



Assessing the timeliness of vaccine administration in children under five years in India, 2013



Abram L. Wagner^{a,*}, Luke M. Shenton^a, Brenda W. Gillespie^{b,c}, Joseph L. Mathew^d, Matthew L. Boulton^{a,e}

^a Department of Epidemiology, School of Public Health, University of Michigan, 1415 Washington Heights, Ann Arbor, MI, USA

^b Department of Biostatistics, School of Public Health, University of Michigan, 1415 Washington Heights, Ann Arbor, MI, USA

^c Consulting for Statistics Computing and Analytics Research, University of Michigan, 915 E Washington St, Ann Arbor, MI, USA

^d Department of Pediatrics, PGIMER, Chandigarh, India

^e Department of Internal Medicine, Division of Infectious Disease, Michigan Medicine, 1500 E Medical Center Drive, Ann Arbor, MI, USA

ARTICLE INFO

Article history:

Received 12 September 2018

Received in revised form 18 December 2018

Accepted 19 December 2018

Available online 27 December 2018

Keywords:

Immunization programs

India

Kaplan-Meier estimate

ABSTRACT

Morbidity from vaccine-preventable diseases is high in India, but precise estimates of vaccination timeliness are difficult to compute because many children lack records of vaccination dates. This study assessed vaccination timeliness after accounting for right and left censoring of data. This cross-sectional study used the 2012–2013 District Level Household and Facility Survey in India. The outcome was vaccination timeliness for 9 vaccine doses: 1 dose Bacillus Calmette-Guérin (BCG), 4 doses oral polio vaccine, 3 doses diphtheria-pertussis-tetanus vaccine (DPT), and 1 dose measles-containing vaccine. Age-specific probabilities of vaccination were calculated using Turnbull estimators: children not yet vaccinated were right censored, and children vaccinated but without a recorded date were left censored. Data from 108,783 children under 5 years were available. For children 25–60 months, maternal recall was a more common source of information than a vaccination record with dates. At one month past the recommended vaccination age, estimated coverage ranged from 35% for DPT-3 to 55% for BCG. Accounting for censored data improved vaccination timeliness measures, and demonstrated little increase in vaccination coverage after age one. Efforts to reduce morbidity from vaccine-preventable diseases in India should focus on eliminating missed opportunities for vaccination and instituting special vaccination programs for older children.

© 2018 Elsevier Ltd. All rights reserved.

1. Introduction

In 2016, approximately one-fifth of the five million deaths among children under 5 years worldwide occurred in India [1]. Almost 20% of deaths among children under 5 years were due to vaccine-preventable diseases, principally pneumonia, diarrhea, and measles [2]. Despite the well-recognized benefits of childhood immunizations, vaccination coverage in low- and middle-income countries, including India, remains far below recommended levels [3,4]. India is home to 3.1 million of the 19.5 million children worldwide who have not received diphtheria-pertussis-tetanus (DPT) dose 3 vaccine, a commonly used measure of immunization system performance [4]. Only 62% of Indian children have been fully vaccinated [5].

Traditionally, immunization programs have been evaluated based on vaccination coverage—the proportion of vaccinated children at specific ages without consideration given to the timeli-

ness of vaccine dose administration [6–8]. India, and other low- or middle-income countries, are currently investing significant resources into increasing the coverage of routine childhood vaccinations [9], and have used vaccination coverage as an overall indicator of immunization system performance and assessment of risk for transmission of vaccine-preventable disease. However, simply looking at vaccination coverage does not account for possible delays in vaccination, and coverage estimates can vary substantially depending on the specific age range(s) addressed in a particular study.

In this study, we assessed timeliness of India's government-funded vaccination program. A prior study performed using 2008 District Level Household and Facility Survey (DLHS3) data found that 69% of BCG doses, 81% of DPT-3 doses, and 65% of MCV doses were delayed [10]. We hypothesized that unacceptably high rates of delayed vaccination would still exist in 2013 although with improvement in vaccination timeliness compared to 2008, given the government's investment in increasing childhood vaccination. We used nationally representative data from the 2012–2013 District Level Household and Facility Survey (DLHS4) to identify the

* Corresponding author at: 1415 Washington Heights, Ann Arbor, MI 48109, USA.
E-mail address: awag@umich.edu (A.L. Wagner).

cumulative probability of vaccination by age by vaccine. We used the Turnbull estimation technique to address left- and right-censored vaccination data [11]. The findings can be used to help ascertain progress towards the Sustainable Development Goal of reducing under 5 mortality to ≤ 25 per 1000 livebirths by 2030 [12], and Turnbull methods can be used in other settings where both left- and right-censored data are common.

2. Methods

2.1. Study population

This study used cross-sectional data from the DLHS4, which was conducted in India during 2012–2013. At the time of data collection, India has 28 states and 7 union territories, further divided into 640 districts. The DLHS4 included data from 18 states and 3 union territories, comprising 273 districts (43% of all districts). Data from another 9 states, representing 284 districts, is available in the Annual Health Survey, a separate survey conducted in 2013; this survey does not include any information on dates of vaccine administration so could not be used in this analysis.

The DLHS used a stratified, multi-stage sampling scheme: (1) the first level comprised 273 districts, (2) at the second level, rural villages and urban blocks were separately selected through a probability-proportionate-to-size method, (3) within each village or block, 25 households were systematically selected, and (4) any ever-married woman 15–49 years old within the household was interviewed. Information was collected about reproductive health, maternal care, childhood immunizations, and childcare. This analysis included the last surviving child from each household who were aged 0–60 months at the time of data collection. Mothers were asked about their child's vaccination status. If a vaccination card was available, the interviewer wrote down the vaccination date. If a vaccination card was not available, the interviewer asked the mother if a certain vaccine was given, and the mother responded without providing a date. Further information regarding the survey methodology for DLHS, and the datasets themselves, are available through the International Institute for Population Sciences [13].

This data analysis considered the timeliness of the 9 vaccine doses, which were part of the government-funded Universal Immunization Program at the time of the DLHS4. Under the Universal Immunization Program, a single bacillus Calmette-Guérin (BCG) vaccine dose is recommended at birth; 4 doses of the oral polio vaccine (OPV-0 through OPV-3) vaccine are recommended at birth, 6 weeks, 10 weeks, and 14 weeks of age; 3 doses of the DPT vaccine (DPT-1 through DPT-3) are recommended at 6 weeks, 10 weeks, and 14 weeks; and one dose of the measles-containing vaccine (MCV) vaccine is recommended at 9 months.

2.2. Outcome

The outcome of interest was vaccination timeliness for each of the 9 vaccine doses examined. Age at vaccination was calculated by subtracting the child's birthdate from the child's vaccination date. Only the month and year of birth were available for each child, so the birth date of each child was imputed as the fifteenth of the month as an approximate median value. Children who were vaccinated within the first 14 days of life were coded as having been vaccinated on day 1. Also, some children's vaccination dates included the month and year, but not day. For these children also, the day was set to the fifteenth of the month. The age of interview in the DLHS was calculated by subtracting the child's birthdate from the interview date.

In the DLHS, mothers who did not have vaccination cards for their children were asked to recall whether their child was vaccinated or not. A child without a vaccination card whose mother indicated that the child was *not* vaccinated was right censored at the age of interview. Right censoring indicated that it was still possible that the child could be vaccinated in the future. A child without a vaccination card, whose mother indicated that the child was vaccinated but did not recall the date, was left censored at the age of interview. Left censoring indicated that the child was vaccinated sometime before the date of the interview.

Several measures of vaccination uptake were assessed. Vaccination coverage refers to administration of a particular dose (regardless of whether dose status was determined through an immunization card or maternal recall); cumulative vaccination coverage refers to the proportion vaccinated at a certain age (and accounting for both left and right censoring); as a proportion, we calculated vaccination timeliness to be the cumulative vaccination coverage at 1 month (i.e., 30 days) after the recommended vaccination age.

2.3. Statistical analysis

The age-specific probability of vaccination was estimated using the Turnbull estimator, which allows the use of left, right, and interval censoring; this possibility permitted many observations to be included in the analysis that might otherwise have been excluded. To produce unbiased cumulative distribution function estimates, we weighted participants to reflect the complex sampling design and the overall inverse probability of being sampled into the DLHS4 dataset. The cumulative distribution function estimates for each vaccine dose were plotted to graphically depict the cumulative vaccination coverage by age.

The median age at vaccination for each vaccine dose was estimated as the number of days after birth at which 50% of children had been vaccinated. For ease of graphically depicting the data, we converted weeks into months for the target age of vaccination (i.e., 6 weeks into 1.5 months, 10 weeks into 2.5 months, and 14 weeks into 3.5 months). The probability of timely vaccination (i.e., vaccination within 30 days of the target age) was estimated as the cumulative probability of vaccination (also called 'coverage') at the target age plus 30 days. The median age at vaccination among just those children who were delayed (i.e., vaccinated 30 or more days after the target age) was also estimated as the age at which 50% of the children not vaccinated by the target age plus 30 days were vaccinated. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary NC, USA).

2.4. Ethics approval

This study was exempt from ethical approval because it was limited to a publicly-available dataset that contained no personally identifiable information. All participants had provided informed consent before being enrolled into the study.

3. Results

The DLHS4 dataset had information on 108,783 children under 5 years. Of these, 80 were excluded because of a missing birthdate, 20 were excluded because of a missing interview date, and 56 were excluded because of missing sampling weights, which left a total of 108,627 children available for analysis. Further exclusions by specific vaccine were made for the few individuals who had no vaccine-related information for a particular vaccine dose, and so neither right- nor left-censoring assumptions could be made (i.e., no information on vaccine administration, the vaccination

recorded with an implausible date, or the mother could not recall whether a dose was given) resulting in the following sample sizes by vaccine dose: 108,094 for BCG, 108,172 for OPV-0, 108,223 for OPV-1, 108,291 for OPV-2, 108,316 for OPV-3, 108,172 for DPT-1, 108,246 for DPT-2, 108,263 for DPT-3, and 108,388 for MCV.

Table 1 lists the source of vaccination information and overall vaccination coverage for children by age. For example, among infants ≤ 12 months, 86% had received BCG, but only 45% of infants in this age range had a documented date of vaccination. Maternal recall was a common source of vaccination data and supplied information for 41% of infants in this age range. In general, vaccination coverage was higher in children over 1 year than under 1 year; for example, OPV-1 coverage was 77% in infants 0–12 months, but above 88% for older children. However, there were not substantial differences in vaccination coverage by age for children more than 1 year old; for example, DPT-3 coverage was 70% for children 13–24 months and 66% for children 49–60 months. Maternal recall was a more common source of information than a vaccine record with a date for older children 25–60 months (Table 1). A vaccination record with a date was more common than maternal recall only for children 0–12 months (BCG, OPV-0, OPV-2, OPV-3, and DPT series, but not MCV and OPV-1), and for children 13–24 months (OPV-2, OPV-3, DPT-2, and DPT-3).

More precise estimates of age-specific probabilities of vaccination were calculated using Turnbull estimators (Table 2), which could account for both left and right censoring. At one month past the targeted age at vaccination, estimated coverage was 55% for BCG and 48% for OPV-0 (both recommended at birth), 66% for OPV-1 and 64% for DPT-1 (both recommended at 6 weeks), 49%

for OPV-2 and 48% for DPT-2 (both recommended at 10 weeks), 37% for OPV-3 and 35% for DPT-3 (both recommended at 14 weeks), and 50% for MCV (recommended at 9 months). This information is graphically depicted in Fig. 1. More uncertainty in the estimates of age at vaccination are seen at older ages because of a large proportion of vaccine doses without precise information on dates of administration.

As shown in Table 3, a large proportion of doses (35% to 65% depending on the antigen dose) were administered after the recommended age for administration. The median age at vaccination exceeded the timeliness range for OPV-2, DPT-2, OPV-3, DPT-3, and MCV: for BCG, which was recommended between birth and 1 month the median age at vaccination was 0.60 months, and for OPV-0, this was 0.80 months. For those who were vaccinated after the recommended age range, the median age at vaccination was before 1 year for all vaccine doses except MCV. Finally, vaccine delay or non-vaccination occurred in over 50% of children for 5 of the 9 vaccine doses. Only for BCG, OPV-0, OPV-1 and DPT-1 did less than 50% of children have delayed vaccine administration.

4. Discussion

Receiving timely administration of the full complement of recommended vaccines can ensure that children have sufficient protection against highly morbid infectious conditions. Using 2013 data from over 100,000 children from 21 states and union territories of India, this study highlights widespread untimeliness of vaccination, and, importantly, suggests that relying solely on

Table 1
Childhood vaccinations received by age and by source of vaccination information, India, 2013.

	Child's age in months at interview				
	0–12 (n = 21,489)	13–24 (n = 21,433)	25–36 (n = 20,606)	37–48 (n = 17,213)	49–60 (n = 7,466)
BCG given	86.26%	90.71%	89.58%	89.01%	88.27%
Recorded, with date	44.75%	42.63%	33.45%	27.48%	24.96%
Recorded, no date	0.37%	0.46%	0.37%	0.34%	0.39%
Maternal recall	41.11%	47.61%	55.76%	61.17%	62.90%
OPV-0 given	71.97%	76.06%	73.73%	72.38%	72.14%
Recorded, with date	38.64%	36.87%	28.85%	23.08%	20.60%
Recorded, no date	0.56%	0.68%	0.57%	0.59%	0.70%
Maternal recall	32.77%	38.50%	44.30%	48.69%	50.82%
OPV-1 given	76.77%	89.92%	89.41%	88.95%	88.74%
Recorded, with date	35.80%	40.85%	32.18%	26.33%	24.11%
Recorded, no date	0.38%	0.37%	0.33%	0.27%	0.29%
Maternal recall	40.57%	48.68%	56.90%	62.35%	64.33%
OPV-2 given	59.87%	80.30%	79.02%	77.86%	76.98%
Recorded, with date	30.89%	39.97%	31.72%	26.02%	23.74%
Recorded, no date	0.45%	0.39%	0.39%	0.23%	0.24%
Maternal recall	28.51%	39.91%	46.92%	51.61%	53.01%
OPV-3 given	44.86%	73.27%	73.63%	73.05%	72.88%
Recorded, with date	25.08%	38.49%	30.81%	25.38%	23.03%
Recorded, no date	0.53%	0.44%	0.42%	0.25%	0.38%
Maternal recall	19.22%	34.31%	42.38%	47.41%	49.47%
DPT-1 given	73.19%	87.40%	86.00%	85.22%	84.79%
Recorded, with date	39.48%	42.67%	33.31%	27.34%	24.86%
Recorded, no date	0.29%	0.28%	0.25%	0.18%	0.27%
Maternal recall	33.39%	44.43%	52.43%	57.71%	59.64%
DPT-2 given	57.93%	78.93%	76.96%	75.69%	74.86%
Recorded, with date	33.91%	42.11%	33.06%	27.05%	24.73%
Recorded, no date	0.00%	0.00%	0.00%	0.00%	0.00%
Maternal recall	23.99%	36.80%	43.90%	48.65%	50.12%
DPT-3 given	43.48%	69.90%	68.11%	66.54%	66.12%
Recorded, with date	26.91%	40.13%	31.81%	26.10%	23.73%
Recorded, no date	0.53%	0.37%	0.34%	0.23%	0.33%
Maternal recall	15.98%	29.36%	35.94%	40.20%	42.05%
MCV given	33.40%	81.10%	82.75%	82.75%	83.18%
Recorded, with date	8.73%	36.18%	29.44%	24.19%	22.38%
Recorded, no date	0.74%	0.62%	0.54%	0.38%	0.42%
Maternal recall	23.85%	44.23%	52.75%	58.16%	60.35%

Abbreviations: BCG, Bacille Calmette-Guérin; DPT, diphtheria-pertussis-tetanus vaccine; OPV, oral polio vaccine; MCV, measles-containing vaccine.

Table 2
Estimated age-specific probability of vaccination among children under 5, India, 2013.

Vaccine series (target age for administration) ^a									
Age in months ^b	BCG (birth)	OPV-0 (birth)	OPV-1 (1.5 m)	DPT-1 (1.5 m)	OPV-2 (2.5 m)	DPT-2 (2.5 m)	OPV-3 (3.5 m)	DPT-3 (3.5 m)	MCV (9 m)
0.5	35.26	32.29							
1	54.97	47.93	6.87	5.42					
1.5	64.95	55.49	22.18	19.34					
2	73.43	61.22	49.64	47.80	5.13	4.22			
2.5	77.63	64.12	65.79	63.92	14.31	13.12			
3	80.35	66.07	73.46	71.45	33.41	32.23	4.15	3.62	
3.5	81.76	67.19	77.18	74.99	49.18	48.03	10.08	9.02	
4	82.89	67.96	79.41	77.15	58.51	57.29	23.82	22.09	
4.5	83.60	68.49	80.86	78.53	63.68	62.28	37.14	34.76	
6	84.94	69.41	83.03	80.62	70.39	68.83	56.43	52.88	
9	86.14	70.35	84.68	82.13	74.03	72.41	65.70	61.46	19.01
10	86.42	70.58	84.99	82.37	74.59	72.94	67.19	62.71	49.98
11	86.68	70.80	85.27	82.61	74.94	73.28	68.11	63.53	66.00
12	87.14	71.21	85.52	82.82	75.27	73.58	68.68	64.03	71.50
18	89.32	73.32	88.80	85.44	77.99	76.13	71.90	66.79	78.79
24	89.56	73.83	89.17	85.81	78.50	76.58	72.83	67.60	82.64
30	89.94	74.25	89.62	86.21	79.00	77.04	73.38	68.06	83.36
36	90.01	74.35	89.77	86.34	79.12	77.19	73.59	68.26	83.96
42	90.13	74.48	89.91	86.47	79.28	77.32	73.81	68.41	84.20
48	90.19	74.54	89.97	86.54	79.35	77.37	73.91	68.50	84.49
60	90.29	74.72	90.09	86.63	79.53	77.46	74.04	68.63	84.69

Abbreviations: BCG, Bacille Calmette-Guérin; DPT, diphtheria-pertussis-tetanus vaccine; OPV, oral polio vaccine; MCV, measles-containing vaccine.

^a N = 108,094 for BCG, 108,172 for OPV-0, 108,223 for OPV-1, 108,291 for OPV-2, 108,316 for OPV-3, 108,172 for DPT-1, 108,246 for DPT-2, 108,263 for DPT-3, and 108,388 for MCV.

^b Each age represents the interval from the given age up to but not including the next age. Probabilities of *timely* vaccination (1 month after the recommended vaccination age) are in bold. Analysis based on the Turnbull estimator, including left- and right-censored data.

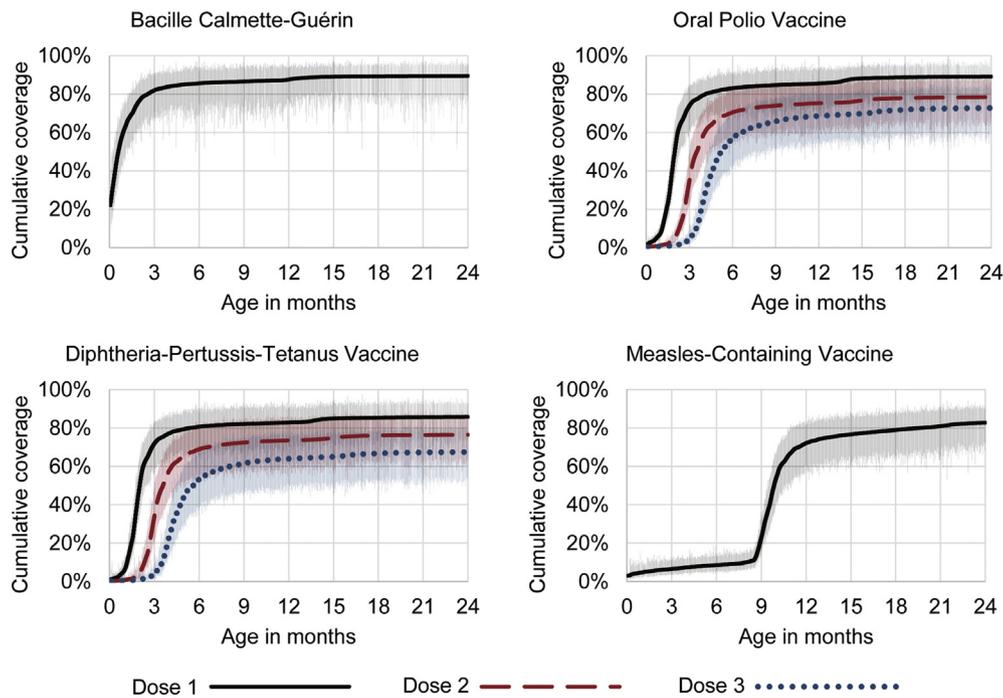


Fig. 1. Cumulative coverage (probability of vaccine administration) by age for four different vaccine series in India, 2013. Faint lines indicate 95% confidence intervals.

estimates of vaccine coverage that do not account for age at vaccination for those children, and for the large proportion of children without information on vaccination dates, can lead to misleading findings. Using DPT-3 as an example, vaccination coverage (regardless of timing) using typical age cut-off measures was 43% for infants < 12 months, but 66% for children 49–60 months; however, only 35% of doses were given within one month of the recommended age (3.5 months of age), and 50% of children were vaccinated after 5.67 months of age. The wide variation in these

figures – all somehow related to the idea of “vaccine uptake” – point to the need to present findings on vaccination timeliness and vaccination coverage in a standardized fashion.

We observed progress in improving vaccination timeliness in our study population of children from 2012 to 2013 compared to a previous analysis from 2007 to 2008 which used similar estimation methods [10]. For example, the proportion of children who were vaccinated within 1 month after the recommended date of administration rose from 31% to 55% for BCG, and from 34% to 50% for MCV.

Table 3
Median age at vaccine administration, and estimates of delay in vaccination^a among children under 5, India, 2013.

Vaccine	Timeliness range	Median age in months at vaccination (IQR)	Median age in months at vaccination among those delayed (IQR)	Probability dose delayed or not given
BCG	0 – 1	0.60 (0.10–1.90)	2.30 (1.57–4.43)	38.10
OPV-0	0 – 1	0.80 (0.17–72.17)	3.60 (1.70–72.47)	46.18
OPV-1	1.5 – 2.5	2.03 (1.57–3.17)	4.37 (2.97–14.93)	34.59
DPT-1	1.5 – 2.5	2.07 (1.63–3.53)	5.07 (3.03–72.23)	36.05
OPV-2	2.5 – 3.5	3.57 (2.83–11.37)	5.97 (4.10–72.23)	50.92
DPT-2	2.5 – 3.5	3.63 (3.20–15.27)	6.27 (4.13–73.03)	52.08
OPV-3	3.5 – 4.5	5.27 (4.07–71.97)	8.97 (5.30–72.37)	62.97
DPT-3	3.5 – 4.5	5.67 (4.13–73.37)	9.83 (6.03–73.37)	65.37
MCV	9.0 – 10.0	10.03 (9.23–13.70)	12.27 (10.53–33.23)	50.14

Abbreviations: BCG, Bacille Calmette–Guérin; DPT, diphtheria-pertussis-tetanus vaccine; IQR, interquartile range; OPV, oral polio vaccine; MCV, measles-containing vaccine.

^a Vaccination delay is defined as occurring 30 days or more beyond the upper limit of the recommended vaccination administration range.

Although it is difficult to make direct comparisons to studies analyzing data from other countries given the different approaches used in measuring timeliness, the timeliness figures for India are likely to be relatively low compared to other countries regardless of the calculation technique. For instance, a study in Colombia from 2012 found that 49% of pentavalent (a DPT-containing vaccine) dose 3 administrations were timely [14], compared to 35% of DPT-3 in our sample and another study from Vietnam in 2011 found that 45% of DPT-3 doses were timely [15].

India's challenges with providing timely vaccinations are further compounded given the size of the annual birth cohort of over 26 million children, which is the largest in the world. Timely administration of vaccines is, therefore, of special importance in terms of limiting preventable morbidity and mortality. One study from Bangladesh found that delayed administration of BCG was associated with decreased childhood survival [16], and the attack rates for measles among an unvaccinated population in India was particularly high in infants < 1 year and children 1–4 years [17], highlighting the importance of vaccinating young children at the recommended ages.

4.1. Implications for vaccination providers

Our study has several implications for pediatricians and other vaccination providers. First, cumulative vaccination coverage appears to essentially plateau after 1 year – meaning that children who are older are not effectively targeted for vaccination. Older children, however, can still be adversely impacted after acquiring a vaccine-preventable disease, and in households with multiple children, older children may serve as efficient vectors for transmitting disease to infants [18]. Community health workers in India, such as Accredited Social Health Activists (ASHAs) typically target infants and younger children for vaccination programs, but given the large proportion of unvaccinated children older than 1 year, there may need to be greater emphasis placed on checking the immunization status of older children and offering catch-up vaccinations.

Additionally, we found that a large proportion of children in India have experienced a missed opportunity for vaccination: for instance, at 24 months of age, 83% of children are estimated to have received MCV, compared to only 68% who have received DPT-3, yet the latter is a vaccine with an earlier recommended age of vaccination; all children who have received the MCV should have also received the DPT-3. Missed opportunities for vaccination have been recently investigated within the US [19]. In one study from 2013 of pediatric practices in the US, 37.8% of children had at least one missed opportunity during which an overdue vaccination could have been administered [20]. Missed opportunities are also a challenge in low- and middle-income countries, where certain days of the week with limited operating hours each day may be designated for administering a minimal set of vaccines (in order

to limit wastage from multi-dose vials). A recent study, which analyzed DHS data from 46 countries, showed that 24% of children had one or more missed opportunities for vaccination during the second year of life. In addition, the higher coverage of MCV at 24 months of age compared to DPT-3 could be explained in part by measles supplementary immunization activities. However, given the low levels of timeliness and the large amount of missed opportunities found in this study, instituting policies that encourage vaccination clinics to be more flexible about how they administer vaccines seems preferable.

4.2. Implications for analysis of vaccination data

The authors are aware of only one other study – our research group's analysis of earlier DLHS data [10] – that utilized Turnbull estimators for vaccination timeliness. Kaplan-Meier survival analysis curves can account for right censoring (but not left censoring), and have been more widely used in high-, middle-, and low-income countries [21–25]. However, in settings where precise vaccination dates are often not available – as is common in many low- and middle-income countries and even in high-income countries when clinical records are unavailable – Kaplan-Meier estimates may not be appropriate. Kaplan-Meier techniques would likely underestimate coverage because the analysis would not include left-censored children (children vaccinated before interview). The prevalence of left-censored children varies substantially by location: the extent to which vaccination cards are used in practice differs by country and within countries; at minimum, studies should report the number of vaccinations for which the occurrence but not exact dates are known, and if that number is high (e.g., over one-third of all vaccinations, as in our study), then Turnbull estimates would be even more necessary as an analytical technique. In addition, given the diversity in how timeliness can be operationalized, a systematic review of vaccination timeliness would be helpful to provide recommendations on how to best present this outcome.

Of course, as more vaccines are added to the immunization schedule, it will be increasingly difficult for mothers to accurately recall children's vaccination histories. In our study, the different modes of administration for DPT, OPV, and BCG likely helped differentiate the vaccines and therefore possibly assisted with maternal recall. In settings without reliable vaccination records, future research will have to identify the best way to ask mothers about children's past vaccinations.

4.3. Limitations and strengths

This study had several strengths and limitations. Several states from central India were not included; although their survey data were collected, it was released separately and did not include

childhood vaccination data comparable to the DLHS4. Because these states have lower vaccination coverage than the states in DLHS4 [26], our study probably overestimated vaccination timeliness on a national scale. We also were limited to ever married mothers; unmarried mothers may have different characteristics. We note that vaccination coverage in recent years may have changed relative to 2014 as the Indian government has increased investment in childhood immunization through programs like Mission Indradhanush. Additionally, by not using survey clustering and strata in the analysis – which is not available in current statistical packages for Turnbull estimation – our estimates are valid but may underestimate standard errors. Children who would have been eligible but died prior to the interview were not included but were probably less likely to have been vaccinated. Collecting and incorporating data on these children could have resulted in lower vaccination rates. For a number of children, only the month and year of birth were available, which affected our ability to calculate an exact age at vaccination. This limitation was minimized by assigning the 15th of the month as the birthday, although this assumes an even distribution of birthdays across the month. We included vaccination data obtained through maternal recall, which has the potential to overestimate or underestimate vaccination uptake. However, previous studies have shown that maternal recall provides relatively accurate, albeit not perfect, estimates of vaccination coverage [27]. Strengths of the study were its use of robust statistical methods to account for a study population with substantial left and right censoring of vaccination data.

5. Conclusions

Estimation of vaccination timeliness in many resource-poor settings remains difficult given the frequent lack of vaccination cards or other reliable ways to accurately ascertain vaccination timing. This study, using vaccination data from the 2012–2013 DLHS in India, found low levels of vaccination timeliness using Turnbull estimation, which can account for both right and left censoring of data. Implementing programs that target vaccination of older children and reducing missed opportunities for vaccination can help lead to more timely administration of vaccines and less morbidity and mortality in a highly vulnerable age group. The impact of vaccination timeliness on disease burden is understudied, but a lack of consideration of its role likely overestimates herd immunity and underestimates transmission risk. As countries seek to attain various national and global targets for infectious disease control, timeliness of vaccination will be an increasingly important consideration.

Acknowledgments

We are grateful to the interviewers and program staff at the International Institute for Population Sciences who have conducted this survey.

Funding

This work was supported by a fellowship award from the PhRMA Foundation (to ALW).

Authors' contributions

ALW conducted a literature review and wrote the first draft of this manuscript, along with LMS. LMS performed most analyses and wrote the first draft of the manuscript, along with ALW. BWG designed the analytical plan and reviewed the manuscript. JLM provided India-specific content expertise, reviewed the analy-

sis, interpreted the findings, and provided critical comments on the manuscript draft. MLB had oversight responsibility for the project. All coauthors provided feedback on the analysis and manuscript.

Conflict of interests

None.

References

- [1] Wang H, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;390:1084–150. [https://doi.org/10.1016/S0140-6736\(17\)31833-0](https://doi.org/10.1016/S0140-6736(17)31833-0).
- [2] Fadel SA, Rasaily R, Awasthi S, Begum R, Black RE, Gelband H, et al. Changes in cause-specific neonatal and 1–59-month child mortality in India from 2000 to 2015: a nationally representative survey. *Lancet* 2017;390:1972–80. [https://doi.org/10.1016/S0140-6736\(17\)32162-1](https://doi.org/10.1016/S0140-6736(17)32162-1).
- [3] Ozawa S, Clark S, Portnoy A, Grewal S, Stack ML, Sinha A, et al. Estimated economic impact of vaccinations in 73 low- and middle-income countries, 2001–2020. *Bull World Health Organ* 2017;95:629–38. <https://doi.org/10.2471/BLT.16.178475>.
- [4] Feldstein LR, Mariat S, Gacic-Dobo M, Diallo MS, Conklin LM, Wallace AS. Global routine vaccination coverage, 2016. *MMWR Morb Mortal Wkly Rep* 2017;66:1252–5.
- [5] Khan J, Shil A, Prakash R. Exploring the spatial heterogeneity in different doses of vaccination coverage in India. *PLoS One* 2018;13. <https://doi.org/10.1371/journal.pone.0207209>.
- [6] Lakew Y, Bekele A, Biadgilign S. Factors influencing full immunization coverage among 12–23 months of age children in Ethiopia: evidence from the national demographic and health survey in 2011. *BMC Public Health* 2015;15:728. <https://doi.org/10.1186/s12889-015-2078-6>.
- [7] Shenton LM, Wagner AL, Bettampadi D, Masters NB, Carlson BF, Boulton ML. Factors associated with vaccination status of children aged 12–48 months in India, 2012–2013. *Matern Child Health J* 2017. <https://doi.org/10.1007/s10995-017-2409-6>.
- [8] Canavan ME, Sipsma HL, Kassie GM, Bradley EH. Correlates of complete childhood vaccination in East African countries. *PLoS One* 2014;9:e95709. <https://doi.org/10.1371/journal.pone.0095709>.
- [9] GAVI. Annual Report 2016 2017.
- [10] Shrivastwa N, Gillespie BW, Lepkowski JM, Boulton ML. Vaccination timeliness in children under India's universal immunization program. *Pediatr Infect Dis J* 2016;1. <https://doi.org/10.1097/INF.0000000000001223>.
- [11] Turnbull BW. The empirical distribution function with arbitrarily grouped, censored and truncated data. *J R Stat Soc Ser B* 1976;38:290–5.
- [12] Macharia K, Donoghue D. General assembly of the united nations. Transforming our world: the 2030 agenda for sustainable development; 2015. doi:10.1017/CBO9781107415324.004.
- [13] International Institute for Population Sciences 2017. <http://iipsindia.org/> [accessed May 9, 2017].
- [14] Narváez J, Osorio MB, Castañeda-Orjuela C, Alvis Zakzuk N, Cediel N, Chocontá-Piraquive LÁ, et al. Is Colombia reaching the goals on infant immunization coverage? A quantitative survey from 80 municipalities. *Vaccine* 2017;35:1501–8. <https://doi.org/10.1016/j.vaccine.2017.01.073>.
- [15] An DTM, Lee J-K, Van Minh H, Trang NTH, Huong NTT, Nam Y-S, et al. Timely immunization completion among children in Vietnam from 2000 to 2011: a multilevel analysis of individual and contextual factors. *Glob Health Action* 2016;9:29189. <https://doi.org/10.3402/gha.v9.29189>.
- [16] Breiman RF, Streatfield PK, Phelan M, Shifa N, Rashid M, Yunus M. Effect of infant immunisation on childhood mortality in rural Bangladesh: analysis of health and demographic surveillance data. *Lancet* 2004;364:2204–11.
- [17] Narain JP, Khare S, Rana SRS, Banerjee KB. Epidemic measles in an isolated unvaccinated population, India. *Int J Epidemiol* 1989;18:952–8.
- [18] Cairncross S, Blumenthal U, Kolsky P, Moraes L, Tayeh A. The public and domestic domains in the transmission of disease. *Trop Med Int Heal* 1996;1:27–34. <https://doi.org/10.1046/j.1365-3156.1996.d01-9.x>.
- [19] Gebremeskel BG, Zhang D, Goveia MG, Marshall GS, O'Brien MA. Vaccine coverage for united states infants at milestone ages: missed opportunities for vaccination. *J Pediatric Infect Dis Soc* 2016;5:473–5. <https://doi.org/10.1093/jpids/piw034>.
- [20] Fu LY, Zook K, Gingold J, Gillespie CW, Briccetti C, Cora-Bramble D, et al. Frequent vaccination missed opportunities at primary care encounters contribute to underimmunization. *J Pediatr* 2015;166:412–7. <https://doi.org/10.1016/j.jpeds.2014.10.066>.
- [21] Laubereau B, Hermann M, Schmitt HJ, Weil J, von Kries R. Detection of delayed vaccinations: a new approach to visualize vaccine uptake. *Epidemiol Infect* 2002;128:185–92.
- [22] Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet* 2009;373:1543–9. [https://doi.org/10.1016/S0140-6736\(09\)60317-2](https://doi.org/10.1016/S0140-6736(09)60317-2).
- [23] Fadnes LT, Jackson D, Engebretsen IMS, Zembe W, Sanders D, Sommerfelt H, et al. Vaccination coverage and timeliness in three South African areas: a

- prospective study. *BMC Public Health* 2011;11:404. <https://doi.org/10.1186/1471-2458-11-404>.
- [24] Babirye JN, Engebretsen IMS, Makumbi F, Fadnes LT, Wamani H, Tylleskar T, et al. Timeliness of childhood vaccinations in Kampala Uganda: a community-based cross-sectional study. *PLoS One* 2012;7:e35432. <https://doi.org/10.1371/journal.pone.0035432>.
- [25] Lernout T, Theeten H, Hens N, Braeckman T, Roelants M, Hoppenbrouwers K, et al. Timeliness of infant vaccination and factors related with delay in Flanders, Belgium. *Vaccine* 2014;32:284–9. <https://doi.org/10.1016/j.vaccine.2013.10.084>.
- [26] Wagner AL, Porth JM, Bettampadi D, Boulton ML. Have community health workers increased the delivery of maternal and child healthcare in India? *J Public Heal* n.d.;in press. doi:10.1093/pubmed/fox087.
- [27] Valadez JJ, Weld LH. Maternal recall error of child vaccination status in a developing nation. *Am J Public Health* 1992;82:120–2.