Vaccine 40 (2022) 6924–6930

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Routine childhood vaccination in India from 2005–2006 to 2015–2016: Temporal trends and geographic variation

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ARTICLE INFO

Article history:
Received 9 February 2022
Received in revised form 22 September 2022
Accepted 7 October 2022
Available online 22 October 2022

Keywords:
Routine childhood vaccination
Timeliness
Coverage
Turnbull estimator

ABSTRACT

Objective: India has experienced a substantial increase in the coverage of routine childhood vaccines in recent years. However, a large fraction of these vaccines is not delivered in a timely manner, i.e., at the recommended age. Further, substantial disparities exist in both coverage and timeliness across states. We aim to quantify the changes in coverage and timeliness of routine childhood vaccination in India over time, their variation across states, and changes in these variations over time.

Methods: We used data from two rounds of India's National Family Health Surveys, NFHS-3 (2005–06) and NFHS-4 (2015–16) on bacille Calmette–Guerin vaccine (BCG), three doses of diphtheria, pertussis, and tetanus vaccine (DPT1, DPT2, DPT3), and measles-containing vaccine (MCV). We used the Turnbull estimator to estimate the cumulative distribution function (CDF) of administering each vaccine by a certain age while accounting for two-sided censoring in the survey data. We then used these estimated CDFs to calculate coverage and timeliness at the national and state levels.

Findings: At the national level, both vaccination coverage and timeliness estimates increased from NFHS-3 to NFHS-4 for all vaccines. The increase in timeliness ranging from 27.3% for DPT3 to 74.0% for MCV continued to be lower than coverage, ranging from 75.3% (95% CI 57.7–87.2) for DPT3 to 74.0% (95% CI 42.2–33.0) for MCV, for all vaccines. Cross-state variation in timeliness was greater than the variation in coverage. Variation in both timeliness and coverage reduced from NFHS-3 to NFHS-4. However, this reduction was greater for timeliness than for coverage.

Conclusions: A large fraction of the children in India receive vaccines later than the recommended age thereby keeping them exposed to vaccine-preventable diseases. Interventions that specifically focus on improving the timely delivery of vaccines are needed to improve the overall effectiveness of the routine immunization program.

1. Background

India's Universal Immunization Program (UIP) is one of the largest routine childhood immunization programs in the world. Since the expansion of the UIP from 2011 to 2017, it aims to administer free vaccines against 12 vaccine-preventable diseases (VPDs) to a target population of approximately 27 million infants annually [1–3]. The National Rural Health Mission (NRHM) launched in 2005, subsumed national programmes and aimed to improve health care architecture through decentralization and capacity-building focusing on a few states [4]. Following the introduction of the NRHM the proportion of children who received all recommended vaccines i.e., one dose of bacille Calmette–Guerin (BCG) vaccine, three doses each of diphtheria, pertussis, and tetanus (DPT) and oral polio vaccine (OPV) and measles-containing vaccine (MCV) by the age of two years, i.e., full immunization coverage (FIC), increased from 44% in 2005–06 to 62% in 2015–16 [5,6]. Despite this improvement, a fourth of roughly 1.5 million deaths of children under the age of five years between 2000 and 2015 were caused by VPDs such as diarrhea, pneumonia, and measles [1,7,8]. Globally, such deaths have been attributed, among other factors, to lack of timeliness, i.e., delay in vaccination beyond the recommended age [9], which is not captured in the metric of vaccination coverage [10–14].

The lack of timeliness, captured in vaccination delays increase the vulnerability of infants to VPDs and can lead to greater transmission thereby compromising the possibility of developing herd

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https://doi.org/10.1016/j.vaccine.2022.10.024
0264-410X/

immunity [15–18,9–12]. For instance, children who do not receive their DPT3 vaccine before six months of age experience substantially higher mortality and morbidity due to pertussis [19]. Moreover, given the pre-determined gaps between successive vaccinations in the immunization schedule, delay in administering one dose can create cascading delays for subsequent doses, increasing the risk of non-completion of the vaccination schedule [12,20]. Furthermore, given that several other child health interventions are delivered during vaccination sessions, delayed vaccination can also cause delays in the provision of other preventive care services such as antenatal care, family planning and building long-standing relationships with community health workers improving future Maternal and Child Health (MCH) provision [21–23].

Findings from recent studies, each using data from a separate round of household surveys, may indicate that coverage and timeliness have increased between 2005–2006 and 2015–2016 at the national level [10–12]. However, it is difficult to make rigorous inferences due to differences in data sources, study designs and cross-sectional estimates. Further, national-level findings may mask significant disparity across states as timeliness is strongly associated with demographic variables such as education, parents' income, and strength of the public health systems (place of delivery, antenatal care) [12] which vary considerably across states. Understanding this variation is crucial for state-level monitoring of VPD clusters [6].

In this paper, we use retrospective data from two successive rounds of nationally representative surveys to report on state-level heterogeneity in coverage and timeliness of childhood vaccination in India and changes in them over a decade (from 2005–06 to 2015–16). These findings allow us to measure the performance of UIP on both coverage and timeliness metrics. Further, access to national and state-level estimates will help local health planners better target health interventions and allocate healthcare workforce such as Local Auxiliary Nurse Midwives (ANMs) and Accredited Social Health Activist (ASHAs) [24,25].

2. Methods

2.1. Data

We used the third and the fourth rounds of the National Family Health Surveys conducted in 2005–06 and 2015–16 (NFHS-3 and NFHS-4, respectively) [35,36]. The survey responses are publicly available, de-identified, a secondary source of data conducted after obtaining informed consent from the participants. Although both surveys covered all 29 states, NFHS-4 was administered in all the 6 union territories (UTs) too.[1] Both surveys employed a two-stage stratified sampling design, with the primary sampling units (PSU) as villages in rural areas and Census Enumeration Blocks (CEBs) in urban areas. Both surveys collected information regarding fertility, mortality, reproductive and child health, and other demographic indicators. Relevant to our study, for all live births to the women respondents, in the five years preceding the survey information on the administration of the following five childhood vaccines was collected: BCG, three doses of DPT and MCV. This included the date of the child receiving these vaccines, if available in the "Mother and Child Protection (MCP)" card. If the date was not available, the survey recorded the mother's recall on whether each of the vaccines was administered to each of the children.

[1] In India's present administrative division, there are 28 states and 8 Union Territories. While the Union Territories are administered centrally through appointments made by the President, health is a state subject.

2.2. Outcome indicators

We used two outcome indicators for our analysis: coverage and timeliness. We defined coverage of a vaccine as the percentage of infants who received that vaccine by the maximum age (in days) up to which it can be safely administered and is effective and beyond which build-up of natural immunity protects the child from the VPD [28–30]. For example, we considered a child to be covered for the BCG vaccine if it was administered when the child was less than 365 days old. See Table 1 for complete details for all vaccines. We defined timeliness as the proportion of children who were vaccinated by the WHO-recommended optimal age interval (in days) [9,10,26–28]. For example, we considered BCG vaccination to be timely if a child received it within 32 days of birth.

2.3. Statistical analysis

We conducted our analysis at the level of child-vaccine combination, i.e., each observation corresponded to information on the administration of one of the five aforementioned vaccines for each child. In both rounds of the survey, we included two most recent live births for whom vaccination data was collected using either the MCP card or relying on mother's recall. We restrict the sample to the youngest two children to avoid any bias owing to diminishing mothers recall with birth order. We excluded observations with a missing and/or implausible date or year for either birth or vaccination. For each observation, using the variables on date of birth and date of receiving a vaccine (uncensored), we estimated the age of the child at vaccination. We include observations without a date of vaccination by censoring. We considered an observation to be right-censored if the date of vaccination was not recorded on the card, if the mother could not recall getting the vaccine for the child, and if it was still possible for the child to receive the vaccination in the future. We considered an observation to be left-censored if the mother recalled the child being administered a particular vaccine but could not remember the exact date.

We estimated the probability of receiving a particular vaccine by a certain age (cumulative distribution function or CDF) using the Turnbull method for nonparametric maximum likelihood estimation [29]. This method, unlike the commonly used Kaplan-Meier method, allowed us to use both right- and left-censored data, increasing the sample size and improving the precision of the estimates [9–11]. We implemented the Turnbull estimation procedure using the lifereg procedure of SAS® software version 9.4 (SAS Institute, Inc., Cary, NC). We then used the estimated CDFs to derive the outcomes of vaccine coverage and timeliness defined above. We used survey weights in the dataset as per the NFHS documentation to obtain national and state representative estimates. Lastly, we test whether the difference between mean NFHS-3 and NFHS-4 estimates for both timeliness and coverage at national level are statistically significant using a *t*-test. The significance level indicates type I error. For example, a 0.01 significance level indicates a 1% risk of concluding that a difference exists when no such difference exists.

2.4. Ethics clearance

We used publicly available, de-identified, secondary data, which was collected after obtaining informed consent from the participants [34]. Hence, we did not seek a separate ethical clearance for our study.

Table 1
Age intervals of childhood vaccination in India.

Vaccine	Recommended age for vaccination (days)	Maximum age for vaccination (days)
BCG	0–32	365
DPT1	42–74	730
DPT2	70–102	730
DPT3	98–130	730
MCV	270–365	1825

Source: National Immunization Schedule (NIS) for Infants, Children and Pregnant Women (NIS, 2018), Summary of WHO position papers- Recommended Routine Immunization for Children (WHO 2019)

3. Results

3.1. Sample description

NFHS-3 and NFHS-4 datasets included immunization data for 45,139 and 231,837 children of last and next-to-last births, aged between 0 and 5 years, respectively. The difference in the number of eligible children is due to the difference in sampling between the two National Family Health Surveys. Furthermore, we restrict our sample to last and next-to-last births for compatibility with DLHS studies and to reduce bias in mother's recall in case of many kids. The sample size, adjusting for response rate of NFHS-4 is 601,509 compared to 109,041 households in NFHS-3. The number of eligible women, men, and children under 5 were determined prior to the surveys using the sampling methodology and the realized figures are close approximations. The determination of the overall sample sizes was governed by the respective objectives of either survey. The main objectives of NFHS-3 were to produce population and health indicators at the national and state levels, whereas NFHS-4 was tasked with producing district and union territory level indicators as well [39,40]. Furthermore, the number of children with vaccination dates available differed for each dose of vaccine and across surveys: for NFHS-3 availability of immunization data on children ranged from 31,363 for MCV to 32,534 for DPT1. Similarly, for NFHS-4 the number of children ranged from 190,820 for BCG to 218,549 for DPT1, as reported in Table 2. In NFHS-3, the uncensored sample size ranged between 8,360 for MCV to 12,366 for DPT1. Similarly, for NFHS-4 the uncensored sample ranged between 80,493 observations for MCV to 108,247 for DPT1. Left censored observations (i.e., children vaccinated based on mother's recall) varied across vaccines and the survey round, ranging from 34% for DPT3 to 50% for BCG in NFHS-3 and from 29% for DPT3 to 48% for MCV in NFHS-4 (Table 2). Similarly, right-censored observations (i.e., children unvaccinated up to the date of interview) ranged from 14% (BCG) to 33% (DPT3) in NFHS-3 and from 10% (BCG) to 25% (DPT3) in NFHS-4.

3.2. National trends in coverage and timeliness

Fig. 1 shows the estimated CDF for the age at vaccination (from birth up to 5 years) for each of the five vaccine doses for the two surveys at the national level. The CDFs for NFHS-4 (2015–2016) in dashed lines lie above those for NFHS-3 (2005–2006) in solid lines indicating an overall increase in the proportion of vaccinated children at every age. As seen in Table 3, national coverage increased for all five vaccines from 2005–2006 to 2015–2016:

BCG from 85.7% (95% CI 75.4–92.2) to 91.4% (95% CI 85.9–94.9), DPT1 from 88.7% (95% CI 78.0–94.6) to 91.9% (95% CI 87.4–94.9), DPT2 from 83.2% (95% CI 70.1–91.3) to 89.0% (95% CI 84.0–92.7), DPT3 from 75.3% (95% CI 57.7–87.2) to 83.8% (95% CI 77.6–88.6) and MCV from 89.6% (95% CI 50.6–98.7) to 94.0% (95% CI 79.7–98.4). Coverage increased for all vaccines, by the following magnitudes: BCG – 6.7%, DPT1 – 3.7%, DPT2 – 7.0%, DPT3 –11.2% and MCV – 5.0% increase. Similarly, timeliness based on the recommended age intervals also increased for all vaccines: 42.4% to 69.5% for BCG, 56.9% to 67.2% for DPT1, 43.3% to 52.7% for DPT2, 27.3% to 36.4% for DPT3, and 74.0% to 82.3% for MCV. This increasing trend at the national level was observed for most states too with 24 out of 29 states experiencing a significant increase in both coverage and timeliness ($p < 0.05$). Similarly, median coverage and timeliness at the state level increased for all vaccines. However, the median improvement was greater for timeliness than for coverage: BCG – 5.2% increase in coverage (from 88.7% to 93.3%) vs. 94.2% increase in timeliness (from 38.3% to 74.4%), DPT1 – 3.4% increase in coverage (from 88.8% to 91.8%) vs. 20% increase in timeliness (from 57.5% to 69.0%), DPT-2–6.2% increase in coverage (from 84.9% to 90.2%) vs. 17.4% increase in timeliness (from 43.5% to 51.1%), DPT-3–9.8% increase in coverage (from 78% to 85.6%) vs. 26.3% increase in timeliness (from 27.7% to 35.0%), MCV – 6.5% increase in coverage (from 89.8% to 95.6%) vs. 8.4% increase in timeliness (from 76.6% to 83.0%)

3.3. Cross-state variation in coverage and timeliness

We found substantial variation in timeliness and coverage across states (as captured by the difference between maximum and minimum). The range of performance was wider for timeliness than for coverage for both NFHS-3 and NFHS-4 (Fig. 2 and Table 4). For example, in 2005–06, coverage for the BCG vaccine varied from 98.8% (Tamil Nadu and Goa) to 50.6% (Nagaland), whereas timeliness varied from 85.2% (Tamil Nadu) to 14.7% (Manipur). In 2015–16, coverage varied from 98.7% (Punjab) to 74.0% (Arunachal Pradesh), whereas timeliness varied from 93.4% (Kerala) to 26.3% (Manipur), as reported in corresponding Supplementary Tables A1–A29. Similar patterns were observed for other vaccines. Variation in both coverage and timeliness reduced from 2005–06 to 2015–16 for most vaccines but the reduction was generally greater for coverage than for timeliness.

To reduce the impact of outliers, we also calculated the interquartile ranges (IQR) to capture the cross-state variation (Table 4). IQR was greater for timeliness than coverage for all vaccines in both observation periods. Furthermore, IQR for both coverage and timeliness reduced from 2005–06 to 2015–16 for almost all vaccines (except for timeliness in DPT3) but the reduction was smaller for timeliness than for coverage: BCG (timeliness from 16.6% to 7.5% and coverage from 28.7% to 24.3%), DPT1 (timeliness from 16.6% to 7.1% and coverage from 24.7% to 19.7%), DPT2 (timeliness from 13.7% to 9.3% and coverage from 22.3% to 22%), DPT3 (timeliness from 13.9% to 11.2% and coverage from 17.6% to 20.4%) and MCV (timeliness from 13.1% to 5.6% and coverage from 20.7% to 10.8%).

Timeliness was positively correlated with coverage for all five vaccines, indicating that states with low or high coverage were likely to have a corresponding low or high level of timeliness as well. However, the correlation reduced from 2005 to 06 to 2015–16 for all vaccines except BCG.

4. Discussion

In this study, we find that both timeliness and coverage for childhood vaccination of BCG, DPT (three doses) and MCV improved over the period from 2005–06 to 2015–16, both at the national level as well as for most states. Although the increase was greater for timeliness than for coverage, the gap the two persisted in 2015–16 for most vaccines in most states. We used two rounds of India's National Family Health Survey (NFHS-3 and NFHS-4) to obtain these national and state-level trends in coverage

Table 2
Details of the sample included in the analysis.

	BCG		DPT1		DPT2		DPT3		MCV	
	NFHS-3	NFHS-4	NFHS-3	NFHS-4	NFHS-3	NFHS-4	NFHS-3	NFHS-4	NFHS-3	NFHS-4
Children with immunization vaccination data, N	32,052	190,820	32,534	218,549	32,135	217,476	31,492	213,874	31,363	215,864
Children with recorded vaccination date N (%)	11,343 (35%)	82,416 (43%)	12,366 (38%)	108,247 (50%)	10,374 (32%)	95,312 (44%)	10,523 (33%)	96,508 (45%)	8,360 (27%)	80,493 (37%)
No. of children unvaccinated based on mother's recall, N (%)	4,569 (14%)	18,826 (10%)	5,448 (17%)	28,122 (13%)	7,568 (24%)	39,063 (18%)	10,345 (33%)	54,353 (25%)	7,621 (24%)	31,907 (15%)
No. of children vaccinated based on mother's recall, N (%)	16,140 (50%)	89,578 (47%)	14,720 (45%)	82,180 (38%)	14,193 (44%)	83,101 (38%)	10,624 (34%)	63,013 (29%)	15,382 (49%)	103,464 (48%)

Note: Immunization data for 45,139 and 231,837 children of last and next-to-last births, aged between 0 and 5 years, were included in NFHS-3 & NFHS-4 datasets, respectively.

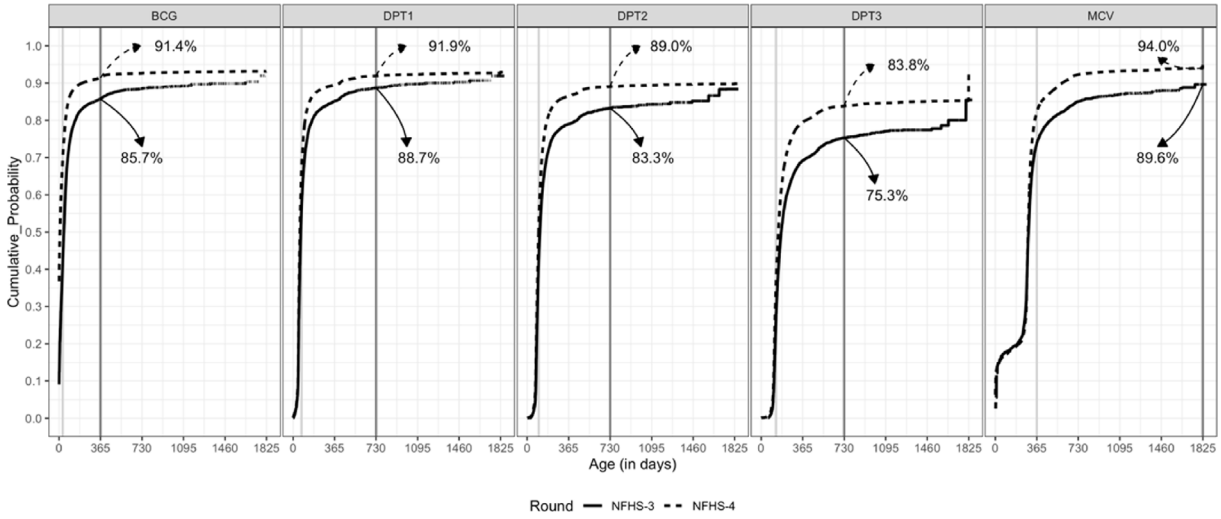

Fig. 1. Cumulative probabilities of vaccination at each age interval (in days) for NFHS-3 (2005–06) and NFHS-4 (2015–16). Vertical reference lines drawn in darker grey depict the maximum ages for each vaccine (in days) and lighter grey depict the upper limit of the recommended age interval for each vaccine. The intersection of these lines with the cumulative incidence curves obtains coverage and timeliness for each vaccine respectively.

Table 3
National estimates for vaccine coverage and timeliness.

Vaccine	Coverage (%)				Timeliness (%)			
	NFHS-3	NFHS-4	NFHS-3	NFHS-4	NFHS-3	NFHS-4	NFHS-3	NFHS-4
	Mean		Median		Mean		Median	
BCG	85.7	91.4	88.7	93.3	42.4	69.5	38.3	74.4
DPT1	88.7	91.9	88.8	91.8	56.9	67.2	57.5	69.0
DPT2	83.2	89.0	84.9	90.2	43.3	52.7	43.5	51.1
DPT3	75.3	83.8	78.0	85.6	27.3	36.4	27.7	35.0
MCV	89.6	94.0	89.8	95.6	74.0	82.3	76.6	83.0

Note: All differences corresponding to mean are statistically significant at 1% level.

and timeliness of vaccination. Our analysis also found that cross-state variation in both coverage and timeliness decreased over the decade but the reduction was greater for coverage than for timeliness for most vaccines.

Similar studies in the Indian context find substantial delays (i.e., lack of timeliness), for instance, Shrivastwa et al. showed that in 2007–08, 31% of children had timely BCG vaccination despite 87% coverage [10]. For MCV, 34% of children received timely vaccination when the 5-year coverage was 76% and timely vaccination of DPT doses ranged from 40.9% (DPT1) to 18.6% (DPT3) while the 5-year coverage varied from 78.4% (DPT1) to 63.3% (DPT3). Wagner et al. updated this study using the subsequent round of the DLHS (2012–2013) data and estimated timeliness to be 35% for DPT-3 to 55% for BCG in 2011–12 [11]. Our results broadly confirm these findings; the proportion of children vaccinated on time (timeliness) was lower than that receiving the vaccine before the specified maximum age (coverage). In the region, a study on vaccination timeliness in eastern China found substantial vaccination delays (only 44.59% were timely vaccinated for DPT1 and 59.25% for MCV) despite high vaccination coverage (95.80% for DPT1 and 92.70% for MCV) [31]. More broadly, a cross-country study across 31 LMICs, however not including India, estimated the median of timely vaccination to be 65% for BCG vaccine (98.1% coverage), 67% for DPT1 (97.0%), 41% for DPT3 (91.4%), and 51% for MCV (89.7%) [30].

In addition to adding to the evidence on delays, a key differentiating factor of our study is that it goes a step further by analyzing coverage and timeliness trends over a decade. We find that the

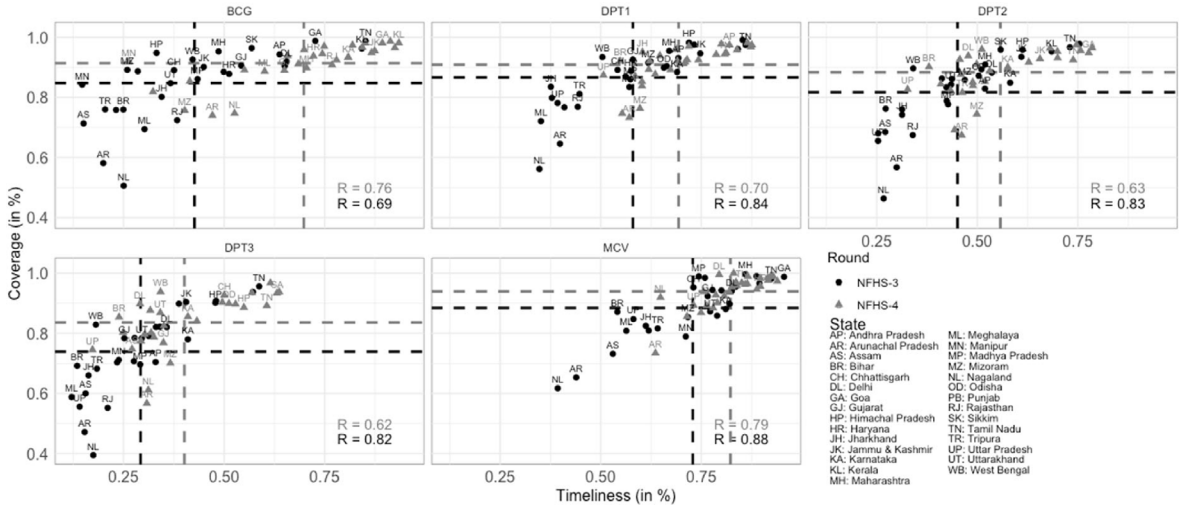

Fig. 2. Scatterplots of state-wise coverage against timeliness for (A) BCG (B) DPT1 (C) DPT2 (D) DPT3 and (E) MCV, for NFHS-3 (2005–2006) and NFHS-4 (2015–2016). Horizontal and vertical reference lines are drawn at national coverage and timeliness respectively for each round. Pearson correlation coefficients are reported.

Table 4
Variation in vaccine coverage and timeliness across states.

Vaccine	Coverage (%)				Timeliness (%)			
	NFHS-3	NFHS-4	NFHS-3	NFHS-4	NFHS-3	NFHS-4	NFHS-3	NFHS-4
	Range (Max − Min)		IQR		Range (Max − Min)		IQR	
BCG	48.2	24.7	76–92.6	89–96.5	70.5	67.1	25.6–54.3	60.1–84.4
DPT1	49.4	25.7	75.8–92.4	88.4–95.5	51.2	36.9	44.3–69	60.3–80
DPT2	51.4	30.1	76–89.7	84.5–93.8	50.1	45.9	31.3–53.6	46.1–68.1
DPT3	56.1	40.1	68.3–82.2	78.7–89.9	46.6	46.4	18.1–35.7	30.8–51.2
MCV	38	26.5	82.5–95.6	92–97.6	56.3	30.3	61.9–82.6	78–88.8

Note: Data for India as a whole. State-wise tables are included in the supplementary Tables A1–A29.

increase in timeliness over this period is greater than the increase in coverage at the national level and the state level for most vaccines. A recent evaluation of Mission Indradhanush (MI), a periodic intensification campaign, did measure temporal changes in coverage and timeliness and found that the increase in full immunization coverage was greater (27%) than that in timeliness (8%) [32]. However, these changes were measured over a shorter time horizon (from 2014 to 2017) and only in select geographies (201 high focus districts with low vaccination rates) thereby making a direct comparison with our results difficult.

Another differentiating feature of our study is the calculation of state-level estimates of timeliness and coverage. To the best of our knowledge, only one study reported state-level estimates of timeliness for India, but it conducted a cross-sectional analysis using NFHS-4 data for three vaccines (BCG, DPT1, and MCV) and did not report changes over time [13]. Our estimates on timeliness for DPT2 and DPT3 add to these findings and taken together, capture the cascading effect of delays in a multi-dose schedule of DPT vaccine. Further, our results also show that this effect persists across two rounds of the NFHS spanning a decade.

A key policy implication of our analysis is that increased coverage, which has been the focus of the UIP, may not automatically translate into a similar increase in timeliness, and hence may be yielding a suboptimal impact on the transmission of VPDs and associated mortality. Hence, it is important to emphasize timeliness (or delayed vaccination) as an additional performance metric for the UIP in addition to coverage, which can be used to predict outbreaks.

Achieving desired policy goals on timeliness, in addition to coverage, requires changes at an operational level including efforts of accredited social health activists (ASHAs) who are responsible for mobilization of beneficiaries and cost-effective delivery of vaccines at the community level [33]. However, under the current incentive scheme, ASHAs get paid based on the administration of vaccines (i.e., coverage) even if it is delayed (i.e., not on timeliness). Taking a cue from other initiatives such as early diagnosis of TB through active case finding (ACF) and early detection of hypertension [37,38], the UIP should consider including a component of ASHA incentive based on timely delivery of vaccines.

A key strength of our study is that its estimates of timeliness and coverage are representative at the national as well as state-level due to the use of data from NFHS. In contrast, previous studies used the District Level Household Surveys (DLHS) thereby excluding data from several key states. A methodological strength of our study is the use of the Turnbull estimator to account for left and right-censored data, which allows us to use a larger sample size to obtain more accurate estimates. In contrast, methods that use only observations with vaccination dates recorded in the MCP cards may result in overestimation as completed MCP cards may be associated with a greater probability of being vaccinated due to greater awareness of the caretaker and/or greater efforts taken by community health workers [10,11,39,40].

However, our study also has certain limitations stemming from its reliance on descriptive analysis of secondary datasets. First, several observations for date of vaccination in the datasets had partially incomplete data, leaving a considerable amount of data to be imputed using statistical methods described above [12,13]. Second, the NFHS-3 survey round was designed to be representative only at the state and national level and does not contain district-level observations. This limits our ability to capture variation in

vaccine coverage and timeliness within states and limits the direct comparison to the district-level improvements observed in periodic intensification campaigns such as MI and IMI. Third, our calculation of timeliness may be overestimated as we counted cases of early vaccination (on average 9.04% and 9.15% of timely vaccinated observations in NFHS-3 and NFHS-4, respectively) as also being timely. Fourth, descriptive results like those in this study can only highlight the need to evaluate the impact of interventions differentially on timeliness and coverage.

5. Conclusion

We analyzed the temporal changes, and spatial variation in coverage and timeliness in India between two national level surveys conducted in 2005–2006 and another in 2015–2016 spanning a decade. We found that, although both measures increased at the national level as well as in most states, a large proportion of children continued to receive vaccines later than the recommended age thereby necessitating a focus on improving the timely delivery of vaccines. The overall effectiveness of routine immunization programs and supplementary interventions is better evaluated if both timeliness and coverage are used as performance indicators.

6. Sources of support/Funding

This work was supported by EY-ISB Initiative in Emerging Markets Studies. The funding entity did not have any role in the study design; in accessing publicly available data, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the article for publication. We are also grateful to Nikhil Choudhary and Vaibhav Beriwal for their excellent research assistance.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.10.024.

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