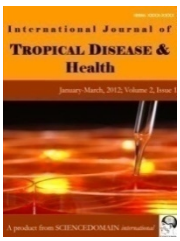

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Timeliness and Out-of-Sequence Vaccination among Young Children in Burkina Faso – Analysis of Health and Demographic Surveillance System (HDSS) Data

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Authors' contributions

This work was carried out in collaboration between all authors. Author NO contributed to the study design, performed the statistical analysis, interpreted the data and wrote the first draft of the manuscript. Authors AS and MK were responsible for the field work of the study and commented on the manuscript. Authors HB and OM designed the study, directed the statistical analysis, the data interpretation and contributed to writing the manuscript. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: The aim of this study is to investigate the timeliness and out-of-sequence vaccination among children aged less than five years through the data of a local Health and Demographic Surveillance System (HDSS) in Burkina Faso.
Study Design: Cross-sectional study nested into an existing HDSS.
Place and Duration of Study: Nouna Health District in north-western Burkina Faso, over the period of September 2008 to December 2009.
Methodology: We used data of 7,644 children born between September 2003 and March 2009. Vaccination data were provided on the basis of events recorded on vaccination cards. We assessed vaccination timeliness and the frequency of out-of-sequence vaccination.
Results: The highest rates of timely administration were observed with vaccines recommended at birth (e.g. 68% for BCG) while the lowest rates were observed with

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vaccines given in late infancy (e.g. 33% for measles). The frequency of out-of-sequence vaccination between BCG and DTP/Penta 1 or between DTP/Penta 3 and measles were respectively around 5% and 4%. Out-of-sequence vaccination in early infancy occurred significantly more frequent in rural compared to urban areas contrary to out-of-sequence vaccination in late infancy. Both, timely and correct sequencing of vaccination have significantly improved in recent years in the study area.

Conclusions: This study supports that significant vaccination delay occurs in SSA communities with high vaccination coverage and that the frequency of out-of-sequence vaccinations varies substantially between countries.

Keywords: Childhood immunization; vaccination timeliness; out-of-sequence vaccination; health and demographic surveillance System; Africa; Burkina Faso.

1. INTRODUCTION

The performance of vaccination programs is typically measured in terms of the proportion of individuals having been vaccinated without regard to the exact age at which vaccine doses were administrated. This method does not reveal the degree to which children experience delays prior to becoming immunized [1,2]. However, the timing and sequence of vaccination are important issues in the appropriate use of vaccines [3]. When children are not vaccinated according to the recommended schedule, they not only fail to receive timely protection from preventable diseases, but are also at increased risk of never fully completing their vaccination course [4]. Moreover, there is increasing evidence for non-specific effects of vaccines on childhood morbidity and mortality, which appear to depend mainly on the sequence of routine vaccinations [5,6]. While BCG and measles vaccine were shown to have non-specific beneficial effects, DTP is said to contribute to increased morbidity and mortality [7,8,9,10,11]. As these non-specific effects appear to depend on the most recent vaccine, out-of-sequence vaccinations may influence child mortality. This has been shown in particular for DTP given together or after the measles vaccine [12,13,14,15,16].

In Burkina Faso, the national routine vaccination program recommends vaccination at birth or first contact with health services (BCG, OPV 0), at 8 weeks (DTP/Penta 1, OPV 1) at 12 weeks (DTP/Penta 2, OPV 2), at 16 weeks (DTP/Penta 3, OPV 3) and at 9 months (measles and yellow fever). Routine vaccinations are provided two times per week in health centres and one time per month in villages located more than 5 km from the health centres. Although high vaccination coverage has been reported in recent years [17] there is evidence for the timing of vaccinations often not being respected in the country [18,19,20,21]. The aim of this study is to investigate the timeliness of immunization among children aged less than five years (under-fives) using the data of a local Health and Demographic Surveillance System (HDSS) in Burkina Faso.

2. MATERIALS AND METHODS

2.1 Study Area and Data Collection

This is a cross-sectional study nested into the existing HDSS of the *Centre de Recherche en Santé de Nouna* (CRSN) in the Nouna Health District in north-western Burkina Faso. The HDSS area includes the town of Nouna and 58 of the surrounding villages. It covers a subset of the district with a multi-ethnic population estimated in 2007 at about 78,000 [22].

The Nouna HDSS performs regular household visits to primarily collect data on vital events [22]. Over the period of September 2008 to December 2009, a questionnaire on vaccination details concerning under-fives was added to the routine HDSS rounds. This questionnaire was filled in once in every household during the study period. The mother or the father (or other household members when parents were not available) were asked about the vaccination status of their children. If the vaccination card of the child was available, it was reviewed by the HDSS team and all data on vaccinations and related information (e.g. vaccines received through campaigns, vitamin A supplementation) were recorded.

2.2 Statistical Analysis

For the analyses, the recommended age for vaccine uptake in Burkina Faso given in weeks or months was converted into days since the number of days in month varies. Age at receipt of a specific vaccine was also calculated in days using the dates of birth and the dates of receipt of the vaccine. The timeliness of receipt of a vaccine was determined by comparing the recommended age and the age at receipt of the given vaccine.

Several definitions of timely and delayed administration of vaccine have been proposed in the literature [2,21,23,24,25,26,27]. However, a number of them do not consider the possibility of a too early administration of antigens. We used the following definitions: (1) early vaccine receipt if the vaccine was received more than three days before the recommended age; (2) on time vaccine receipt if the vaccine was received in a time period between three days before and 28 days after the recommended age, (3) delayed vaccine receipt if the vaccine was given beyond 28 days after the recommended age.

Finally, we assessed out-of-sequence vaccinations with regard to DTP/Penta and BCG vaccinations as well as with regard to DTP/Penta and measles vaccinations. Out-of-sequence vaccinations were defined as BCG having been administered with or after DTP/Penta 1, 2 or 3, and DTP/Penta 1, 2 or 3 having been administered with or after measles vaccine.

Stata MP 11.0 was used for the statistical analysis. The chi-square test was used for comparing proportions in vaccination coverage (early, on time and delayed) between males and females and between rural and urban locality. The ANOVA test was used to compare mean age at vaccine receipt among subgroups of the study population.

3. RESULTS AND DISCUSSION

3.1 Overview of Vaccine Administration

A total of 7,644 under-fives with an existing vaccination card and born between September 2003 and March 2009 were included in the analysis (7,644/11,906; 64% of all eligible children). The mean age of all study children was 2.5 years. There were 2,129 (18%) children between 0 and 11 months, 2,593 (22%) children between 12 and 23 months, 2,364 (20%) children between 24 and 35 months, 2,326 (19%) children between 36 and 47 months and 2,494 (21%) children between 48 and 59 months.

Table 1 shows the average age at receipt of vaccines given routinely in the study area. Most often, the vaccine administration was delayed. The difference between the mean ages at receipt and the recommended ages ranges from 20 days for OPV 1 to 44 days for OPV 3

and from 20 days for DTP/Penta 1 to 43 days for DTP/Penta 3. There were significant differences in administration delays between urban and rural areas, with more pronounced delays in the rural areas directly after birth and more pronounced delays in the urban areas in later infancy (e.g. 20 days in urban against 28 days in rural areas for BCG, $p<0.001$; 49 days in urban against 31 days in rural areas for measles, $p< 0.001$).

3.2 Timeliness of BCG and OPV0 Administration

The mean age at receipt of BCG and OPV 0 vaccination was 26 days [95% CI 25.6-26.9] and 23 days [95% CI 22.0-22.9]), respectively (Table 1). Approximately one third (32%) and one quarter (27%) of the study population, respectively, received BCG and OPV 0 beyond four weeks after birth with a significant difference between urban and rural area: 20% in urban vs. 36% in rural area for BCG and 19% in urban vs. 29% in rural area for OPV 0 ($p<0.001$) (Table 2).

3.3 Timeliness of OPV 1-3 and DTP/Penta 1-3 Administration

OPV 1 and DTP/Penta 1: Roughly 15% of the study population received these antigens earlier than the recommended age. Both antigens were administrated in the correct time window in roughly 61% of cases. The remaining 24% of children received OVP 1 and DTP/Penta 1 with delay (Table 3).

OPV2 and DTP/Penta 2: Nearly 10% of the study children received these antigens too early, 53% received them in an acceptable time frame, and roughly 37% received them with delay (Table 4).

OPV 3 and DTP/Penta 3: Roughly 6% of the study population received these antigens too early, 46% received them in acceptable time frame, and 48% received them with a delay (Table 5).

3.4 Timeliness of Measles and Yellow Fever Administration

About 5% of children received measles and yellow fever vaccination too early, nearly 34% received both antigens in acceptable time frame, and about 61% received them with a delay (Table 6). Rate of early, in acceptable time frame and delayed administration of the antigens differ by area, with significantly more children receiving an early or in time vaccination in the rural compared to the urban area and significantly less children receiving a delayed vaccination in the rural compared to the urban area ($p<0.001$).

Table 1. Differences between recommended and real age at receipt of vaccines among young children in urban vs. rural area of Burkina Faso

Vaccine	Age at vaccine administration (days)							Difference schedule-mean (days)		
	Schedule (days)	Median (days)			Mean and 95% CI (days)					
		Urban	Rural	All	Urban	Rural	All	Urban	Rural	All
BCG	0	12	22	19	20 [18-21]	28 [28-29]	26 [26-27]	20	28	26
OPV0	0	12	20	19	19 [18-20]	24 [23-24]	23 [22-23]	19	24	23
OPV1	56	65	70	69	75 [73-77]	76 [75-77]	76 [76-77]	19	20	20
OPV2	84	106	104	104	120 [118-123]	115 [113-116]	116 [115-117]	36	31	32
OPV3	112	144	138	139	165 [161-168]	154 [152-155]	156 [155-157]	53	42	44
DTP/Penta 1	56	65	70	69	75 [73-77]	76 [75-77]	76 [75-77]	19	20	20
DTP/Penta 2	84	105	104	104	120 [118-123]	114 [113-116]	116 [115-117]	36	31	32
DTP/Penta 3	112	144	138	139	164 [161-168]	153 [152-154]	155 [154-157]	52	41	43
Measles	270	293	285	286	318 [314-323]	301 [299-303]	305 [303-307]	49	31	35
Yellow fever	270	293	285	286	316 [312-321]	300 [298-302]	303 [301-305]	46	30	33

The mean age at the receipt decreased significantly over the years for all vaccines, for example from 29 days in 2003 to 23 days in 2008 for BCG ($p<0.001$), and from 331 days in 2003 to 282 days in 2008 for measles ($p<0.001$).

Table 2. Timeliness of BCG and OPV0 vaccinations in young children of Burkina Faso

Definition	Antigens (recommended schedule: birth)					
	BCG			OPV0		
	Urban	Rural	Total	Urban	Rural	Total
Acceptable time frame (0-28 days)	1,324 (80.39%)	3,526 (64.21%)	4,850(67.95%)	1,317 (81.15%)	3,831 (70.67%)	5,148 (73.08%)
Delayed (≥ 29 days)	323 (19.61%)	1,965 (35.79%)	2,288 (32.05%)	306 (18.85%)	1,590 (29.33%)	1,896 (26.92%)
Total	1,647 (100%)	5,491 (100%)	7,138 (100%)	1,623 (100%)	5,421 (100%)	7,044 (100%)

Table 3. Timeliness of OPV 1 and DTP/Penta 1 vaccinations in young children of Burkina Faso

Timeliness	Vaccines (recommended schedule: 8 weeks or 56 days)					
	OPV 1			DTP/Penta 1		
	Urban	Rural	Total	Urban	Rural	Total
Early (<7.5 weeks)	368 (23.32%)	699 (12.97%)	1,067 (15.32%)	360 (23.23%)	690 (12.96%)	1,050 (15.27%)
Acceptable time frame (7.5-12 weeks)	835 (52.92%)	3,420 (63.47%)	4,255 (61.08%)	823 (53.10%)	3,382 (63.51%)	4,205 (61.16%)
Delayed (>12 weeks)	375 (23.76%)	1,269 (23.55%)	1,644 (23.60%)	367 (23.68%)	1,253 (23.53%)	1,620 (23.56%)
Total	1,578 (100%)	5,388 (100%)	6,966 (100%)	1,550 (100%)	5,325 (100%)	6,875 (100%)

Table 4. Timeliness of OPV 2 and DTP/Penta 2 vaccinations in young children of Burkina Faso

Timeliness	Vaccines (recommended schedule: 12 weeks or 84 days)					
	OPV 2			DTP/Penta 2		
	Urban	Rural	Total	Urban	Rural	Total
Early (<11.5 weeks)	212 (14.48%)	434 (8.37%)	646 (9.71%)	214 (14.72%)	437 (8.48%)	651 (9.85%)
Acceptable time frame (11.5-16 weeks)	645 (44.06%)	2,898 (55.88%)	3,543 (53.28%)	643 (44.22%)	2,867 (55.65%)	3,510 (53.13%)
Delayed (> 16 weeks)	607 (41.46%)	1,854 (35.75%)	2,461 (37.01%)	597 (41.06%)	1,848 (35.87%)	2,445 (37.01%)
Total	1,464 (100%)	5,186 (100%)	6,650 (100%)	1,454 (100%)	5,152 (100%)	6,606 (100%)

Table 5. Timeliness of OPV 3 and DTP/Penta 3 vaccinations in young children of Burkina Faso.

Timeliness	Vaccines (recommended schedule: 16 weeks or 112 days)					
	OPV 3			DTP/Penta 3		
	Urban	Rural	Total	Urban	Rural	Total
Early (< 15.5 weeks)	106 (8.08%)	282 (5.71%)	388 (6.21%)	106 (8.12%)	286 (5.86%)	392 (6.33%)
Acceptable time frame (15.5-20 weeks)	506 (38.57%)	2,365 (47.87%)	2,871 (45.92%)	508 (38.93%)	2,341 (47.93%)	2,849 (46.03%)
Delayed (> 20 weeks)	700 (53.35%)	2,293 (46.42%)	2,993 (47.87%)	691 (52.95%)	2,257 (46.21%)	2,948 (47.63%)
Total	1,312 (100%)	4,940 (100%)	6,252 (100%)	1,305 (100%)	4,884 (100%)	6,189 (100%)

Table 6. Timeliness of measles and yellow fever vaccinations in young children of Burkina Faso

Timeliness	Vaccines (recommended schedule: 9 months or 270 days)					
	Measles			Yellow fever		
	Urban	Rural	Total	Urban	Rural	Total
Early <35.5 weeks	25 (2.40%)	236 (6.01%)	261 (5.25%)	27 (2.58%)	244 (6.18%)	271 (5.43%)
Acceptable time frame (35.5-40 weeks)	283 (27.21%)	1,379 (35.10%)	1,662 (33.45%)	284 (27.15%)	1,394 (35.32%)	1,678 (33.61%)
Delayed (> 40 weeks)	732 (70.38%)	2,314 (58.90%)	3,046 (61.30%)	735 (70.27%)	2,309 (58.50%)	3,044 (60.97%)
Total	1,040 (100%)	3,929 (100%)	4,969 (100%)	1,046 (100%)	3,947 (100%)	4,993 (100%)

3.5 Out-of-sequence vaccinations

The majority of our study population (95%, 99% and 100%) received the BCG vaccination before DTP/Penta 1, DTP/Penta 2 and DTP/Penta 3, respectively. The detailed pattern of out-of-sequence vaccinations in early infancy is shown in Table 7. Out-of-sequence vaccinations were nearly equally attributed to BCG having been administered after DTP/Penta 1 and to BCG having been administered together with DTP/Penta 1. Out-of-sequence vaccination between BCG and DTP/Penta 1 was significantly higher in the rural compared to the urban area (6% in rural vs. 2% in urban area, *p<0.001*) and in the older compared to the younger birth cohort (5% among children born in 2003 vs. 3% in children born among 2008, *p<0.001*). With regard to BCG and DTP/Penta 1, there was no significant difference in the frequency of out-of-sequence vaccinations between boys and girls (*p= 0.101*).

Table 7. Out-of-sequence vaccinations in early infancy

Sequences	Place of living		Sex		Total
	Urban	Rural	Girls	Boys	
BCG after DTP/Penta 1	19 (1.26%)	137 (2.65%)	89 (2.67%)	67 (2.00%)	156 (2.34%)
BCG with DTP/Penta 1	5 (0.33%)	173 (3.35%)	81 (2.43%)	97 (2.90%)	178 (2.67%)
BCG before DTP/Penta 1 (correct sequence)	1,484 (98.41%)	4,858 (94.00%)	3,160 (94.89%)	3,182 (95.10%)	6,342 (95.00%)
Total	1,508 (100%)	5,168 (100%)	3,330 (100%)	3,346 (100%)	6,676 (100%)

The majority of our study population (100%, 98% and 96%) received the DTP/Penta 1, DTP/Penta 2 and DTP/Penta 3, respectively, before the measles/yellow fever vaccination. The detailed pattern of out-of-sequence vaccinations with regard to DTP/Penta 3 is shown in Table 8. Out-of-sequence vaccination was attributed to DTP/Penta 3 having been administered together with measles/yellow fever vaccines (2.5%) and to DTP/Penta 3 having been administered after measles/yellow fever vaccines (1.3%). Out-of-sequence between measles and DTP/Penta 3 was significantly higher in urban compared to rural area (6% vs. 3%, *p<0.001*) and in the older birth cohort compared to the younger birth cohort (13% among children born in 2003 vs. 1% among children born in 2008, *p<0.001*).

Table 8. Out-of-sequence vaccinations in late infancy

Sequences	DTP/Penta 3 - Measles				
	Urban	Rural	Girls	Boys	Total
DTP/Penta after Measles	20	41	38	23	61
	2.00	1.06	1.56	0.95	1.26
DTP/Penta with Measles	44	77	70	51	121
	4.39	2.00	2.88	2.11	2.49
DTP/Penta before Measles	938	3,732	2,323	2,347	4,670
(correct sequence)	93.61	96.94	95.56	96.94	96.25
Total	1,002	3,850	2,431	2,421	4,852
	100	100	100	100	100

With regard to DTP/Penta 3 and measles vaccine, there was a significant difference in the frequency of out-of-sequence between boys and girls (4% among girls vs. 3% among boys, p<0.001).

3.6 Discussion

The findings from this study demonstrate significant delays in the administration of vaccinations during infancy despite rather high vaccination coverage in a remote area of Burkina Faso [17]. This supports published findings from Burkina Faso and a number of other developing countries [21,28,29]. This study also supports the evidence for the timeliness of childhood vaccinations having significantly improved in recent years in developing countries [21].

In the Burkina Faso study area, the highest rates of timely vaccination were observed for vaccines recommended at birth while the lowest rates were observed for vaccines given at nine months. In contrast to other analysis [21,27], this study differentiated between early and timely vaccination. Early vaccination rates were rather high for vaccines administered in early infancy (e.g. 15% for OPV1 and DTP/Penta 1) and lower for vaccines administered in late infancy (e.g. 5% for measles). These results contrast with findings from other studies [25,27]. In general, early vaccinations can't be considered as fully contributing to valid coverage figures and may thus lead to an overestimation of population immunity [23,24,27].

A number of studies have demonstrated that out-of-sequence administration of vaccines can be detrimental to child survival [12,13,30]. A rather high frequency of out-of-sequence vaccine administration has been shown in a number of studies from developing countries, ranging from 9% for DTP3/measles vaccine administration in Malawi to 70% BCG/DTP1 administration in India [29,31,32,33]. In West-Africa, a high frequency of out-of-sequence vaccine administration (i.e. 54% for BCG and 28% for measles) has recently been reported from Guinea Bissau and Ghana [29,33]. Comparatively, the proportion of out-of-sequence vaccination is rather small in this study area in Burkina Faso and correct sequencing of vaccinations has significantly improved in recent years in West-Africa [29,33]. However, the finding that out-of-sequence vaccination is significantly higher in urban compared to rural areas deserves further attention. Urbanization is also increasing rapidly in SSA, and further research on the reasons for incorrect sequencing of childhood vaccinations is thus warranted. Out-of-sequence vaccinations in the Nouna study area are most likely explained by differential stock-outs of selected vaccines. Such variations are currently not registered in routine childhood vaccination programs. Given their potential for increasing morbidity and mortality [5,6,11], the frequency of out-of-sequence vaccinations should be added as an indicator for monitoring vaccination programs.

The strength of this study is that it has been carried out in a large population of under-fives in a district which is rather representative for Burkina Faso [22], and that the data have been collected from a very experienced field team in the frame of an HDSS. Limitations are that the analysis is based only on the two third of eligible children with existing vaccination cards and that it is confined to only one health district of Burkina Faso.

4. CONCLUSION

This study supports that significant vaccination delay occurs in SSA communities with high vaccination coverage and that the frequency of out-of-sequence vaccinations varies substantially between countries.

CONSENT

Not applicable.

ETHICAL APPROVAL

The protocol for this study was approved by the local Ethical Committee in Burkina Faso and the Ethical Commission of the Medical School at the Heidelberg University. Informed community consent was sought for the implementation of the additional survey questionnaire during routine HDSS procedures.

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COMPETING INTERESTS

We declare that we have no conflicts of interest.

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