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Effects of zero-dose vaccination status in early childhood and level of community socioeconomic development on learning attainment in preadolescence in India: a population-based cohort study

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ABSTRACT

Introduction 'Zero-dose' children (infants who fail to receive the first dose of diphtheria-tetanus-pertussis-containing vaccine) face substantial adversity in early childhood and may be at risk of failure to thrive. To inform a new global policy, we studied the relationship between zero-dose vaccination status in early childhood and learning attainment in preadolescence, and considered whether community socioeconomic development moderated these relationships.

Methods We constructed a population cohort from the 2019 India Human Development Survey panel dataset to study the comparative performance of zero-dose versus vaccinated children identified in wave I (2004–2005) on basic learning tests at ages 8–11 in wave II (2011–2012). The outcome was a sum of reading, writing and math scores ranging from 0 (no knowledge) to 8. We fit three linear regression models examining whether child zero-dose status predicts learning attainment: a crude model, a main effects model including all prespecified covariates, and a model including an interaction between child zero-dose status and community development level.

Results The analytic sample included 3781 children from 3781 households in 1699 communities, representing 18.2 million children. Predicted learning attainment scores for zero-dose children were lower than those for vaccinated children by −1.698 (95% CI −2.02 to −1.37; p<0.001) points (crude model) and −0.477 (95% CI −0.78 to −0.18; p<0.001) points (adjusted for all prespecified covariates). We found strong evidence of effect modification. The model including all prespecified correlates and an interaction predicted no effect of child zero-dose status in urban areas (p=0.830) or more developed rural villages (p=0.279), but an important effect in the least developed rural villages, where zero-dose children were expected to have test scores −0.750 (95% CI −1.15 to −0.344; p<0.001) points lower than vaccinated children.

Conclusion Zero-dose children living in contexts of very low socioeconomic development are at elevated risk of poor learning attainment in preadolescence.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Endorsed by the World Health Assembly in 2020, Immunization Agenda 2030 is a new global strategy that aims to reach 'zero-dose' children—those who fail to receive any basic vaccines (represented by non-receipt of the first dose of diphtheria-tetanus-pertussis vaccine)—with the goal of enhancing child survival, and contributing to children's ability to thrive.

⇒ While the survival benefits of immunisation are well established, empirical evidence on developmental outcomes for zero-dose children is scant.

⇒ To inform zero-dose policy, we sought to characterise the relationship between zero-dose vaccination status in early childhood and learning attainment in preadolescence, a critical child development milestone.

WHAT THIS STUDY ADDS

⇒ We found that zero-dose vaccination status was associated with poor learning outcomes at ages 8–11 years for some, but not all, children, and that risk was differentiated by the level of community socioeconomic development.

⇒ In specific contexts of deprivation, child zero-dose status is an early indicator of systematic disadvantage over the life course, signalling children at elevated risk of being developmentally not-on-track with respect to primary education readiness and learning attainment.

INTRODUCTION

The Immunization Agenda 2030 (IA2030) is an ambitious global immunisation strategy for the decade 2021–2030, designed to improve health security, universal health coverage (UHC), immunisation access and equity,

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We see an important opportunity for new policy initiatives that unite the zero-dose strategy and the early childhood development and learning agendas encapsulated in Sustainable Development Goal 4.1: 'By 2030, ensure that all girls and boys complete free, equitable and quality primary and secondary education leading to relevant and effective learning outcomes'.

⇒ A multisectoral intervention strategy focussing on zero-dose children in high-needs geographies could contribute to transformative change, enabling children from systematically marginalised households and communities to survive, thrive and realise their full potential.

and innovation, thereby saving an anticipated 50 million lives.[1]

The goal of reaching 'zero-dose' children—those who fail to receive basic vaccines—is a cornerstone of IA2030.[1] Specifically, IA2030 aspires to achieve a 50% reduction in the number of zero-dose children (defined operationally as children who fail to receive the first dose of diphtheria, pertussis, tetanus (DTP)-containing vaccine) at country, regional and global levels, from an estimated 14 million in 2019 to 7 million in 2030.[2]

Designed to support the UN Sustainable Development Goals (SDGs) call to 'leave no one behind', the IA2030 zero-dose strategy diverges sharply from traditional vaccination initiatives. While vaccination strategies have usually been designed from a biomedical perspective to combat risks of death and disability due to specific infectious pathogens, delivery of the first dose of DTP vaccine does not in itself offer a meaningful health benefit. Rather, what motivates the new zero-dose focus is a commitment to equity informed by the social determinants of health. Worldwide, zero-dose children are believed to be among the poorest and most vulnerable.[1] Reaching them is seen as a critical opportunity for 'first contact', which can be leveraged to deliver full vaccination and other services for zero-dose children, their families and communities, thereby strengthening primary healthcare and UHC.[1] Via this approach, the zero-dose strategy aspires to contribute not only to child survival, but also to children's ability to thrive and flourish,[3] and to the SDG aim of transformative development.[4 5]

The child survival benefits of vaccination are well-established,[6] and it is plausible that the IA2030 zero-dose strategy can help to reduce child mortality by delivering the benefits of full immunisation. Recent evidence from 90 low-income and middle-income countries demonstrates that almost 60% of children who receive the first dose of DTP vaccine go on to receive the full basic vaccination series.[7] However, whether and how best the new zero-dose strategy can also contribute to transformative child development—children's ability to survive, thrive and realise their full potential[3]—is less clear.

New empirical research suggests that zero-dose children are at high risk of mortality and failure to thrive. It underscores the intersecting forms of disadvantage and marginalisation faced by zero-dose children and their families, including barriers related to gender, poverty, education, and other socioeconomic and cultural factors, lower access to health services, and, in some contexts, higher prevalence of stunting and other forms of malnutrition.[8–12] A focus on zero-dose children may thus be an appropriate policy entry point for a transformative strategy.

However, empirical evidence on medium-term and long-term developmental outcomes for zero-dose children is scant and the potential impacts of the zero-dose strategy on children's ability to thrive therefore uncertain. We were unable to identify any empirical studies that trace longer-term outcomes for zero-dose children. We found only two studies documenting outcomes for the related theme of unvaccinated children, and these have important statistical and conceptual shortcomings. A 2012 observational study by Bloom and colleagues investigated the impact of early childhood immunisation on the height, weight and cognitive test scores of preadolescent children in the Philippines.[13] Using propensity scores to compare fully vaccinated to unvaccinated children, the authors found that full immunisation had no effect on height or weight, but that it increased test scores, suggesting that vaccination may be a useful investment in human capital. This study used rigorous statistical methods but is limited by a small sample size of only 85 fully vaccinated children, and unobserved confounding.[13] A 2022 observational study by Joe and Kumar Verma studied childhood vaccination and learning attainment in India, using two waves of the India Health and Development Survey (IHDS).[14] The authors found that fully vaccinated children had better reading, writing and math performance than unvaccinated children, and argue that enhancing child vaccination coverage could improve educational outcomes.[14] While based on a large, nationally representative sample, this study failed to consider the hierarchical structure of the data in the statistical analysis. It fitted a simple logistic regression without robust SEs which necessarily failed to account for data clustering. The SEs reported are likely to be too small, resulting in inflated type I errors that may lead to erroneous inference. Conceptually, both studies are limited by a focus on individual biomedical pathways (immunisation as a possible cause of poor learning attainment), rather than considering how complex forms of adversity (such as poverty, social exclusion, conflict and gender norms) interact to shape receipt of immunisation and learning outcomes in defined contexts. In the language of critical realist inquiry, these studies fail to investigate contexts, mechanisms and outcomes in configuration.[15] Notwithstanding, as signalled in SDG 4.1, achievement of critical learning outcomes such as reading and mathematics can enable a transformative step-change in child development trajectories. The relationship between zero-dose vaccination status and learning attainment thus merits further investigation.

The strategy to reach zero-dose children and 'missed' communities (home to clusters of zero-dose and under-immunised children) is at the forefront of IA2030 and the 2021–2025 ('5.0') and 2023–2025 ('5.1') strategic plans for Gavi, the Vaccine Alliance. Gavi has made a direct investment of US$600 million to reach zero-dose children, and reoriented health system strengthening channels valued at US$1.2 billion towards these goals.[16] These policies are motivated by a commitment to transformative change. Global stakeholders urgently require evidence to assess their potential impact and to strengthen intervention modalities.

India is a large and diverse country with the world's second highest number of zero-dose children.[17] In this study, we reanalysed data from the IHDS to examine the relationship between zero-dose vaccination status in early childhood and proficiency in reading, writing and numeracy at ages 8–11. Our analyses were informed by the nurturing care framework for human development, which links individual-level biological and social processes to wider contexts and policies.[18] Commensurate with this framework, we hypothesised that vulnerability would be highest for zero-dose children living in contexts of grave deprivation. With a view to informing zero-dose policy, our objectives were to characterise the relationship between zero-dose vaccination status in early childhood and learning attainment in preadolescence, and to establish whether the level of community socioeconomic development moderates these relationships.

METHODS

Design, setting and participants

We analysed data from the IHDS panel dataset, a nationally representative sample of the Indian population that harmonises data from the IHDS (2004–2005) and IHDS-II (2011–2012) survey waves to permit analysis of changes over time.[19]

India's only nationally representative panel survey, the IHDS sample was drawn using multistage, stratified random sampling from all states and union territories of India, excepting Lakshadweep, and Andaman and Nicobar. The initial IHDS collected data on 41 554 randomly selected households (overall response rate 92%), and 85% of these households, including any split households, were reinterviewed at IHDS-II.[19] The urban sample added 2134 new households due to greater urban attrition, resulting in an IHDS-II sample of 42 152 households.[19] The IHDS households are located in 971 urban blocks and 1503 rural villages across 382 of India's 612 (in 2001) districts.[19]

Data collection for the initial IHDS occurred from November 2004 to October 2005, while IHDS-II was fielded from January 2011 to May 2013.[19] During both waves, data were collected in face-to-face interviews of roughly 1 hour via distinct questionnaires for households and women. Additional survey modules included brief reading, writing and arithmetic tests administered to all children aged 8–11 years available in the household, and assessments of village characteristics and local infrastructure.[19]

For the present analysis, we defined a population cohort using the harmonised IHDS panel dataset, which comprises 40 018 households containing more than 200 000 individuals surveyed in both waves.[19] We identified all surviving children ages 12–59 months with vaccination information recorded at wave I, and classified children as either zero-dose or vaccinated (reflecting any vaccination). We then examined the comparative performance of zero-dose versus vaccinated children on basic learning tests at ages 8–11 at wave II. In addition to estimating overall relationships, our analysis explored how relationships varied by context by investigating subnational heterogeneity related to community of residence. Online supplemental table S1 describes construction of the analysis sample.

Conceptual framework

To conceptualise the factors contributing to poor learning attainment in mid-childhood and the possible role of zero-dose vaccination status within these, we referred to the nurturing care framework, a state-of-the-art life course model of human flourishing from preconception to 20 years of age.[18 20 21] The framework proposes five essential and indivisible elements of nurturing care—good health, adequate nutrition, responsive caregiving, opportunities for learning, and safety and security—required for children to thrive.[18] All five components are viewed as necessary and interdependent, and none is sufficient; however, disruptions in multiple components are more likely to negatively impact developmental trajectories.[18 20]

We operationalised this framework considering the following five discrete but interrelated pathways: (1) a nutritional path linking malnutrition and infectious diseases in early childhood to schooling attainment, related especially to intra-uterine growth restriction and stunting.[18 21 22] Vaccination could play a limited but direct role in this pathway by preventing some forms of infectious diseases that may lead to suboptimal cognitive development, either directly or in interaction with chronic malnutrition. We also considered other indirect pathways in which child-zero dose vaccination status serves principally as a marker of adverse living conditions. These include: (2) a pathway related to responsive caregiving, reflecting stimulation and learning opportunities within the household and care-seeking behaviour.[18] We hypothesised that parents who are proactive in protecting their children's health through vaccination may also support their children's learning informally through greater early childhood stimulation and nurturing or through formal mechanisms such as paid tuition. (3) Social and environmental determinants such as community and household poverty, gender inequality and illiteracy, poor conditions of water, sanitation and hygiene, and food insecurity and poor dietary diversity, could reinforce exposure to illness and malnutrition and are correlated with

Table 1 Characteristics of zero-dose and vaccinated children at ages 1–4 years (2004–2005) and learning outcomes at 8–11 years (2011–2012), India*

	Zero dose (no DTP1)				Vaccinated				All children			
	n (000)	(95% CI)	%	(95% CI)	n (000)	(95% CI)	%	(95% CI)	N (000)	(95% CI)	%	(95% CI)
All	3584	(3017 to 4151)	19.70	(17.19 to 22.47)	14 612	(13 737 to 15 486)	80.30	(77.53 to 82.81)	18 196	–	100	–
Wealth quintile												
WQ1 (bottom)	1573	(1188 to 1958)	43.88	(37.44 to 50.54)	2699	(2328 to 3070)	18.47	(16.29 to 20.87)	4272	(3714 to 4829)	23.48	(21.08 to 26.06)
WQ2	900	(654 to 1145)	25.10	(19.93 to 31.09)	2653	(2331 to 2975)	18.16	(16.30 to 20.18.)	3553	(3141 to 3964)	19.52	(17.68 to 21.51)
WQ3	70	(492 to 903)	19.45	(14.88 to 25.02)	3494	(3059 to 3928)	23.91	(21.72 to 26.25)	4191	(3696 to 4685)	23.03	(20.95 to 25.25)
WQ4	304	(215 to 394)	8.49	(6.20 to 11.53)	3281	(2900 to 3662)	22.45	(20.39 to 24.67)	3585	(3197 to 3974)	19.70	(17.84 to 21.71)
WQ5 (top)	110	(67 to 153)	3.08	(2.04 to 4.62)	2485	(2230 to 2741)	17.01	(15.23 to 18.95)	2595	(2337 to 2854)	14.26	(12.76 to 15.92)
Household size (persons)												
2–4	395	(260 to 529)	11.01	(8.05 to 14.88)	4649	(4177 to 5121)	31.82	(29.48 to 34.25)	5044	(4550 to 5538)	27.72	(25.58 to 29.97)
5–6	1710	(1400 to 2021)	47.73	(43.30 to 52.19)	6024	(5589 to 6460)	41.23	(38.76 to 43.74)	7735	(7195 to 8275)	42.51	(40.28 to 44.77)
≥7	1479	(1180 to 1778)	41.26	(36.49 to 46.21)	3939	(3495 to 4382)	26.95	(24.71 to 29.32)	5417	(4849 to 5986)	29.77	(27.58 to 32.06)
Mother's education (years)												
None (0)	2708	(2219 to 3196)	75.55	(70.50 to 79.98)	5344	(4796 to 5892)	36.57	(33.95 to 39.27)	8052	(7292 to 8811)	44.25	(41.64 to 46.89)
1–5	5	(357 to 706)	14.84	(11.12 to 19.53)	2450	(2181 to 2720)	16.77	(15.12 to 18.56)	2982	(2634 to 3331)	16.39	(14.73 to 18.19)
6–9	218	(148 to 287)	6.07	(4.36 to 8.39)	3697	(3272 to 4121)	25.30	(23.13 to 27.60)	3914	(3487 to 4342)	21.51	(19.58 to 23.58)
10–11	71	(24 to 118)	1.98	(1.00 to 3.86)	1525	(1289 to 1760)	10.43	(8.97 to 12.11)	1595	(1356 to 1834)	8.77	(7.53 to 10.18)
≥12	56	(25 to 87)	1.56	(0.88 to 2.75)	1596	(1379 to 1814)	10.93	(9.50 to 12.53)	1652	(1433 to 1872)	9.08	(7.92 to 10.39)
Father's education (years)												
None (0)	1476	(1153 to 1800)	41.19	(35.39 to 47.26)	3076	(2682 to 3470)	21.05	(18.85 to 23.43)	4552	(4042 to 5063)	25.02	(22.84 to 27.34)
1–5	927	(675 to 1179)	25.86	(20.70 to 31.80)	2526	(2237 to 2815)	17.29	(15.54 to 19.20)	3453	(3062 to 3844)	18.98	(17.17 to 20.93)
6–9	623	(466 to 780)	17.39	(13.79 to 21.68)	3943	(3606 to 4280)	26.99	(24.92 to 29.16)	4566	(4199 to 4934)	25.09	(23.30 to 26.98)
10–11	367	(214 to 520)	10.24	(6.94 to 14.85)	2263	(1790 to 2736)	15.49	(12.85 to 18.55)	2630	(2132 to 3128)	14.45	(12.20 to 17.05)
≥12	191	(81 to 301)	5.32	(3.05 to 9.12)	2803	(2458 to 3149)	19.19	(17.10 to 21.47)	2994	(2633 to 3355)	16.45	(14.68 to 18.40)
Social group												
Forward +	261	(166 to 357)	7.30	(5.05 to 10.43)	3172	(2808 to 3536)	21.71	(19.48 to 24.12)	3434	(3059 to 3809)	18.87	(16.95 to 20.96)
OBC	1364	(999 to 1729)	38.06	(31.59 to 44.99)	5035	(4553 to 5517)	34.46	(31.87 to 37.14)	6399	(5770 to 7028)	35.17	(32.59 to 37.83)
Dalit	874	(624 to 1124)	24.39	(19.21 to 30.43)	3504	(3009 to 3999)	23.98	(21.44 to 26.72)	4378	(3803 to 4952)	24.06	(21.65 to 26.64)
Adivasi	275	(171 to 380)	7.68	(5.22 to 11.15)	1109	(905 to 1314)	7.59	(6.30 to 9.12)	1385	(1145 to1625)	7.61	(6.38 to 9.05)
Muslim	809	(587 to 1031)	22.58	(17.40 to 28.75)	1791	(1492 to 2091)	12.26	(10.40 to 14.39)	2600	(2198 to 3003)	14.29	(12.31 to 16.53)
Place of residence												
Urban	449	(347 to 551)	12.52	(9.61 to 16.17)	3858	(3516 to 4199)	26.40	(23.77 to 29.21)	4306	(3939 to 4674)	23.67	(21.31 to 26.20)

Continued

Table 1 Continued

	Zero dose (no DTP1)				Vaccinated				All children			
	n (000)	(95% CI)	%	(95% CI)	n (000)	(95% CI)	%	(95% CI)	N (000)	(95% CI)	%	(95% CI)
More dev village	1125	(815 to 1436)	31.40	(24.46 to 39.29)	5072	(4339 to 5805)	34.71	(30.88 to 38.76)	6197	(5381 to 7013)	34.06	(30.45 to 37.87)
Less dev village	2010	(1529 to 2491)	56.07	(48.05 to 63.80)	5682	(5027 to 6337)	38.89	(35.21 to 42.70)	7692	(6791 to 8593)	42.27	(38.51 to 46.13)
Child gender												
Boy	1846	(1521 to 2170)	51.50	(45.72 to 57.24)	8111	(7515 to 8706)	55.51	(53.17 to 57.82)	9956	(9278 to 10 634)	54.72	(52.60 to 56.82)
Girl	1738	(1364 to 2112)	48.50	(42.76 to 54.28)	6501	(5987 to 7016)	44.49	(42.18 to 46.83)	8240	(7609 to 8870)	45.28	(43.18 to 47.40)
Child age at testing (years)												
8	1553	(1220 to 1887)	43.34	(38.38 to 48.44)	3816	(3373 to 4259)	26.11	(23.88 to 28.47)	5369	(4788 to 5950)	29.51	(27.32 to 31.79)
9	894	(703 to 1084)	24.93	(20.73 to 29.67)	4518	(4117 to 4919)	30.92	(28.68 to 33.25)	5411	(4978 to 5845)	29.74	(27.81 to 31.74)
10	816	(632 to 1000)	22.77	(18.72 to 27.40)	4125	(3720 to 4531)	28.23	(26.20 to 30.36)	4941	(4497 to 5385)	27.16	(25.29 to 29.11)
11	321	(172 to 470)	8.96	(5.91 to 13.35)	2153	(1898 to 2408)	14.73	(13.12 to 16.51)	2474	(2181 to 2767)	13.60	(12.14 to 15.20)
Outcomes	**Min**	**Max**	**Mean**	**95% CI**	**Min**	**Max**	**Mean**	**95% CI**	**Min**	**Max**	**Mean**	**95% CI**
Learning test score	0	8	3.16	(2.85 to 3.47)	0	8	4.86	(4.73 to 4.98)	0	8	4.52	(4.39 to 4.66)
Math	0	3	0.93	(0.84 to 1.03)	0	3	1.54	(1.49 to 1.59)	0	3	1.42	(1.37 to 1.47)
Reading	0	4	1.72	(1.52 to 1.92)	0	4	2.55	(2.48 to 2.62)	0	4	2.39	(2.31 to 2.36)
Writing	0	1	0.51	(0.45 to 0.56)	0	1	0.77	(0.73 to 0.80)	0	1	0.71	(0.69 to 0.74)
Failure score	0	3	1.15	(1.01 to 1.29)	0	3	0.45	(0.41 to 0.50)	0	3	0.59	(0.54 to 0.64)

*National survey-weighted estimates from the India Human Development Survey (IHDS) panel (2019).

Table 2 Relationship between child zero-dose vaccination and learning outcomes, India†

	Model 1: crude		Model 2: all main effects		Model 3: model 2+interaction	
	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
Zero-dose child	−1.698***	(−2.02 to 1.37)	−0.477**	(−0.78 to −0.18)	0.051	(−0.41 to 0.51)
Place of residence						
Urban‡			–		–	
More developed village			−0.142	(−0.40 to 0.12)	−0.114	(−0.39 to 0.16)
Less developed village			−0.249	(−0.50 to 0.01)	−0.104	(−0.37 to 0.16)
Interaction (zero-dose by community type)						
Zero-dose child×Urban					–	
Zero-dose child×More developed village					−0.316	(−0.95 to 0.32)
Zero-dose child×Less developed village					−0.801**	(−1.39 to −0.21)
Wealth quintile						
WQ5 (top)‡			–		–	
WQ1 (bottom)			−1.025***	(−1.43 to −0.62)	−1.033***	(−1.44 to −0.63)
WQ2			−0.632***	(−0.99 to −0.28)	−0.656***	(−1.01 to −0.30)
WQ3			−0.359*	(−0.67 to −0.04)	−0.392*	(−0.72 to −0.07)
WQ4			−0.168	(−0.44 to 0.10)	−0.193	(−0.46 to 0.08)
Household size (persons)						
2–4‡			–		–	
5–6			−0.058	(−0.28 to 0.16)	−0.059	(−0.28 to 0.16)
≥7			−0.051	(−0.33 to 0.23)	−0.054	(−0.33 to 0.22)
Mother's education (years completed)						
12 or more‡			–		–	
None (0)			−0.685***	(−1.06 to −0.31)	−0.701***	(−1.08 to −0.32)
1–5			−0.275	(−0.65 to 0.10)	−0.290	(−0.67 to 0.09)
6–9			−0.198	(−0.55 to 0.16)	−0.210	(−0.57 to 0.15)
10–11			−0.324	(−0.69 to 0.05)	−0.316	(−0.69 to 0.05)
Father's education (years completed)						
12 or more‡			–		–	
None (0)			−1.301***	(−1.69 to −0.91)	−1.301***	(−1.70 to −0.90)
1–5			−0.891***	(−1.28 to −0.50)	−0.887***	(−1.29 to −0.49)
6–9			−0.750***	(−1.07 to −0.44)	−0.756***	(−1.08 to −0.44)
10–11			−0.446*	(−0.81 to −0.09)	−0.438*	(−0.80 to −0.08)
Social group						
Forward‡			–		–	
OBC			0.064	(−0.20 to 0.33)	0.071	(−0.19 to 0.34)
Dalit			−0.436**	(−0.71 to −0.17)	−0.427**	(−0.70 to −0.16)
Adivasi			−0.543*	(−0.96 to −0.13)	−0.545*	(−0.96 to −0.13)
Muslim			−0.354*	(−0.68 to −0.03)	−0.362*	(−0.68 to −0.04)
Child gender						
Boy‡			–		–	
Girl			−0.027	(−0.20 to 0.14)	−0.020	(−0.19 to 0.15)
Age at learning assessments						
8‡			–		–	
9			0.442***	(0.20 to 0.68)	0.451***	(0.21 to 0.69)
10			0.811***	(0.57 to 1.05)	0.829***	(0.59 to 1.07)

Continued

Table 2 Continued

	Model 1: crude		Model 2: all main effects		Model 3: model 2+interaction	
	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
11			1.217***	(0.92 to 1.52)	1.235***	(0.93 to 1.54)
State or state group						
Jammu and Kashmir			–		–	
Himachal Pradesh			0.650	(–0.02 to 1.32)	0.622	(–0.04 to 1.29)
Uttarakhand			–0.087	(–1.01 to 0.83)	–0.125	(–1.04 to 0.79)
Punjab			0.340	(–0.37 to 1.05)	0.326	(–0.38 to 1.04)
Haryana			–0.028	(–0.74 to 0.68)	–0.039	(–0.74 to 0.66)
Delhi			–0.423	(–1.39 to 0.54)	–0.388	(–1.34 to 0.57)
Uttar Pradesh			–1.014**	(–1.69 to –0.34)	–1.024**	(–1.69 to –0.36)
Bihar			–0.812*	(–1.62 to –0.01)	–0.800*	(–1.60 to –0.00)
Jharkhand			–0.475	(–1.24 to 0.29)	–0.490	(–1.24 to 0.27)
Rajasthan			–0.312	(–1.03 to 0.40)	–0.321	(–1.03 to 0.39)
Chhattisgarh			–0.540	(–1.34 to 0.27)	–0.548	(–1.34 to 0.25)
Madhya Pradesh			–0.441	(–1.12 to 0.24)	–0.455	(–1.13 to 0.22)
Northeast			0.682	(–0.15 to 1.51)	0.677	(–0.16 to 1.51)
Assam			–0.463	(–1.40 to 0.48)	–0.432	(–1.36 to 0.50)
West Bengal			0.912**	(0.23 to 1.59)	0.880*	(0.21 to 1.55)
Orissa			–0.077	(–0.82 to 0.66)	–0.115	(–0.85 to 0.62)
Gujarat			–0.707	(–1.42 to 0.00)	–0.719*	(–1.42 to –0.02)
Maharashtra and Goa			–0.602	(–1.23 to 0.03)	–0.600	(–1.22 to 0.03)
Andhra Pradesh			–0.291	(–0.97 to 0.39)	–0.281	(–0.96 to 0.40)
Karnataka			–0.560	(–1.24 to 0.12)	–0.558	(–1.23 to 0.12)
Kerala			0.015	(–0.69 to 0.72)	0.038	(–0.66 to 0.74)
Tamil Nadu			–1.078**	(–1.78 to –0.37)	–1.048**	(–1.75 to –0.35)

Data are coefficients and their associated 95% CIs from survey-weighted linear regression models. To derive coefficients, models were simultaneously adjusted for all correlates indicated in the table. Zero-dose: all surviving children aged 12–59 months who did not receive first dose of diphtheria-pertussis-tetanus-containing (DTP1) vaccine.
*p<0.05; **p<0.01; ***p<0.001.
†India Human Development Survey (IHDS) panel (2019).
‡Reference category.
§Northeast: Arunachal Pradesh, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim, Tripura.

non-vaccination[8 11] and human capital achievement.[23 24] (4) A pathway related to governance, services and infrastructure, reflecting differential accessibility and quality of basic amenities such as health services[10] and schools. Finally, we considered (5) a social exclusion pathway, involving factors such as gender inequality[8 11] discrimination, maltreatment, bullying and violence that could impact learning. In keeping with a critical realist lens, we hypothesised that these pathways would be activated to a greater or lesser degree under specific contextual conditions.

Variables and measurement

Outcomes

The IHDS administered learning assessments based on validated measures[25] developed by the Indian non-governmental organisation Pratham, which specialises in basic education. For the IHDS, modules designed to assess a child's basic numeracy, literacy and ability to write were translated into 12 Indian languages and English, and children aged 8–11 years were encouraged to take the test in their preferred language. To enhance comfort, the tests were administered one-on-one with surveyors. The reading assessment tool classified children into five mutually exclusive literacy levels: cannot read at all ('0'), can identify letters but not words ('1'), can read short words but not a paragraph ('2'), can read a short paragraph but not a story ('3'), can read a story corresponding to a standard two text ('4'). The arithmetic tool assigned children to one of four categories: no number recognition ('0'), able to read single-digit but not double-digit numbers ('1'), able to subtract a two-digit number from another two-digit number ('2') and able to divide a

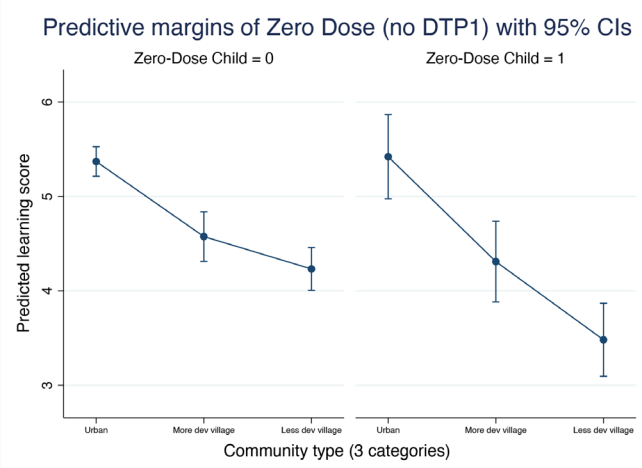

Figure 1 Predictive margins of child zero-dose (no DTP1) vaccination status with 95% CIs, by community type. Outcome: learning test—sum of all three (math, reading, writing) learning assessment scores. DTP1, first dose of diphtheria, tetanus and pertussis.

three-digit number by a one-digit number ('3'). Writing was coded dichotomously: unable to write ('0'); able to write ('1').

For the main analysis, we summed reading, math and writing test results to create a composite score ranging from 0 to 8. After verifying linearity, we treated this learning assessment score as continuous. To facilitate interpretation, we also created a failure score, ranging from 0 to 3, which captured the number of times a child scored '0' (completely unable) over the three tests.

Exposures

The exposure of interest for this study was child zero-dose vaccination status, which represents children never reached by immunisation services.[1] The IHDS panel survey included information from a single female respondent of reproductive age on vaccination of her last surviving child under 5 years of age. If the vaccination card was available, vaccination data were transcribed from the card. In addition, surveyors probed to identify any vaccinations received but not recorded on the card. If no vaccination card was available, information was taken via recall. In wave I of the IHDS (2004–2005), only 26% of all children (and 3.65% of zero-dose children) had a vaccination card that was seen.

The IA2030 monitoring definition currently used by WHO, UNICEF and partners considers all children 12–23 months who do not receive the first dose of diphtheria-pertussis-tetanus-containing vaccine (DTP1) as zero-dose.[2] For the main analysis, we adapted this definition to the broader IHDS age range and considered all surviving children 12–59 months who did not receive the DTP1 as zero-dose, and those who received DTP1 as vaccinated.[2] To facilitate comparisons, we also constructed variables to represent children who received no routine immunisation (RI) and completely unvaccinated children who received no vaccines of any kind (online supplemental methods).

Table 3 Predictive margins of child zero-dose (ZD) vaccination status at ages 1–4 years on learning outcomes at ages 8–11 years, India*

Margin	Coefficient	95% CI
Urban and ZD=0	5.37	(5.21 to 5.53)
Urban and ZD=1	5.42	(4.97 to 5.87)
More developed village and ZD=0	4.58	(4.31 to 4.84)
More developed village and ZD=1	4.31	(3.88 to 4.74)
Less developed village and ZD=0	4.23	(4.01 to 4.46)
Less developed village and ZD=1	3.48	(3.09 to 3.87)

Zero-dose: all surviving children aged 12–59 months who did not receive the first dose of diphtheria, tetanus and pertussis vaccine.
*Coefficient estimates mean learning score (from 0 to 8) for table 2, model 3 (fully adjusted model with interaction), treating each group as a subpopulation.

Adjustment variables

We considered potential effect modifiers and confounders likely to be related to receipt of immunisation and learning outcomes. To gain insights into the role of context, we considered community socioeconomic development. The IHDS classified communities (urban blocks and rural villages) into four categories based on a combination of location and development indicators.[19] IHDS-I communities were tagged as either urban or rural based on 2001 census data. Due to differences in living conditions, the urban category was further subdivided to distinguish India's six largest metropolitan areas from other urban centres. Rural villages were also subdivided into two categories based on level of infrastructure. Villages were classified as more developed if they had at least six of ten specific amenities (such as electricity, paved roads, piped water and telephones in the community); other villages were categorised as less developed.[26] Due to a low prevalence of some key variables in metropolitan areas, we collapsed urban areas into a single category, and used the resulting three-category indicator (urban, more developed rural, less developed rural) in analyses.

As some smaller geographies included in the IHDS have relatively small sample sizes, to adjust for variation by state, we used a recommended grouping that combines the 33 geographies surveyed into 22 states and state groups.[19] We considered household economic status using the IHDS household assets quintiles, the most temporally stable of the three IHDS economic measures. The IHDS evaluated household assets as the sum of 30 dichotomous items that measured household ownership of durable goods and housing quality, divided into quintiles.[19] We included a three-category variable to distinguish relatively small, medium and large households based on

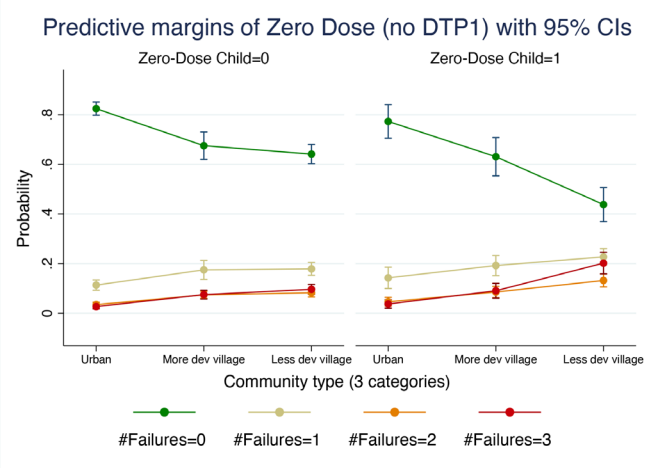

Figure 2 Predictive margins of child zero-dose (no DTP1) vaccination status with 95% CIs, by community type. Outcome: failure score—counts the number of times the child scores 0 over all 3 (math, reading, writing) test. DTP1, first dose of diphtheria, tetanus and pertussis.

the number of resident members. We constructed variables for father's education and mother's education by grouping self-reported years of schooling into five categories salient to India's education system. To categorise social groups, we created a five-category classification distinguishing respondents who self-identified as Dalits (commonly known as scheduled caste), Adivasis (Tribal groups), Muslims, Other Backwards Castes (OBC) and a residual more advantaged group comprising Hindu Brahmin and forward castes, Sikhs, Christians and Jains. As girls may be disadvantaged with respect to immunisation and schooling due to gender-related social norms, we also considered a dichotomous variable (girl=1) representing parental report of child gender. We considered child age at the time of the learning tests to improve model precision.

Statistical methods

Sample construction and descriptive data

We restricted the sample to children with information on immunisation at wave I and learning tests at wave II, and complete information on covariates. As the IHDS panel retained only the last-born child, we limited the sample to one child per household. To compute sample characteristics, we applied the appropriate sampling weights to generate prevalence estimates and confidence intervals that take into account the complex sampling design, using subpopulation estimation to further adjust estimates to the analysis subset.

Main analyses

To study the relationship between child zero-dose vaccination status and learning attainment, we implemented linear regression models, linear fixed-effects models and generalised ordinal regression models using analogous modelling strategies. All regression analyses were survey-weighted; subpopulation estimation was used in linear and ordinal models.

Linear models

We fit three linear regression models to assess the association between the binary exposure child zero-dose vaccination status (no DTP1) and the continuous outcome learning attainment score. To estimate the crude association, we implemented a simple linear regression model. To assess potential confounding, we estimated a multiple linear regression model examining whether child zero-dose status predicts learning attainment, including all prespecified adjustment variables as main effects. To assess whether community context modifies the effect of child zero-dose vaccination status, we re-estimated the multiple linear regression model and added an interaction between child zero-dose status and community socioeconomic development. Postestimation commands were used to compute coefficients and uncertainty estimates for individual predictors.

Linear fixed-effects models

We re-estimated all three linear models including fixed effects for communities (primary sampling units, or PSUs). By including fixed effects for villages and urban blocks, we were able to control for time-invariant observed and unobserved community features that could simultaneously influence children's vaccination status and learning outcomes, enabling comparison of vaccinated and unvaccinated children living within the same community. Although the main effects of community socioeconomic development are absorbed by the community fixed effects and cannot be estimated, we are able to estimate how learning outcomes are conditioned by community characteristics.[26] As model estimation requires within-group variation, non-informative clusters were iteratively dropped to avoid biasing SEs.[27]

Ordinal models

We regressed the ordinal dependent variable 'failure score' on the zero-dose exposure. After conducting a χ^2 test to verify the proportional odds assumption, we implemented three partial proportional odds models to estimate the crude association, main effects and assess effect modification.

Sensitivity analyses

We considered alternative definitions of the zero-dose exposure variable by repeating previous analyses, substituting the variables 'no RI' and 'unvaccinated' for 'no DTP1'.

All analyses were performed by MJ and validated by EN in Stata V.17, using native commands for survey data analysis, and user-written packages for fixed-effects[27] and generalised ordinal[28] regression. We provide analysis code required to reproduce study results.[29]

RESULTS

Participants

A child was eligible for inclusion if she or he belonged to a household surveyed at wave I and wave II, was of vaccination age at wave I (2004–2005), eligible for the learning tests at wave II (2011–2012), and had complete information on outcomes (ie, completed all three learning tests) and the exposure (vaccination information). After application of eligibility criteria, 3891 children were eligible, 11 children were randomly excluded from households with multiple births (twins) and 99 children (<3%) were excluded due to missing values on adjustment variables. In total, 3781 children with complete information from 3781 households were included in the analyses (online supplemental table S1). These children belonged to 1699 communities containing on average 2.225 children (range 1–16, SD=1.471). After application of survey weights, they represent a population cohort of 18.2 million children.

Descriptive and outcome data

As compared with vaccinated children, zero-dose children were systematically disadvantaged and scored lower on all learning tests (table 1). The mean learning score (out of 8) was 3.16 (95% CI 2.85 to 3.47) for zero-dose children versus 4.86 (95% CI 4.73 to 4.98) for vaccinated children.

Main results

Table 2 presents linear regression results. Model 1 (crude association) predicted that learning assessment scores for zero-dose children would be lower than those for vaccinated children by −1.698 (95% CI −2.02 to −1.37; p<0.001) points (out of 8). According to model 2 (all main effects), after adjusting for wealth quintile, household size, maternal and paternal education, social group, and child age at testing, zero-dose children were expected to score lower than vaccinated children by −0.477 (95% CI −0.78 to −0.18; p<0.001) points. However, model 3 (effect modification) identified a statistically significant interaction, suggesting that the effect of child zero-dose vaccination status on learning outcomes depends on the level of community socioeconomic development. The model predicted no effect of child zero-dose status in urban areas (p=0.830) or more developed rural villages (p=0.279), but an important effect in the least developed rural villages, where zero-dose children were expected to have test scores lower by −0.750 (95% CI −1.15 to −0.344; p<0.001) points as compared with vaccinated children, after adjustment for all prespecified correlates (table 3; figure 1).

Three fixed-effects regression models compared zero-dose children to vaccinated children living within the same PSU (community). After elimination of 694 singletons, fixed-effect regressions included 3130 children in 1014 communities. Results were qualitatively similar to those for linear regression, with model 1 (crude) and model 2 (main effects) supporting a relationship between child zero-dose status and learning outcomes, and model 3 suggesting effect moderation. Specifically, model 3 predicted no effect of child zero-dose status on learning attainment in urban areas (p=0.866) or more developed rural villages (p=0.711), but an important effect in the least developed rural villages, where zero-dose children were expected to have test scores lower by −0.552 (95% CI −0.957 to −0.147; p<0.008) points as compared with vaccinated children, after adjustment for all prespecified correlates (online supplemental table S2, online supplemental figure S1).

Three ordinal regression models considered an extreme outcome counting the number of reading, writing and math tests with a '0' score for each child, indicating complete inability to perform these tasks. Results were qualitatively similar to those for linear outcome models, with model 1 (crude) and model 2 (main effects) supporting a relationship between child zero-dose status and learning outcomes, and model 3 suggesting effect modification by level of community socioeconomic development. Specifically, model 3 indicated that, as compared with vaccinated children, zero-dose children experienced no increase in risk for any level of the outcome in urban areas (p=0.135) and more developed rural villages (p=0.303), while those in rural less developed villages had an increased odds of scoring zero (OR 2.62, 95% CI 1.88 to 3.65, p<0.001) for each level of the outcome (figure 2, online supplemental table S3).

Other analyses

Sensitivity analyses considering alternative formulations of the exposure variables yielded similar results (online supplemental figures S2 and S3).

DISCUSSION

Principal findings

To our knowledge, ours is the first study to analyse learning outcomes for zero-dose children, the third to focus on outcomes for unvaccinated children, and the first to study the moderating role of geographical context on these relationships. Analyses used India's only national panel dataset representing a cohort of 18.2 million children living in very diverse settings. We highlight two major findings from the quantitative analysis, before tracing their implications for zero-dose policy.

First, we found that the effect of child zero-dose vaccination status on learning outcomes at ages 8–11 years was moderated by the level of community socioeconomic development. Linear, linear fixed effects and ordinal regression statistical models considering an interaction between child zero-dose status and community socioeconomic development consistently revealed a strong, negative effect of zero-dose status on learning attainment in less developed rural villages, while no association was present in more developed rural villages or in urban areas. These findings were robust across models

adjusting for important confounding factors, and in numerous sensitivity analyses.

Second, for zero-dose children living in contexts of low socioeconomic development, the magnitude of the learning deficits is meaningful. In less developed rural settings, zero-dose children were at substantially higher risk of scoring zero (no knowledge) on reading, writing and math tests individually, and jointly, as compared with vaccinated children. Based on the metric developed by the World Bank and UNESCO, which focusses on ability to read and understand a simple text,[30] zero-dose children living in contexts of low socioeconomic development are at elevated risk of learning poverty.

Limitations

First, like other household surveys, the IHDS may fail to capture all zero-dose children.[31] Vaccination information is collected only for surviving children, while zero-dose children may be more likely to die prior to the survey. Sampling procedures may systematically under-represent groups expected to have higher proportions of zero-dose children, such as those living in areas affected by conflict and transient populations. Our analysis may fail to capture risks for the most vulnerable groups in urban settings. Second, due to the low proportion of children with a vaccination card seen by surveyors, ascertainment of vaccination status may be affected by recall bias. Notwithstanding, this problem may be less severe for determining child zero-dose vaccination status, the key exposure variable for our analysis, than for full immunisation, as it is relatively easy for parents to recall whether a child has had any vaccine doses by injection. In addition, the IHDS panel included information only on the youngest child, specifically to reduce recall bias. However, we considered children from 12 to 59 months in the analysis, a broader range than the standard 12–23 months that might increase recall bias. Third, several variables of interest were missing from the analyses. For example, malnutrition in the first 1000 days from conception, especially intra-uterine growth restriction and stunting, is associated with schooling attainment.[20] Although height and weight measurements of children less than age 5 and their mothers were collected by the IHDS, due to quality considerations, the 2004–2005 anthropometric data were not included in the IHDS panel. Contemporaneous data from India's National Family Health Survey demonstrated a 25% higher prevalence of severe stunting among zero-dose children.[11] Responsive caregiving, including early childhood stimulation and a supportive environment for learning, is likely to be associated with zero-dose vaccination status and learning attainment; maternal education is a weak proxy. Inclusion of additional confounding characteristics would likely weaken the association between child zero-dose status and learning attainment. Fourth, although the IHDS sample captures a very diverse range of living conditions, the extent to which these findings are generalisable to other time-periods or countries is unknown.

Relationship to other studies

An important literature has investigated the question of whether vaccination is causally linked to broader health and productivity benefits.[32] While several high-quality analyses[33–35] have found that vaccination may be causally linked to improved cognitive outcomes, our results do not suggest a universal relationship at the population level. Strongly inconsistent patterns of association across subnational geographies suggest that child zero-dose status is primarily a marker rather than a cause of poor learning outcomes, most salient in contexts of underdevelopment where multiple deprivations coexist and interact. It is nonetheless consistent with our findings that vaccination against specific diseases may play a limited causal role in contexts of high infectious disease risk.[35] In addition to focusing on specific vaccines and using strong study designs, our findings suggest that future causal inference studies on the cognitive benefits of vaccination should consider excluding zero-dose children from comparisons, as they are likely to differ from vaccinated children in measured and unmeasured ways.[9–11] Moreover, they should consider heterogeneity in outcomes related to local community context.

Our study diverges from earlier studies in its theoretical lens, which may largely explain these differences. While earlier studies have attended to individual biomedical pathways such as lack of immunisation as possible causes (and solutions) of learning failures, our analysis conceptualises immunisation among complex, intersecting pathways of child development and considers the relationship of local context to causal processes.[15 36]

Interpretation and policy implications

In specific contexts of deprivation, child zero-dose status is an easy-to-measure early indicator of systematic disadvantage over the life course, signalling children at elevated risk of being developmentally not-on-track with respect to primary education readiness and learning attainment.

Our findings suggest two important orientations for how the new IA2030 zero-dose strategy can best contribute to transformative child development. First, they demonstrate that not all zero-dose children are equally at risk of failure to thrive. A differentiated approach that focusses programmatic efforts on zero-dose children in the most underdeveloped contexts is likely to be most relevant, efficient and impactful. Second, they support the need for holistic, multisectoral intervention strategies to address complex chains of causality working in synergy.

Recent scholarship frames two criteria for a transformative development strategy: first, it addresses 'root causes'—the social and economic structures and relations that generate and reproduce economic, social, political and environmental harms and inequities, not merely their symptoms.[37] Second, it initiates strategic changes leading to large scale, sustained impacts that can accelerate or shift the development trajectory of a country.[37 38] We believe that a suitably reoriented zero-dose strategy

has the ability to meet these criteria. The World Bank and UNESCO underscore that low learning levels represent a worldwide learning crisis threatening countries' efforts to build human capital, reduce poverty and achieve the SDGs.[30] Effective, equity-oriented interventions to promote optimal development through early childhood protection, nurturing and stimulation, teaching, learning and well-being exist.[18 39] As the global community advances the zero-dose vaccination agenda, a wealth of data on missed communities with high proportions of zero-dose children is becoming available.

The COVID-19 pandemic has set back immunisation programmes[17 40] and schooling.[41] In the recovery period, there is an important opportunity for new policy initiatives that unite the zero-dose and early childhood development (ECD) and learning agendas. A targeted approach that focusses on identifying missed communities with high proportions of zero-dose children in the most underdeveloped geographies, and offering integrated interventions that address multiple causes of disadvantage in these geographies, could substantially increase the impact, cost-effectiveness and sustainability of delivering essential interventions to vulnerable populations and catalyse transformative change. A recent initiative for codelivery of immunisation and nutrition interventions offers a precedent.[42]

CONCLUSIONS

Zero-dose children living in contexts of very low socioeconomic development are at elevated risk of poor learning attainment in preadolescence. A holistic, multisectoral intervention strategy focussing on zero-dose children in high-needs geographies could contribute to transformative change, enabling children from systematically marginalised households and communities to survive, thrive and realise their full potential.

Additional research is required to understand the local mechanisms underlying the relationship between child zero-dose vaccination status and learning outcomes in contexts of underdevelopment, and to design integrated intervention strategies that leverage the immunisation, ECD and school platforms to address these complex, interrelated causes of disadvantage.

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Competing interests MJ is a former Independent member of the Evaluation Advisory Committee for Gavi, the Vaccine Alliance and former Chair of the Steering Committee for the Evaluation of Gavi's contribution to reaching zero-dose children and missed communities. EN is part of the Secretariat of the Global Burden of Disease Independent Advisory Committee (GBD IAC). The GBD IAC is supported by a grant by the Bill & Melinda Gates Foundation.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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