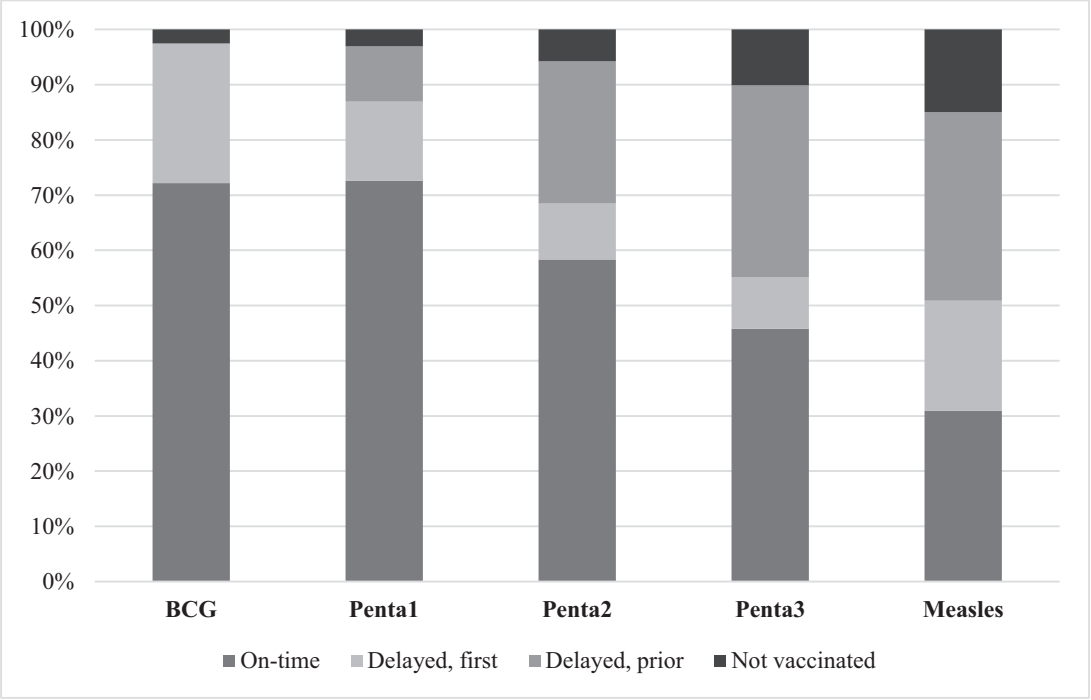

Figure 1. Percentage of children by vaccination status across the recommended series in the pooled analytic sample, weighted using country weights provided by DHS.
BCG, Bacille Calmette-Guerin; DHS, Demographic and Health Surveys; Penta, pentavalent combination vaccine.

card available (n=53,659) or to implausible/missing vaccination dates sporadically throughout their records (n=8,740). Although the characteristics of the children stratified on the restriction criteria did not differ substantially between groups, the analytic sample (n=70,006) represented children who had considerably higher rates of vaccination schedule completion overall at the time of interview than children excluded from analysis (Table 2).

In terms of undervaccination, the proportion of children missing the recommended doses or receiving delayed doses increased with each subsequent visit across the vaccination milestone visits, using BCG, Penta1–3, and measles vaccination statuses as representative of the 5 vaccine administration encounters across the schedule because Penta1–3 are administered concomitantly with Polio1–3 (Figure 1). Although <1% of children received no vaccines in their first year of life, the other 20% of children who did not complete their schedule by age 12 months had missed an important number of doses when considering the full 8-dose–recommended series: 5% missing 4–7 doses, 6% missing 2–3 doses, and 9% missing ≥1 dose (country-specific estimates are in Appendix Table 1, available online).

Among vaccinated children across countries, late administration by ≥4 weeks was 25.9% for BCG; 23.5% for the first, 38.2% for the second, and 49.1% for the third doses of Penta; and 63.6% for measles (Table 3). The proportion of children receiving delayed vaccination repeatedly across the schedule was consistently highest for higher birth order (7+) children or those who were born in non-institutional settings with no skilled assistance. By contrast, the proportion of delayed vaccination trended substantially lower for children born to mothers with higher levels of educational attainment and household wealth. For example, in the wealthiest households, only 35.3% of children were delayed for Penta3 vaccination compared with 58.7% in the poorest households. Similarly, there was a substantial difference in the prevalence of delayed Penta3 vaccination between children of mothers who had high educational attainment (24.4%) and those of mothers with no education (60.8%). For children who were vaccinated against measles, the proportion affected by delays did not vary as substantially across childhood and maternal predictors as was observed for other vaccination delays. Nonetheless, except for parental marital status and child's sex, all sociodemographic characteristics demonstrated some level of significant association with delayed vaccination, either as a first instance or following previous delays (p<0.05) (Appendix Table 3, available online).

Children with delayed vaccination were at increased odds of not finishing their schedules by age 12 months

Table 3. Proportion of Children Aged 12–35 Months With Delayed Vaccination Across the Immunization Series Stratified by Descriptive Characteristics (n=70,006)

	BCG		Penta, first dose		Penta, second dose		Penta, third dose		Measles, first dose	
	Birth		6 or 8 weeks		10, 12, or 16 weeks		14, 16, or 24 weeks		9 months	
Characteristics	%	*p*-value[a]	%	*p*-value[a]	%	*p*-value[a]	%	*p*-value[a]	%	*p*-value[a]
Overall[b]	25.9		23.5		38.2		49.1		63.6	
Child's sex		0.33		0.24		0.46		0.51		0.23
Male	25.7		24.9		38.4		49.3		63.9	
Female	26.1		25.4		38.0		49.0		63.3	
Child's age (at interview), months		0.20		0.61		0.05		**0.02**		**0.01**
12–23	25.7		25.1		37.8		48.6		62.8	
24–35	26.2		25.3		38.8		49.9		64.6	
Birth order		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
First	21.8		20.9		32.8		42.9		59.3	
Second to third	23.2		22.7		35.3		46.4		63.5	
Fourth to fifth	29.0		28.4		42.2		53.4		66.2	
Sixth+	35.9		34.1		49.5		61.4		66.9	
Birth setting		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Institutional delivery, public	19.8		0.2109		33.9		45.3		62.2	
Institutional delivery, private	18.9		0.1782		29.3		39.0		64.2	
Home delivery, skilled attendant	35.7		0.3164		45.7		54.9		62.2	
Home delivery, traditional attendant	45.7		0.3942		54.1		65.2		67.7	
Home delivery, no attendant	48.9		0.3948		54.4		64.7		70.2	
Fully immunized		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Incomplete	36.0		40.6		55.6		60.9		71.2	
Complete	23.5		21.6		38.4		47.5		63.0	
Not coadministered with Polio1	—		41.1	**<0.001**	52.2	**<0.001**	58.1	**<0.001**	66.9	**<0.001**
Not coadministered with Polio2	—		—		48.6	**<0.001**	53.3	**<0.001**	64.8	**<0.001**
Not coadministered with Polio3	—		—		—		53.3	**<0.001**	66.0	**<0.001**
Mother's age, years (at childbirth)		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Under 20	28.0		26.3		40.3		51.1		61.7	
20–29	25.2		24.6		36.9		47.9		63.3	
30–39	25.6		25.1		38.8		49.6		64.7	
40–44	29.1		28.4		43.1		54.0		66.8	
Mother's educational attainment		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
None	33.3		33.3		48.8		60.8		64.1	
Primary	26.6		23.9		37.1		48.4		65.7	
Secondary	17.4		17.8		28.7		38.8		61.3	
Higher	10.1		11.4		17.9		24.4		57.6	

(*continued on next page*)

Table 3. Proportion of Children Aged 12–35 Months With Delayed Vaccination Across the Immunization Series Stratified by Descriptive Characteristics (*n*=70,006) (*continued*)

	BCG		Penta, first dose		Penta, second dose		Penta, third dose		Measles, first dose	
	Birth		6 or 8 weeks		10, 12, or 16 weeks		14, 16, or 24 weeks		9 months	
Characteristics	%	*p*-value[a]	%	*p*-value[a]	%	*p*-value[a]	%	*p*-value[a]	%	*p*-value[a]
Mother's marital status		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Never married	18.2		19.6		30.8		38.3		58.0	
Formerly married	25.1		25.3		39.8		50.5		65.6	
Currently married	26.6		25.6		38.7		50.0		64.0	
Household wealth quintile		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Poorest	34.3		31.9		46.8		58.7		66.9	
Poorer	31.5		29.2		43.3		54.4		64.9	
Middle	27.1		25.5		39.2		50.7		63.5	
Richer	21.3		21.8		34.9		45.8		62.4	
Richest	14.1		16.6		25.8		35.3		60.2	
Place of residence		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Rural	31.0		28.0		42.1		53.6		64.7	
Urban	16.3		19.7		30.9		40.7		61.5	
Observations,[c] *n*	67,335		66,849		65,036		62,271		57,501	

Note: Boldface indicates statistical significance ($p<0.05$).
All proportions in the pooled sample account for each country's survey design using sampling weights provided by DHS. N represents the number of children who are age eligible for inclusion who had a vaccination card available at the time of interview with complete dates for administered doses of BCG, Penta3, Polio3, and measles if received.
[a]*p*-values are calculated from chi-square test for independence between levels of categorical characteristics.
[b]Overall reflects the proportion of children vaccinated late, according to the cut offs defined in Table 1, regardless of being the first instance of delay or having a previous history of delayed vaccination, among children who were vaccinated.
[c]Differences in the number of observations between vaccination doses reflect dropout owing to not receiving a dose or list-wise deletion owing to missing values for covariates/predictors. For BCG, 1,863 children did not receive the dose, and another 808 children were excluded owing to missing values for birth setting and maternal education; for Penta, 1,982 (Dose 1), 3,900 (Dose 2), and 6,977 (Dose 3) children did not receive doses in the vaccination series, and another 811, 796, and 758 children were excluded from the respective analytic samples owing to incomplete vaccination dates or missing values for birth setting or maternal education; and for measles, 10,593 children did not receive the vaccine, and another 729 children were excluded owing to missing values for birth setting and/or maternal education.
BCG, Bacille Calmette-Guerin; DHS, Demographic and Health Surveys; Penta, pentavalent combination vaccine.

Table 4. Association Between Dose-Specific Delayed Vaccination and Not Completing the Basic Immunization Schedule by 12 Months of Age in Children Aged 12–35 Months Across 33 Countries in SSA

Timeliness predictor, by vaccine	BCG[a]	Penta 1	Penta 2 OR (95% CI)	Penta 3	Measles	BCG[a]	Penta 1	Penta 2 AME (95% CI)	Penta 3	Measles
Delayed, first instance										
ref=on time	**1.93 (1.83, 2.02)**	**1.99 (1.83, 2.14)**	**1.88 (1.74, 2.02)**	**1.50 (1.36, 1.63)**	**3.76 (3.37, 4.15)**	**0.129 (0.11, 0.15)**	**0.131 (0.11, 0.15)**	**0.106 (0.08, 0.12)**	**0.056 (0.04, 0.07)**	**0.106 (0.09, 0.12)**
Delayed, previous instance										
ref=on time	—	**2.91 (2.71, 3.12)**	**2.79 (2.63, 2.94)**	**2.46 (2.32, 2.60)**	**8.21 (7.50, 8.91)**	—	**0.212 (0.19, 0.23)**	**0.186 (0.17, 0.21)**	**0.143 (0.12, 0.16)**	**0.215 (0.20, 0.23)**
Observations	67,335	66,849	65,036	62,271	58,684	67,408	66,849	65,036	62,271	57,501

Note: Boldface indicates statistical significance ($p<0.001$).
Logistic regression results are presented as OR and AME. For consistency across models for BCG, Penta1, Penta2, Penta3, and measles, all models adjust for continuous child's age, birth order, and setting; mother's age at childbirth and educational attainment by time of interview; household wealth quintile and location (rural/urban); survey year and country. Models for Penta and measles include controls for missed opportunities of vaccination associated with the recommended concomitant vaccination of Penta and polio at 6, 10, and 14 weeks (not shown). Odds of not completing the basic immunization schedule by 12 months of age (i.e., receiving BCG, Penta1–3, and Measles1) are compared between children who receive delayed vaccination and children who are vaccinated on time. The 3-level delay category captures 2 types of delay: first instance of delayed receipt in the schedule and delayed at a given instance after having experienced delays at previous vaccination instances. AME shows the average change in probability of the outcome when making a discrete level change in the categorical predictor defining delayed vaccination versus on-time vaccination, that is, how much higher (or lower) the expected mean probability of not completing the vaccination series is in the study population when a child is delayed (either at first instance or with previous delays) in receiving a specific vaccine dose versus receiving the dose on time, holding all other variables at their observed values.
[a]The only type of delay recognized for BCG is first instance because it is the first dose (administered at birth) in the series.
AME, average marginal effect; BCG, Bacille Calmette-Guerin; Penta, pentavalent combination vaccine; SSA, Sub-Saharan Africa.

compared with children who received on-time vaccination (Table 4). The magnitude of this association was large for children who received delayed vaccination against measles as the first occurrence of delay in the schedule (AOR=3.76, 95% CI=3.37, 4.15) or following a pattern of delayed vaccination across the schedule (AOR=8.21, 95% CI=7.50, 8.91) compared with those who received on-time vaccination. However, children who were both delayed in receiving measles and did not complete their schedules by age 12 months often did finish their schedules at an older age. The median age of measles vaccination for these children was 4.25 months after the recommended age (13.25 months), driving their undervaccination status at age 12 months.

Patterns of repeated delays across the childhood schedule resulted in a significantly higher probability ($p<0.001$) of drop off from the recommended series than receiving on-time vaccination (Penta1 delay with previous delays: 21.2% higher; measles delay with previous delays: 21.5% higher) (Table 4). Both first instance delays and with previous delays at the first dose of Penta significantly predicted incompletion rates, which were sustained for delays at Penta2, Penta3, and measles, although the predicted probability of incompletion declined with each subsequent dose (Figure 2). In the country-stratified models explored as a sensitivity analysis, there was variation across countries in the magnitude of the association between dose-specific delays and not finishing the basic childhood vaccination schedule (Appendix Figures 1–3, available online). However, children with vaccination delays in ≥1 dose compared with those who had on-time doses consistently showed a higher probability of not completing the schedule.

DISCUSSION

Assessment of vaccination timeliness is essential to identifying age-specific risks of VPDs, which continue to contribute to under-5 mortality in SSA.[27,28] Similarly, defining the role that delayed vaccination plays in hindering the completion of the recommended schedule in the first year of life is needed for evidencing the value of programmatic interventions that target timely vaccination as a means to improving protective coverage overall. Although the uptake of individual vaccine doses has improved (i.e., Penta3 increased from 77% to 81% in Eastern and Southern Africa and 65% to 70% in West and Central Africa during 2010–2019), aggregate measures of coverage are an imprecise predictor of the population risk profile for VPDs. These measures do not account for the timing of vaccination and the resulting age-specific protection or the lack thereof when delays lead to additional delays or eventual dropout and

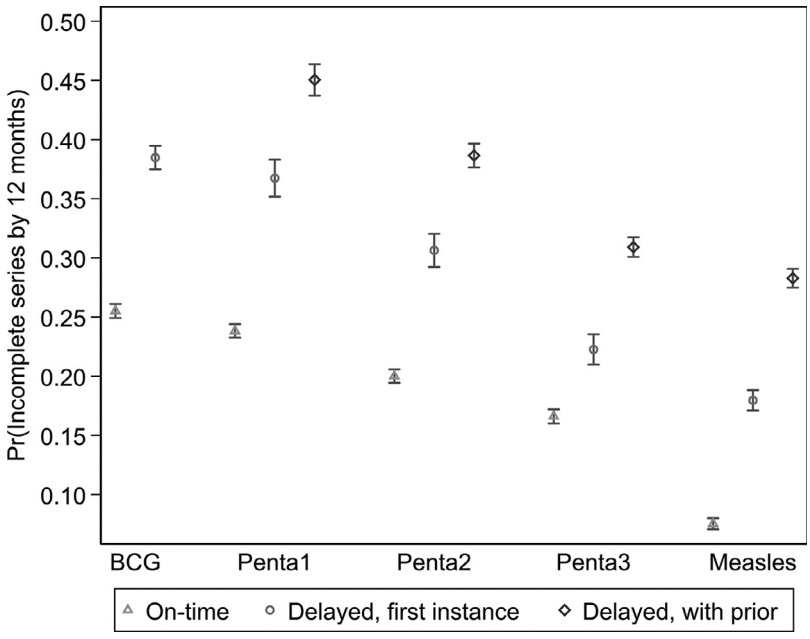

Figure 2. Predicted probability of not being fully vaccinated by 12 months of age for categories of vaccination timeliness at each dose: on time, delayed (first instance), or delayed (with previous instances).
BCG, Bacille Calmette-Guerin; Penta, pentavalent combination vaccine.

undervaccination.[29] This study explored the association between children having dose-specific delays and completing their immunization schedules before age 12 months. Using recent nationally representative survey data from 33 SSA nations, the findings suggest that dose-specific delays are common and that those delays lead to a significantly higher probability of dropping off the schedule, resulting in prolonged susceptibility to specific VPDs beyond the first year of life.

To the authors' knowledge, previous studies on the determinants of undervaccination in SSA have not considered the role of adherence to age-specific vaccination recommendations besides on-time vaccination at birth. Studies in both low- and higher-income settings alike have found that the risk of programmatic dropout associated with delayed initiation of vaccination at birth is significant.[16,17,30] In this study, delayed administration of any dose was significantly associated with an increased likelihood of not completing the immunization schedule during the first year of life. Across immunization programs in SSA, education and outreach designed to improve community demand for on-time vaccination services could lessen the programmatic burden of follow-up, when children fall behind in their schedules, and reduce the resulting risk of undervaccination. However, vaccine stockouts and other service disruptions are often unavoidable barriers to access. In these scenarios, outreach and catch-up campaigns remain important for bringing children up to date on their vaccination.

It is worth clarifying that some delays may result from intentional adjustments to the schedule for individual children after delayed initiation of a multi-dose series. This is because a 4-week interval is recommended between doses to avoid blunting the immune response.[8] Nonetheless, across countries, delays were predictive of subsequent delays that extended beyond the minimum recommended interval between doses and even predictive of dropout, both of which can contribute to undervaccination after the first year of life. For example, instead of using the minimum interval required, 88% and 86% of delayed Penta2 and Penta3 vaccination, respectively, occurred >4 weeks after delayed receipt of the previous dose in the series.

Consistent with immunization research in SSA,[14,15,31–33] delayed vaccination observed across countries was most prevalent among families with socioeconomic and educational disadvantages. Although, notably, the prevalence of delayed measles vaccination as a first instance of delay did not differ as substantially across wealth and maternal education as compared with the variation across socioeconomic groups observed for delayed doses earlier in the schedule. Instead, there were consistently high levels of delay for receipt of measles (>60%). Since the launch of the Expanded Programme on Immunization in 1979, countries have measured the success of their immunization programs by the coverage achieved with DTP3. Using administrative coverage of DTP3, immunization program

performance may appear to be improving, yet when delays result in undervaccination against measles, the threat of a measles resurgence becomes an important concern and one that has come to recent fruition in a number of SSA countries.[34]

Considering existing challenges to reducing undervaccination in the context of the destabilizing threat that pandemic spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses for weak public health systems, immunization programs must consider how to prioritize timely vaccination throughout the course of the schedule to ensure age-specific protection and to increase the likelihood of completing all recommended vaccines. Although standard outreach activities may not be feasible, continued emphasis on education for mothers and providers about the contingency plans for completing their infants' immunization schedules, either through campaigns or health facility visits, will be needed. Where substantial concern for interrupted immunization activity may exist,[35] immunization programs also could consider vaccinating against measles at younger infant ages in settings that warrant such an approach.[8]

Limitations

Despite contributing a new perspective on vaccination timeliness and undervaccination in SSA, the approach and data sources used to study this association have some limitations. Children were excluded if they lacked complete vaccination histories, including those who had died before the interview. Both subpopulations likely differ substantially in their overall health, risk factors, and access to immunization from surviving children with complete records, which limits the generalizability of this study. Assuming that delayed vaccination is correlated with access to services and availability of a vaccination card is an indicator of access, it also might be assumed that delayed vaccination and dropout may occur more frequently in children who do not have records. This would lead to underestimating the prevalence of vaccination delays and their contribution to overall completion rates. On the other hand, in the absence of electronic immunization registries, this study may have incorrectly classified vaccination outcomes if dates were not correct or administered doses were not documented, although data quality measures are embedded in the DHS program to change implausible dates to missing and survey data are generally considered the gold standard for assessing immunization uptake.[36,37] Although the surveys are cross-sectional, the availability of vaccination dates for the sample allowed the authors to establish the sequential timing of vaccine administration across the schedule and temporally associate delays, classified as a first-time delay or previous delays, with vaccination schedule completion as the ultimate outcome in the timing sequence. Finally, programming constraints and barriers to access predictive of undervaccination undoubtedly vary across countries in SSA. Although the heterogeneity in the magnitude and direction of the main effects across countries was explored, identifying and adjusting for country-specific observed and unobserved confounding was outside the scope of this research aim to generally establish delays as predictive of overall vaccination status in SSA. Future studies on the country-specific nuances of each program could contribute more precise recommendations on how to intervene in cases where clear patterns of bottlenecks in schedule completion arise owing to dose-specific delays.

CONCLUSIONS

This study identified delayed vaccination at birth and delays in subsequent doses as important impediments to completing the routine schedule in SSA. Although children in SSA who have contact with the immunization program likely have a higher probability of survival associated with general health services access, the benefit of on-time and full immunization of individuals extends beyond the individuals themselves. Targeting on-time delivery of vaccines across the immunization schedule among individuals and communities may contribute to achieving greater levels of protection at the population level.

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REFERENCES

1. You D, Hug L, Ejdemyr S, et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Inter-Agency Group for Child Mortality Estimation [published correction appears in *Lancet*. 2015;386(10010):2256]. *Lancet*. 2015;386 (10010):2275–2286. https://doi.org/10.1016/S0140-6736(15)00120-8.
2. Victora CG, Requejo JH, Barros AJ, et al. Countdown to 2015: a decade of tracking progress for maternal, newborn, and child survival [published correction appears in *Lancet*. 2016;387(10032):1998]. *Lancet*. 2016;387(10032):2049–2059. https://doi.org/10.1016/S0140-6736 (15)00519-X.
3. Chang AY, Riumallo-Herl C, Perales NA, et al. The equity impact vaccines may have on averting deaths and medical impoverishment in developing countries. *Health Aff (Millwood)*. 2018;37(2):316–324. https://doi.org/10.1377/hlthaff.2017.0861.
4. Chopra M, Bhutta Z, Chang Blanc D, et al. Addressing the persistent inequities in immunization coverage. *Bull World Health Organ*. 2020;98(2):146–148. https://doi.org/10.2471/BLT.19.241620.
5. USAID. STATcompiler: the DHS program. http://www.statcompiler.com. Accessed April 20, 2020.
6. Sartorius B, Cohen C, Chirwa T, Ntshoe G, Puren A, Hofman K. Identifying high-risk areas for sporadic measles outbreaks: lessons from South Africa. *Bull World Health Organ*. 2013;91(3):174–183. https://doi.org/10.2471/BLT.12.110726.
7. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet*. 2009;373 (9674):1543–1549. https://doi.org/10.1016/S0140-6736(09)60317-2.
8. Immunization, vaccines, and biologicals: vaccine position papers. WHO. http://www.who.int/immunization/documents/positionpapers/. Accessed October 2, 2020.
9. WHO. Immunisation agenda 2030: a global strategy to leave no one behind. Geneva, Switzerland: WHO. https://www.who.int/immunization/immunization_agenda_2030/en/. Published April 2, 2020. Accessed October 2, 2020.
10. Akmatov MK, Kimani-Murage E, Pessler F, et al. Evaluation of invalid vaccine doses in 31 countries of the WHO African Region. *Vaccine*. 2015;33(7):892–901. https://doi.org/10.1016/j.vaccine.2014.10.089.
11. Miyahara R, Jasseh M, Gomez P, et al. Barriers to timely administration of birth dose vaccines in the Gambia, West Africa. *Vaccine*. 2016;34(29):3335–3341. https://doi.org/10.1016/j.vaccine.2016.05.017.
12. Mbengue MAS, Mboup A, Ly ID, et al. Vaccination coverage and immunization timeliness among children aged 12−23 months in Senegal: a Kaplan-Meier and Cox regression analysis approach. *Pan Afr Med J*. 2017;27(suppl 3):8. https://doi.org/10.11604/pamj.supp.2017.27.3.11534.
13. Ashbaugh HR, Hoff NA, Doshi RH, et al. Predictors of measles vaccination coverage among children 6−59 months of age in the Democratic Republic of the Congo. *Vaccine*. 2018;36(4):587–593. https://doi.org/10.1016/j.vaccine.2017.11.049.
14. Masters NB, Wagner AL, Carlson BF, Boulton ML. Vaccination timeliness and co-administration among Kenyan children. *Vaccine*. 2018;36(11):1353–1360. https://doi.org/10.1016/j.vaccine.2018.02.001.
15. Boulton ML, Carlson BF, Wagner AL, Porth JM, Gebremeskel B, Abeje Y. Vaccination timeliness among newborns and infants in Ethiopia. *PLoS One*. 2019;14(2):e0212408. https://doi.org/10.1371/journal.pone.0212408.
16. Kiely M, Boulianne N, Talbot D, et al. Impact of vaccine delays at the 2, 4, 6 and 12 month visits on incomplete vaccination status by 24 months of age in Quebec, Canada. *BMC Public Health*. 2018;18 (1):1364. https://doi.org/10.1186/s12889-018-6235-6.
17. Yusuf HR, Daniels D, Smith P, Coronado V, Rodewald L. Association between administration of the hepatitis B vaccine at birth and completion of the hepatitis B and 4:3:1:3 vaccine series. *JAMA*. 2000;284 (8):978–983. https://doi.org/10.1001/jama.284.8.978.
18. Guerra FA. Delays in immunization have potentially serious health consequences. *Paediatr Drugs*. 2007;9(3):143–148. https://doi.org/10.2165/00148581-200709030-00002.
19. Zaman SM, Howie SR, Ochoge M, et al. Impact of routine vaccination against Haemophilus influenzae type b in the Gambia: 20 years after its introduction. *J Glob Health*. 2020;10(1):010416. https://doi.org/10.7189/jogh.10.010416.
20. Cutts FT, Izurieta HS, Rhoda DA. Measuring coverage in MNCH: design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. *PLoS Med*. 2013;10(5):e1001404. https://doi.org/10.1371/journal.pmed.1001404.
21. Who we are. USAID, The DHS Program: Demographic and Health Surveys, ICF International. https://www.dhsprogram.com/Who-We-Are/About-Us.cfm . Accessed April 20, 2020.
22. Corsi DJ, Neuman M, Finlay JE, Subramanian SV. Demographic and health surveys: a profile. *Int J Epidemiol*. 2012;41(6):1602–1613. https://doi.org/10.1093/ije/dys184.
23. ICF International. Sampling and household listing manual: demographic and health survey sampling and household listing manual. Calverton, MD: ICF International, 2012. https://dhsprogram.com/pubs/pdf/DHSM4/DHS6_Sampling_Manual_Sept2012_DHSM4.pdf. Published September 2012. Accessed October 26, 2020.
24. Croft TN, Marshall AMJ, Allen CK. *Guide to DHS statistics, DHS-7. The Demographic and health surveys program*. Rockville, MD: ICF International. https://www.dhsprogram.com/pubs/pdf/DHSG1/Guide_to_DHS_Statistics_DHS-7.pdf. Published August 2018. Accessed October 8, 2020.
25. ICF International. Interviewer's manual: demographic and health surveys interviewer's manual. MEASURE DHS basic documentation no. 2. Calverton, MD: ICF International. https://www.dhsprogram.com/pubs/pdf/DHSM1/DHS6_Interviewer_Manual_19Oct2012_DHSM1.pdf. Published October 2012. Accessed October 2, 2020.
26. ICF International. Standard recode manual for DHS 6. Description of the demographic and health surveys individual recode data file. Calverton, MD: ICF International, 2013. https://www.dhsprogram.com/pubs/pdf/DHSG4/Recode6_DHS_22March2013_DHSG4.pdf. Published March 22, 2013. Accessed October 26, 2020.
27. McAllister DA, Liu L, Shi T, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. *Lancet Glob Health*. 2019;7(1):e47–e57. https://doi.org/10.1016/S2214-109X(18)30408-X.
28. GBD 2016 Diarrhoeal Disease Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis*. 2018;18(11):1211–1228. https://doi.org/10.1016/S1473-3099(18)30362-1.
29. Immunization, vaccines and Biologicals: measles and rubella surveillance data. WHO. http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthly_data/en/#. Updated October 12, 2020. Accessed August 6, 2019.
30. Emmanuel OW, Samuel AA, Helen KL. Determinants of childhood vaccination completion at a peri-urban hospital in Kenya, December 2013 - January 2014: a case control study. *Pan Afr Med J*. 2015;20:277. https://doi.org/10.11604/pamj.2015.20.277.5664.
31. Odutola A, Afolabi MO, Ogundare EO, et al. Risk factors for delay in age-appropriate vaccinations among Gambian children. *BMC Health Serv Res*. 2015;15(1):346. https://doi.org/10.1186/s12913-015-1015-9.
32. Akmatov MK, Mikolajczyk RT. Timeliness of childhood vaccinations in 31 low and middle-income countries. *J Epidemiol Community Health*. 2012;66(7):e14. https://doi.org/10.1136/jech.2010.124651.
33. Bangura JB, Xiao S, Qiu D, Ouyang F, Chen L. Barriers to childhood immunization in sub-Saharan Africa: a systematic review. *BMC Public Health*. 2020;20(1):1108. https://doi.org/10.1186/s12889-020-09169-4.

34. Scobie HM, Ilunga BK, Mulumba A, et al. Antecedent causes of a measles resurgence in the Democratic Republic of the Congo. *Pan Afr Med J.* 2015;21(1):30. https://doi.org/10.11604/pamj.2015.21.30.6335.
35. Nelson R. COVID-19 disrupts vaccine delivery. *Lancet Infect Dis.* 2020;20(5):546. https://doi.org/10.1016/S1473-3099(20)30304-2.
36. Danovaro-Holliday MC, Dansereau E, Rhoda DA, Brown DW, Cutts FT, Gacic-Dobo M. Collecting and using reliable vaccination coverage survey estimates: summary and recommendations from the "meeting to share lessons learnt from the roll-out of the updated WHO Vaccination Coverage Cluster Survey Reference Manual and to set an operational research agenda around vaccination coverage surveys", Geneva, 18-21 April 2017. *Vaccine.* 2018;36(34):5150–5159. https://doi.org/10.1016/j.vaccine.2018.07.019.
37. Cutts FT, Claquin P, Danovaro-Holliday MC, Rhoda DA. Monitoring vaccination coverage: defining the role of surveys. *Vaccine.* 2016;34(35):4103–4109. https://doi.org/10.1016/j.vaccine.2016.06.053.