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Is vaccination coverage a good indicator of age-appropriate vaccination? A prospective study from Uganda

Lars T. Fadnes[a,*], Victoria Nankabirwa[b], Halvor Sommerfelt[a,c], Thorkild Tylleskär[a], James K. Tumwine[b], Ingunn M.S. Engebretsen[a], for the PROMISE-EBF Study Group[1]

[a] Centre for International Health, University of Bergen, 5018 Bergen, Norway
[b] Department of Paediatrics and Child Health, Makerere University, Uganda
[c] Division of Infectious Disease Control, Norwegian Institute of Public Health, Norway

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ABSTRACT

Background: Timely vaccination is important to protect children from common infectious diseases. We assessed vaccination timeliness and vaccination coverage as well as coverage of vitamin A supplementation in a Ugandan setting.
Methods and findings: This study used vaccination information gathered during a cluster-randomized trial promoting exclusive breastfeeding in Eastern Uganda between 2006 and 2008 (ClinicalTrials.gov no. NCT00397150). Five visits were carried out from birth up to 2 years of age (median follow-up time 1.5 years), and 765 children were included in the analysis. We used Kaplan–Meier time-to-event analysis to describe vaccination coverage and timeliness. Vaccination coverage at the end of follow-up was above 90% for all vaccines assessed individually that were part of the Expanded Program on Immunization (EPI), except for the measles vaccine which had 80% coverage (95%CI 76–83). In total, 75% (95%CI 71–79) had received all the recommended vaccines at the end of follow-up. Timely vaccination according to the recommendations of the Ugandan EPI was less common, ranging from 56% for the measles vaccine (95%CI 54–57) to 89% for the Bacillus Calmette–Guérin (BCG) vaccine (95%CI 86–91). Only 18% of the children received all vaccines within the recommended time ranges (95%CI 15–22). The children of mothers with higher education had more timely vaccination. The coverage for vitamin A supplementation at end of follow-up was 84% (95%CI 81–87).
Conclusions: Vaccination coverage was reasonably high, but often not timely. Many children were unprotected for several months despite being vaccinated at the end of follow-up. There is a need for continued efforts to optimise vaccination timeliness.

1. Introduction

Timely vaccination is important to obtain adequate disease protection [1–3]. Delayed immunisation is a strong risk factor for disease; in particular for pertussis and *Haemophilus influenzae* type B invasive disease [1,2,4]. It has been shown that late administration of the Bacillus Calmette–Guérin (BCG) vaccine is associated with reduced survival, while early administration improves survival [5].

Some studies have shown that high vaccination coverage rates for individual vaccines do not necessarily imply timely vaccination [3,6–9]. There may also be unspecific effects of vaccines that can be influenced by the timing of the vaccinations, with poten-

Abbreviations: BCG, Bacillus Calmette–Guérin; CI, confidence interval; DTP, diphtheria, tetanus and pertussis; EPI, Expanded Programme on Immunization; HBV, hepatitis B; HiB, *Haemophilus influenza* type B; WHO, World Health Organisation.

* Corresponding author. Tel.: +47 55 58 85 86.
E-mail addresses: lars.fadnes@cih.uib.no, research@fadnes.net (L.T. Fadnes), nankabirwav@gmail.com (V. Nankabirwa), halvor.sommerfelt@cih.uib.no (H. Sommerfelt), thorkild.tylleskar@cih.uib.no (T. Tylleskär), kabaleimc@gmail.com (J.K. Tumwine), ingunn.engebretsen@cih.uib.no (I.M.S. Engebretsen).

[1] List of Members of the PROMISE-EBF Study Group: *Steering Committee*: Thorkild Tylleskär, Philippe van de Perre, Eva-Charlotte Ekström, Nicolas Meda, James K Tumwine, Chipepo Kankasa, Debra Jackson. *Participating countries and investigators*: *Norway*: Thorkild Tylleskär, Ingunn MS Engebretsen, Lars T Fadnes, Eli Fjeld Falnes, Knut Fylkesnes, Jørn Klungsøyr, Anne Nordrehaug-Åstrøm, Øystein Evjen Olsen, Bjarne Robberstad, Halvor Sommerfelt. *France*: Philippe Van de Perre. *Sweden*: Eva-Charlotte Ekström, Barni Nor. *Burkina Faso*: Nicolas Meda, Hama Diallo, Thomas Ouedrago, Jeremi Rouamba, Bernadette Traoré Germain Traoré, Emmanuel Zabsonré. *Uganda*: James K. Tumwine, Caleb Bwengye, Charles Karamagi, Victoria Nankabirwa, Jolly Nankunda, Grace Ndeezi, Margaret Wandera. *Zambia*: Chipepo Kankasa, Mary Katepa-Bwalya, Chafye Siuluta, Seter Siziya. *South Africa*: Debra Jackson, Mickey Chopra, Mark Colvin, Tanya Doherty, Carl Lombard, Ameena E Goga, Lungiswa Nkonki, David Sanders, Sonja Swanevelder, Wanga Zembe (Country PI first, others in alphabetical order of surname).

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Table 1
Coverage and timeliness of all the vaccines in the Ugandan EPI program. Coverage at the end of follow-up and the proportion receiving the vaccinations within the recommended time periods (timely vaccination) are presented with 95% confidence intervals. Similarly, untimely vaccination are categorised into vaccines given earlier or later than recommended.

	Coverage (at end of follow-up)	Timely vaccination	Given too early	Given too late	Not given (at end of follow-up)
BCG vaccine	100% (99–100)	89% (86–91)	0% (0–0)	11% (9–13)	0% (0–1)
Polio 0 (1st oral polio vaccine)	94% (92–96)	67% (63–70)	0% (0–0)	27% (25–29)	6% (4–8)
Polio 1 (2nd oral polio vaccine)	99% (98–100)	70% (68–72)	1% (1–2)	27% (25–30)	1% (0–2)
DPT1 + Hib + HBV (1st pentavalent vaccine[a])	99% (98–100)	70% (68–73)	1% (1–2)	28% (25–30)	1% (0–2)
Polio 2 (3rd oral polio vaccine)	98% (96–99)	77% (74–78)	2% (1–3)	19% (17–21)	2% (1–4)
DPT2 + Hib + HBV (2nd pentavalent vaccine)	97% (96–99)	76% (73–78)	2% (1–3)	20% (18–22)	3% (1–4)
Polio 3 (4th oral polio vaccine)	93% (90–94)	81% (79–83)	2% (1–3)	9% (9–10)	7% (6–10)
DPT3 + Hib + HBV (3rd pentavalent vaccine)	93% (90–94)	83% (81–85)	1% (1–2)	9% (8–9)	7% (6–10)
Measles vaccine	80% (76–83)	56% (54–57)	12% (9–15)	12% (12–12)	20% (17–24)
Vitamin A supplementation	84% (81–87)				

[a] The pentavalent vaccine protects against diphtheria, pertussis, tetanus, *Haemophilus influenzae* type B and hepatitis B.

tial negative consequences of delayed immunisation [10]. Thus, it is important to take timeliness into account, as relying only on vaccination status can lead to a false assumption of disease protection.

Although some studies have evaluated timely vaccination of some selected vaccines, we are only aware of one study in the United States where timely vaccination for all nationally recommended vaccines has been evaluated [9]. Only two studies have assessed timely vaccination for some selected vaccines in an African setting [8,11]. In this study, we assessed immunisation timeliness and vaccination coverage in line with the Expanded Program on Immunization (EPI) including vitamin A supplementation in Mbale district, Eastern Uganda. To our knowledge, this is the first study outside the United States assessing timeliness for all the nationally recommended vaccines for young children.

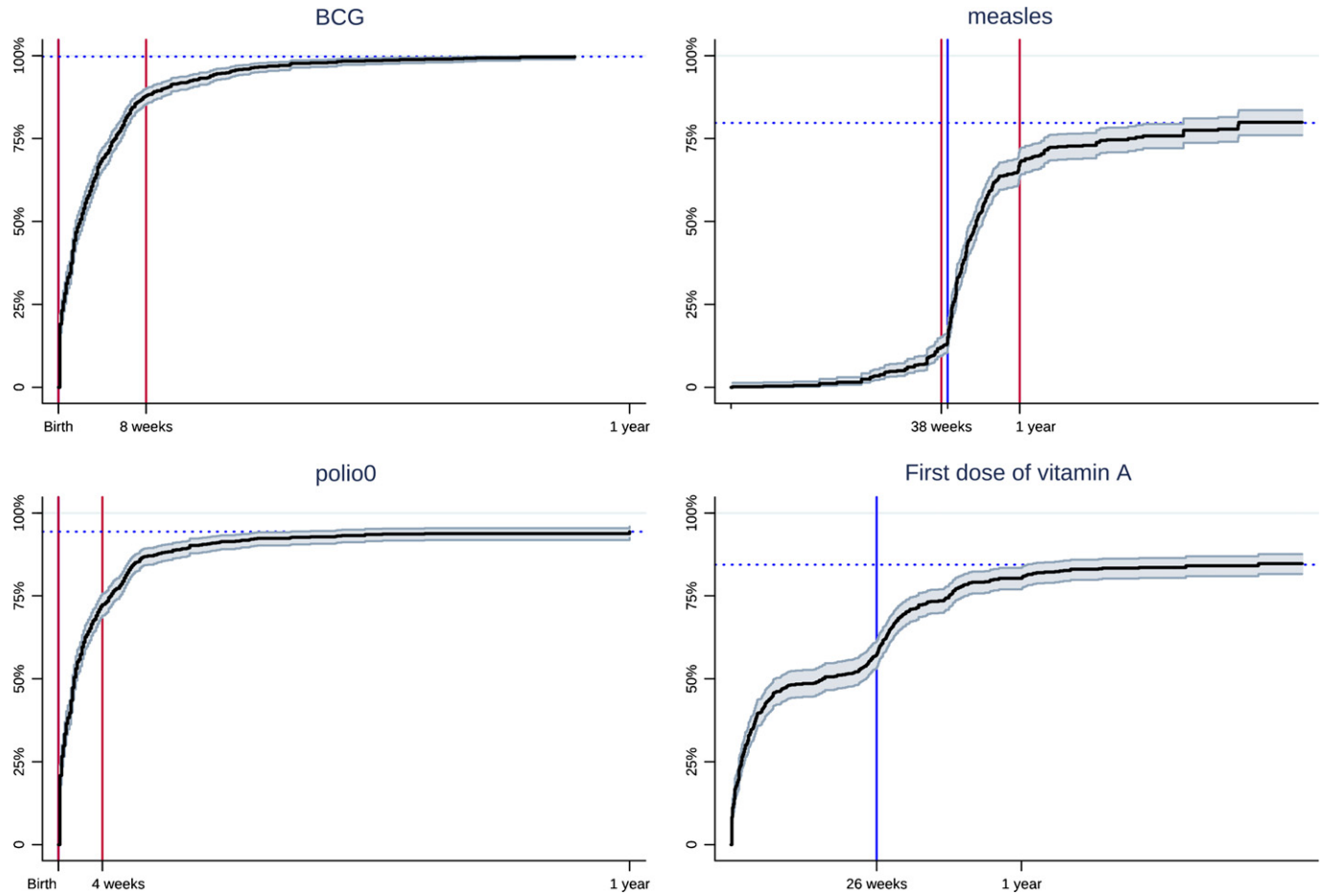

Fig. 1. Time when receiving vaccines presented with Kaplan–Meier plots (inverse and cumulative) for the BCG- and polio0 vaccines (first vaccination visit), measles vaccine (fifth vaccination visit), as well as vitamin A. The *y*-axis indicates the proportion having received the vaccines at each time point. (1) The blue vertical lines indicate the recommended age for vaccination (overlapping with red lines at birth for BCG and first polio vaccine), while the red lines indicate the outer ranges for the recommended age. The horizontal dotted lines represent coverage at the end of follow-up. (2) The labels on the *x*-axis indicate the outer ranges for recommended vaccination age. One year of age is indicated as a scaling, but is also the upper recommended age for the measles vaccine. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

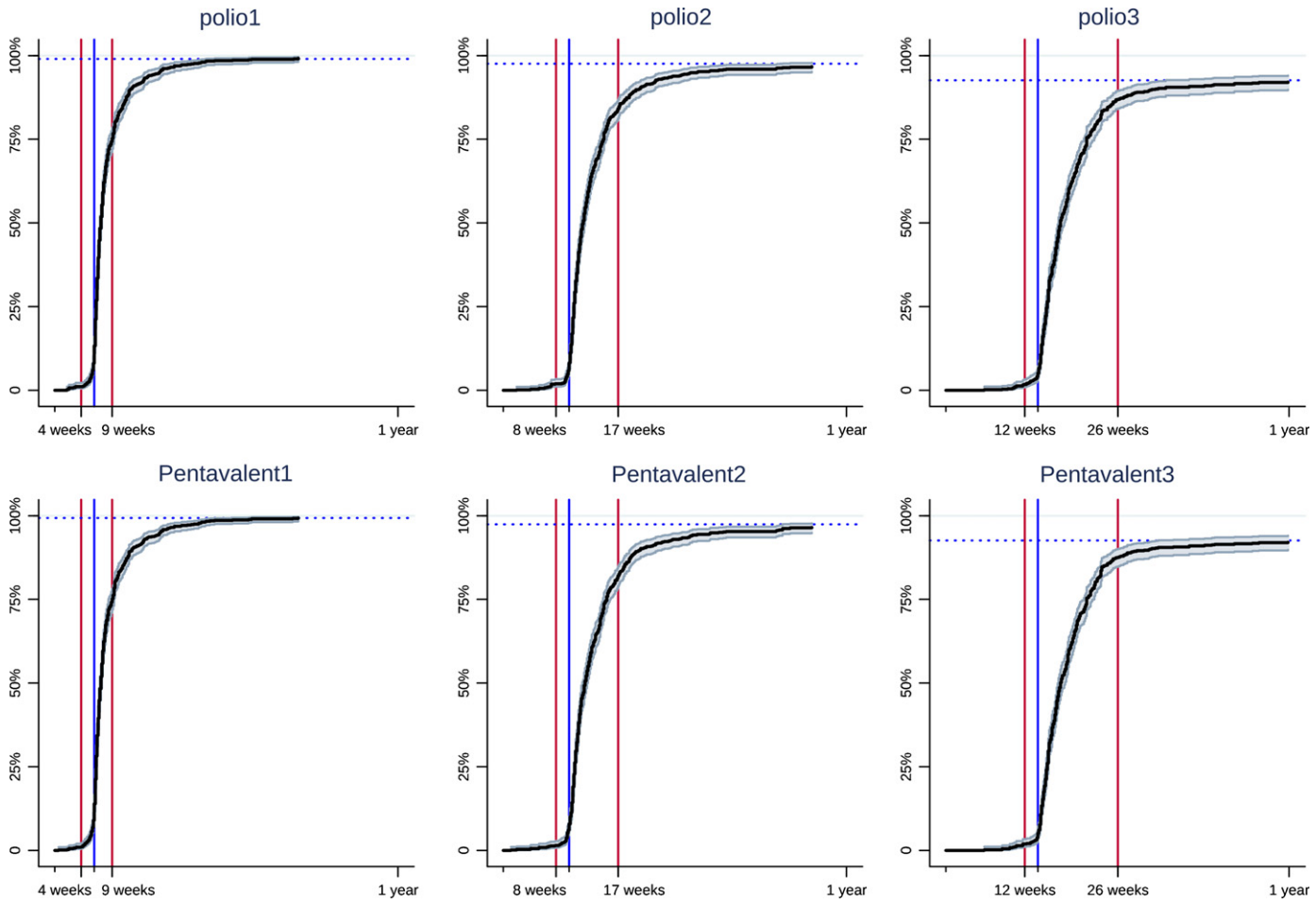

Fig. 2. Time when receiving vaccines presented with Kaplan–Meier plots (inverse and cumulative) for the second, third and fourth vaccination visits where pentavalent vaccines are given together with polio vaccines. The *y*-axis indicates the proportion having received the vaccines at each time point. (1) The blue vertical lines indicate the recommended age for vaccination, while the red lines indicate the outer ranges for the recommended age. The horizontal dotted lines represent coverage at the end of follow-up. (2) The labels on the *x*-axis indicate the outer ranges for recommended vaccination age. One year of age is indicated as a scaling, but is also the upper recommended age for the measles vaccine. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

2. Materials and methods

This study used vaccination information collected between 2006 and 2008 during a community-based cluster-randomized controlled trial promoting exclusive breastfeeding (ClinicalTrials.gov no. NCT00397150) [12]. A total of 24 clusters accessible from roads within a half an hour drive from Mbale Municipality in Mbale District were chosen, with a population of more than 1 000 inhabitants in each cluster. Six of the clusters were from urban areas and 18 of the clusters from rural areas. Each cluster had access to a water source, primary school and market or trading centre – independent of other clusters. From these clusters, 886 women were approached with consecutive sampling of women who were at least 7 months (or visibly) pregnant, intended to breastfeed and remain in the cluster for the coming year, and 863 recruited. Among these, 98 were excluded due to mother having moved or being lost-to-follow-up, twin delivery, death of the infant or mother before 3 weeks after birth, or severe malformations, Fig. S1. Vaccination assessment was done both for the intervention and control arms. Thus, 765 mother–infant pairs remained in the analysis. The mother–infant pairs were scheduled to be interviewed at 3, 6, 12 and 24 weeks after birth, with an additional follow-up interview at around 2 years of age. The median follow-up time was 1.5 years.

2.1. Study settings

In 2008, Mbale had a population of 403,100 [13]. The district is predominantly rural with 59% home deliveries, and an antenatal attendance of 95% [13]. The under-5-mortality rate was 137 per 1000 live births in 2004–2005, and the HIV-prevalence in Eastern Uganda was 6.2% [13,14].

2.2. Data management

Data was collected through interviews by data collectors speaking the local language Lumasaaba, and entered directly into handheld computers with the program EpiHandy using an electronic questionnaire. Stata was used for analysis (version SE11.1, Stata Corporation).

2.3. Vaccination timeliness and coverage

The EPI in Uganda recommends the following vaccines to be given at specific ages (time ranges given in parentheses) [8,15]: The first vaccination is at birth where the BCG (birth to 8 weeks) and oral polio (birth to 4 weeks) vaccines are given. The following three vaccination visits includes the oral polio vaccine and a

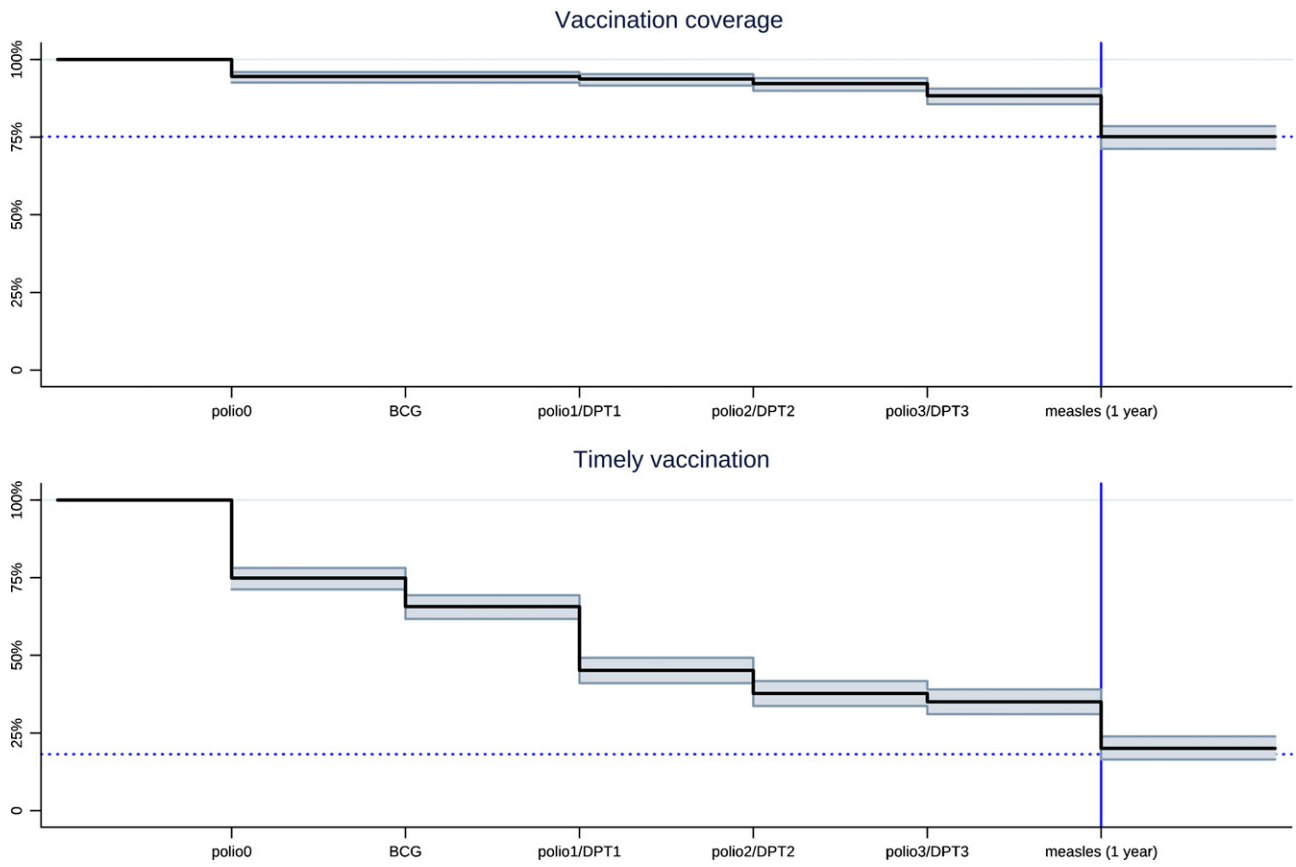

Fig. 3. Complete immunisation coverage and timeliness. The upper graph illustrates the proportion of the children receiving all the vaccines up to each specific vaccine. The lower graph illustrates the proportion receiving all the respective vaccines within the recommended time ranges up to the specific time points. (1) Coverage: The line drops represent the proportion that has got all the vaccines to that point, but does not get the given vaccine (e.g. if a child get all vaccines except the last pentavalent vaccine, the child will add to the line drop at polio3/DTP3). (2) Timeliness: The line drops represent the proportion that has got all the vaccines to that point within their recommended time ranges, but does not get the given vaccine within the recommended range (e.g. if a child get all vaccines within recommend time except the measles vaccine, the child will add to the line drop at measles).

pentavalent vaccine which protects against diphtheria, tetanus and pertussis (DTP), *H. influenzae* type B (Hib) disease and hepatitis B (HBV). The first dose is given at 6 weeks (4 weeks to 2 months), then again at 10 weeks (8 weeks to 4 months), and at 14 weeks (12 weeks to 6 months). The measles vaccine is given at 9 months (38 weeks to 12 months). Coverage was determined at the end of follow-up. In Uganda, vitamin A supplementation is part of the Expanded Program on Immunization [15], and was also assessed.

2.4. Analysis

Vaccination timeliness was analysed with Kaplan–Meier time-to-event analysis in line with Laubereau et al. [16]. Vaccination data and dates of birth were gathered from the children's health cards. Vaccination information based on maternal recall was also collected, but the data from the health cards are regarded to be of better quality. Thus, the health card information has been used for analysis when available. Most vaccinations were dated in the health cards, but when vaccinations were registered without a date, we assumed that the age when the children were given the specific vaccines was similar as for those with dated vaccinations. The confidence intervals were estimated with Greenwood's point-wise method. To investigate determinants of timely vaccination, we used cluster adjusted Cox regression analysis. As the Cox regression model evaluated timeliness which has an accepted time range, there will be several ties (with the same vaccination time). We used the exact partial-likelihood method for handling ties to improve model robustness. The assumption of proportional hazards was checked with Schoenfeld residuals, both graphically, with a significance test, and using a piecewise regression method. Tied cases were handled with the exact partial-likelihood method. Rational interactions were evaluated and were included in the model only if they had significant and meaningful effects. Log linearity was checked with plotting of Martingale residuals for the complete model vs. a model with one omitted variable. No variables were strongly correlated with each other. We present a univariable as well as a multivariable model, the latter using stepwise selection with removal of covariates when $p > 0.1$.

Socioeconomic wealth index was constructed with the use of multiple correspondence analysis based on ownership of assets as furniture and household characteristics including electricity, a water source, roof material and toilet type. This method is analogous to principal component analysis, and better suited for categorical data [17]. The children's families were grouped into quintiles on the basis of socioeconomic rank.

2.5. Ethics

Ethical approval was granted by Makerere University Medical School Research, Ethics Committee and the Uganda National Council for Science and Technology, and Regional Committees for Medical and Health Research Ethics, Western Norway. Signed or thumb-printed informed consent was obtained from each mother prior to study participation. The consent procedure was approved by the ethical committees.

Table 2
Baseline characteristics for study participants presented with number (*n*) and percentages, and determinants for untimely vaccination (not receiving the vaccines within the recommended time period) estimated with a Cox regression model with 95% confidence intervals (cluster adjusted).

	n (%)765	Hazard ratio for failure to timely vaccination with 95% CI (unadjusted model[a])
Mother's age		
≤19	130 (17)	1
20–24	246 (33)	0.84 (0.63–1.12)
25–29	179 (24)	0.87 (0.65–1.18)
≥30	200 (26)	1.01 (0.74–1.36)
Marital status		
Married or cohabiting	701 (92)	1
Single, widowed, separated or divorced	57 (8)	0.79 (0.49–1.26)
Gender of infant		
Girl	375 (49)	1
Boy	387 (51)	0.99 (0.83–1.18)
Mother's education		
None	56 (7)	1
Primary education (1–6 years)	342 (45)	0.87 (0.67–1.12)
Secondary education (7–10 years)	284 (38)	0.76 (0.58–0.99)
Higher education (11 years or above)	74 (10)	0.53 (0.36–0.80)
Socio-economic wealth index		
Poorest quintile	153 (20)	1
2nd quintile	183 (24)	1.04 (0.83–1.30)
3rd quintile	125 (16)	1.17 (0.91–1.51)
4th quintile	155 (20)	0.99 (0.77–1.28)
Least poor quintile	149 (19)	0.98 (0.78–1.22)
Living area		
Rural	566 (74)	1
Urban	199 (26)	0.95 (0.73–1.22)
Place of delivery		
Home	354 (48)	1
In facility (hospital, health clinic)	378 (52)	0.91 (0.74–1.11)
Health councelling		
Normal	369 (48)	1
Additional peer-counselling	396 (52)	1.03 (0.90–1.17)
Number of siblings		
None	173 (23)	1
1–2	232 (31)	1.02 (0.75–1.38)
3 or above	347 (46)	1.26 (0.95–1.67)
Mother's body mass index (BMI)		
<20	125 (19)	1
20–24.9	446 (68)	0.98 (0.81–1.18)
25–29.9	74 (11)	1.12 (0.88–1.43)
≥30	10 (2)	1.24 (0.72–2.15)

[a] Only unadjusted model is presented as the only variable that was significantly associated with vaccination timeliness was mother's education. Interactions were checked and none were considered meaningful to include.

3. Results

A health card was seen for 750 (98%) of the 765 participants. Of these, 732 (96%) were dated for at least one vaccine, Fig. S2. The majority had dated health cards available for most of the interviews with the exception of the 2 years interview, when many cards had been lost or were no longer readable due to wear and tear.

Vaccination coverage at the end of follow-up ranged from 80% for the measles vaccine (95% confidence interval 76–83) to 100% for the BCG vaccine (95%CI 99–100), see Table 1 and Figs. 1 and 2, Fig. S3. The vaccination coverage rates for each vaccine at specific ages (3 months, 6 months, 12 months and 18 months) and median delays with inter-quartile ranges (IQR) are available in Table S1. The proportion of infants that had received all the vaccines was 75% (95%CI 71–79), see Fig. 3 which represents cumulative vaccination.

The coverage for vitamin A supplementation based on health card information was 84% (95%CI 81–87). Of these, 68% received supplementation together with vaccines – in particular together with the BCG vaccine. Self-reported information on vitamin A supplementation differed from health card information, with 94% reporting that their children had been given vitamin A.

Timely vaccination ranged from 56% for the measles vaccine (95%CI 54–57) to 89% for the BCG vaccine (95%CI 86–91). Among those who were vaccinated late with the measles vaccine, the median age at vaccination was 64 weeks. This is equivalent to a median delay of 24 weeks from the recommended timing (11 weeks delay from the end of the recommended range.) Only 18% received all the vaccines within the recommended time ranges (95%CI. 15–22).

3.1. Determinants of timely vaccination

The Cox regression model revealed a dose–response relationship between mother's education and timely vaccination, both in the univariable analysis and the multivariable models, see Table 2. This association was evident also when using years of schooling as a continuous variable (hazard ratio 0.94 per year of education; 95%CI 0.91–0.97; $p < 0.001$). Vaccination did not differ between the intervention and control clusters of the intervention promoting exclusive breastfeeding for 6 months through peer counselling.

4. Discussion

Although the coverage for the individual EPI vaccines was reasonably high with the exception of the measles vaccine, timely and age-appropriate vaccination was lower. About a quarter of the vaccines were given outside the recommended time ranges. Around 75% of the children received all the recommended vac-

cines, but only 18% got all vaccines within their recommended time ranges. The coverage rates for the individual vaccines we report were slightly different from the national reported statistics from Uganda in 2008 [18,19]. According to these, Mbale District had a coverage rate of 85% for the third oral polio vaccine (compared to our estimate of 93%), which is higher than the national estimate of 79%. For measles, the reported number in Mbale was 105% (compared to our estimate of 80%), with a national estimate of 77%. It is necessary to recognise that there is substantial variation across the districts, and that the nationally reported numbers may not accurately reflect district-specific estimates, for example due to '*cross boundary immunisation*'.

There is hardly any data on vaccination timeliness in Uganda, but findings from studies having assessed timeliness elsewhere indicate that timely vaccination is often far from optimal [3,6–9,11]. This strengthens the argument to monitor not only *whether* children are vaccinated, but also *when* they receive the recommended vaccines.

Despite gradual improvements in vaccination coverage and a large reduction in measles, pertussis and tetanus mortality, in 2008, these diseases were still responsible for about 4% of the child mortality globally, and nearly 6% of around 190 000 child deaths in Uganda [20]. These deaths are vaccine preventable, and diseases such as measles can potentially be eliminated with vaccination [21,22]. A coverage rate of measles vaccine exceeding 95% has been indicated as a necessary level when aiming for elimination [23,24]. This study population had measles vaccine coverage far below this threshold (80% coverage, and 56% received the measles vaccine within the recommended time period). This leaves many children susceptible to diseases after their maternal antibodies drop to levels insufficient to protect them [1–3]. For the BCG vaccine, it has been suggested that late administration may have an adverse impact [5]. There may also be indirect effects of timing of immunisation, but larger studies are needed before conclusions about these potential effects can be made [10].

For the measles vaccine, it can be argued that early vaccination which was given to 12% in this study is an advantage, but this will then require re-immunisation as evoked immune responses are weakened [23,25,26]. In addition, severely immunocompromised children may develop active measles disease caused by the measles vaccination, which complicates immunisation assessment of some HIV-positive children [27].

Vitamin A was in this study given to nearly half of the babies already in the neonatal period. There is good evidence of a beneficial effect on mortality from vitamin A supplementation between the age of 6 months and 5 years, but conflicting evidence when given early in infancy [28–32]. The information on vitamin A from this study exemplifies how self-reported data can differ from recorded data, with an absolute discrepancy of 10%. As it may be difficult to remember whether a capsule was given to the child several months ago, we assume that the prospectively collected data from the health cards is of better quality. The fact that many lost their health cards, further complicates the decision for health personnel on whether the children should give a vaccine or vitamin A dose when they come for a visit to the health clinic. These issues are likely to remain unsolved as long as only paper-based records are used as they are today.

It should be kept in mind that a complex system is required to have a well functioning vaccination program [33]. Both contextual and individual factors are essential for utilization of health services [34]. Identified characteristics of a well functioning vaccination system include good availability of health services and short waiting time, media promotion and campaigns [33]. Another key factor is the distance to the clinics [35]. In Uganda, there are several programmatic challenges that could partly explain the untimely vaccinations. These include logistical challenges such as storage of sufficient vaccine stocks at all times, maintaining a cold chain system, and inadequate staffing at health facilities.

A review of the effect of vaccination reminders concluded that these were effective in improving vaccination rates – particularly phone call reminders [36]. In settings where mobile phones are becoming widespread, a strategy using either text messages or phone call reminders could be a feasible option. There are already some digital-based systems for immunisation in the pipeline targeted also for low-income countries [37]. We think such a strategy could give a better overview of the children's vaccination status, as well as opening opportunities for automated messages to remind parents about vaccination visits. This could improve both timeliness and coverage [36]. Connecting programs with different disease preventive strategies can improve the quality as well as reducing cost [38]. One suggestion has been to link measles vaccination with distribution bed-nets for malaria prevention.

Mother's education was associated with timely vaccination. There was an exposure-response trend with timely vaccination and education – the more education the better timeliness. It has also been reported that maternal education has been associated with better vaccine coverage [39]. The association between timely vaccination and higher education has also been suggested by a study from the United States [9]. Other studies have also indicated that poorer families often are more difficult to reach with immunisation [40]. We did not find any associations between socioeconomic status and timely vaccination, and there were no tendencies to less timely vaccinations among the poorest which is encouraging.

4.1. Limitations and strengths

The children who died during follow-up might have had different vaccination status compared to the surviving majority [41], but mortality was low and therefore this is unlikely to have biased the estimates substantially. As most of the clusters were close to main roads, the clusters might have been easier accessible than several other areas. Generalisability of the rates of timely vaccination and vaccination coverage is therefore limited to settings with similar characteristics. The nationally reported statistics on vaccination can give some indications on how the findings relate to other areas in Uganda, but these statistics are sub-optimal. The much lower rates of timely vaccination than vaccination coverage has also been reported in several other settings, and are likely to be applicable to a wider area. The timeliness of the few children who had immunisation indicated as received but not dated in the health card, could be different from the many where it was dated. However, these children had similar baseline characteristics (data not shown), and we therefore believe that this has not biased the estimates markedly. Contraindications for vaccination were not assessed [27], but this is applicable only for a few children. In some cases, it may be justified to postpone vaccination temporarily when children are moderately or severely ill [27]. Vaccination is then recommended to be given soon after recovery. Some children may have been HIV-positive with severe immune suppression. Assessment of whether and when measles vaccination for these children should be given is more complicated [27]. Among those few who had tested their children, none reported that their children were HIV-positive (data not shown).

5. Conclusions

This study shows that high immunisation coverage rates do not necessarily imply age-appropriate vaccination status. Many children were unprotected by vaccination for several months despite being vaccinated at the end of follow-up. For the future, immunisation monitoring should focus not only on *whether* children get

immunised, but also *when* they do. Continued efforts are needed to improve vaccination timeliness.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2011.02.093.

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