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### Permalink

<https://escholarship.org/uc/item/4cp157xr>

### Journal

Annals of the New York Academy of Sciences, 1449(1)

### ISSN

0077-8923

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### Publication Date

2019-08-01

### DOI

10.1111/nyas.14127

Peer reviewed

## ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Special Issue: *Annals Reports*

ORIGINAL ARTICLE

***Haemophilus influenzae* type b vaccination and anthropometric, cognitive, and schooling outcomes among Indian children**Arindam Nandi,<sup>1</sup> Anil B. Deolalikar,<sup>2</sup> David E. Bloom,<sup>3</sup> and Ramanan Laxminarayan<sup>4,5</sup><sup>1</sup>Center for Disease Dynamics, Economics and Policy, Washington, DC. <sup>2</sup>School of Public Policy and Department of Economics, University of California, Riverside, California. <sup>3</sup>Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. <sup>4</sup>Center for Disease Dynamics, Economics and Policy, New Delhi, India.<sup>5</sup>Princeton Environmental Institute, Princeton University, Princeton, New Jersey

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*Haemophilus influenzae* type b (Hib) affects 337,000 Indian children every year. A vaccine against Hib was introduced in 2011 as part of the pentavalent vaccine and scaled up nationwide. This study investigated the associations between Hib vaccination and child anthropometry, cognition, and schooling outcomes in India. We used longitudinal survey data and employed propensity score matching to control for observed systematic differences between children who reported receipt or nonreceipt of Hib vaccine before age 6 years ( $n = 1824$ ). Z-scores of height-for-age (HAZ) and BMI-for-age (BMIZ), percentage scores of English, mathematics, reading, and Peabody Picture Vocabulary tests, and attained schooling grade of children were examined. Hib-vaccinated children had 0.25 higher HAZ, scored 4.09 percentage points (pp) higher on the English test and 4.78 pp higher on the mathematics test, and attained 0.16 more schooling grades than Hib-unvaccinated children at age 11–12 years. At age 14–15 years, they had 0.18 higher HAZ, scored 3.63 pp higher on the reading test and 3.22 pp higher on the mathematics test, and attained 0.15 more schooling grades than Hib-unvaccinated children. The findings indicate potential long-term health, cognitive, and schooling benefits of the Hib vaccine, subject to the effect of unobserved confounding factors.

**Keywords:** India; *Haemophilus influenzae*; Hib vaccine; child development; young lives

**Introduction**

*Haemophilus influenzae* type b (Hib) is a bacterial pathogen that causes pneumonia and bacterial meningitis and, to a lesser extent, epiglottitis and other infections among children under age 5.<sup>1,2</sup> Although the national burden of Hib has declined by 84% since 2000, India continues to have the largest number of Hib cases and associated deaths in the world.<sup>3</sup> An estimated 337,270 Hib cases and 15,634 deaths occurred among Indian children aged 1–59 months in 2015;<sup>3</sup> pneumonia and meningitis comprised 99% of the cases. The Hib vaccine has been privately available in India since 1997. In 2011, the Indian government introduced Hib immunization as part of the pentavalent vaccine, in combina-

tion with vaccines for diphtheria, tetanus, pertussis, and hepatitis B. The pentavalent vaccine was introduced on a trial basis in two states and currently covers 88% of children under the age of 2 years nationwide.<sup>4,5</sup>

Infectious diseases in the first 5 years of life are frequently linked to worse health and non-health outcomes over the life cycle.<sup>6,7</sup> Childhood pneumonia—a small proportion of which is currently due to Hib—may increase the risk of reduced physical growth or stunting, diminished learning capacity, and lower economic productivity.<sup>6–8</sup> It may also increase the adult risk of asthma, chronic obstructive pulmonary disease, and bronchiectasis.<sup>9–11</sup> Episodes of Hib pneumonia

doi: 10.1111/nyas.14127

**Table 1.** Summary statistics of YLS younger cohort in India

	2013 Survey (11–12 year olds)		2016 Survey (14–15 year olds)	
	Hib-vaccinated Mean $\pm$ SD	Hib-unvaccinated Mean $\pm$ SD	Hib-vaccinated Mean $\pm$ SD	Hib-unvaccinated Mean $\pm$ SD
Height-for-age Z-score (HAZ)	-1.3 $\pm$ 1	-1.6 $\pm$ 1	-1.3 $\pm$ 0.9	-1.6 $\pm$ 1
BMI-for-age Z-score (BMIZ)	-1.3 $\pm$ 1.4	-1.4 $\pm$ 1.3	-1 $\pm$ 1.4	-1.2 $\pm$ 1.3
English percentage score	66 $\pm$ 18.5	58.6 $\pm$ 20.5	-	-
PPVT percentage score (0–100)	76 $\pm$ 13.5	75.3 $\pm$ 14	83.8 $\pm$ 14.3	82.7 $\pm$ 13.5
Language percentage score (0–100)	57.8 $\pm$ 18.2	54.7 $\pm$ 18.8	-	-
Reading percentage score (0–100)	-	-	58.3 $\pm$ 17.2	52.9 $\pm$ 17.3
Mathematics percentage score (0–100)	47.8 $\pm$ 22.4	41.5 $\pm$ 22.8	36.1 $\pm$ 17.1	31.2 $\pm$ 15.9
Highest schooling grade attained	5.5 $\pm$ 1.2	5.4 $\pm$ 1.4	8.5 $\pm$ 1.2	8.3 $\pm$ 1.3
Age of child in months	143.7 $\pm$ 3.8	143.9 $\pm$ 3.8	179.8 $\pm$ 3.8	180.1 $\pm$ 3.8
Whether child was born premature	0.1 $\pm$ 0.3	0.1 $\pm$ 0.3	0.1 $\pm$ 0.3	0.1 $\pm$ 0.3
Whether child is female	0.5 $\pm$ 0.5	0.4 $\pm$ 0.5	0.5 $\pm$ 0.5	0.4 $\pm$ 0.5
Rural household	0.6 $\pm$ 0.5	0.8 $\pm$ 0.4	0.6 $\pm$ 0.5	0.8 $\pm$ 0.4
Household size	4.8 $\pm$ 1.5	4.9 $\pm$ 1.9	4.6 $\pm$ 1.5	4.9 $\pm$ 1.8
Whether scheduled caste (SC)	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4
Whether scheduled tribe (ST)	0.2 $\pm$ 0.4	0.1 $\pm$ 0.3	0.2 $\pm$ 0.4	0.1 $\pm$ 0.3
Whether other backward classes (OBCs)	0.5 $\pm$ 0.5	0.5 $\pm$ 0.5	0.5 $\pm$ 0.5	0.5 $\pm$ 0.5
Whether Muslim	0.1 $\pm$ 0.3	0.1 $\pm$ 0.2	0.1 $\pm$ 0.3	0.1 $\pm$ 0.2
Whether Christian	0 $\pm$ 0.2	0.1 $\pm$ 0.2	0 $\pm$ 0.2	0.1 $\pm$ 0.2
Whether Buddhist	0 $\pm$ 0.1	0 $\pm$ 0.1	0 $\pm$ 0.1	0 $\pm$ 0.1
Whether household head is female	0.1 $\pm$ 0.3	0.1 $\pm$ 0.3	0.2 $\pm$ 0.4	0.1 $\pm$ 0.3
Age of household head in years	41.1 $\pm$ 7.7	41.4 $\pm$ 8.1	43.2 $\pm$ 7.3	43.6 $\pm$ 7.8
Head's schooling: literate but <6 years	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	0.3 $\pm$ 0.4	0.3 $\pm$ 0.5
Head's schooling: $\geq$ 6 years but $\leq$ 11 years	0.3 $\pm$ 0.5	0.3 $\pm$ 0.5	0.4 $\pm$ 0.5	0.4 $\pm$ 0.5
Head's schooling: $\geq$ 12 years	0.4 $\pm$ 0.5	0.3 $\pm$ 0.4	0.2 $\pm$ 0.4	0.1 $\pm$ 0.4
Mother's schooling: literate but <6 years	0.1 $\pm$ 0.4	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4
Mother's schooling: $\geq$ 6 years but $\leq$ 11 years	0.3 $\pm$ 0.5	0.2 $\pm$ 0.4	0.3 $\pm$ 0.5	0.2 $\pm$ 0.4
Mother's schooling: $\geq$ 12 years	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	0.1 $\pm$ 0.4	0.1 $\pm$ 0.3
Mother's age in years	34.3 $\pm$ 4	34.8 $\pm$ 4.5	37.3 $\pm$ 4.1	37.8 $\pm$ 4.5
Household belongs to wealth quintile 2	0.2 $\pm$ 0.4	0.3 $\pm$ 0.4	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4
Household belongs to wealth quintile 3	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4
Household belongs to wealth quintile 4	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4
Household belongs to wealth quintile 5	0.3 $\pm$ 0.4	0.1 $\pm$ 0.3	0.3 $\pm$ 0.4	0.1 $\pm$ 0.3
Sample size	783	1041	783	1041

NOTE: Data are from 2013 and 2016 rounds of the Young Lives Survey, comprising 1824 children in the younger cohort in India. The sample is divided based on Hib vaccination information from the 2006 round. SD denotes standard deviation. Empty cells indicate outcome variables not measured in that survey round.

in childhood—the most common form of Hib infection—may be associated with preschool or school absenteeism, thereby adversely affecting learning and schooling outcomes.<sup>12–14</sup> Finally, bacterial meningitis in childhood, such as that caused by Hib, could impede brain development and cause neurological disabilities, deafness, blindness, and paralysis, although such severe consequences may be rare.<sup>15–24</sup>

Most studies focus on the long-term negative effects of Hib infection in high-income countries, but these findings may not be generalizable to low- and middle-income countries (LMICs), where the underlying socioeconomic conditions and disease burdens are different. To the best of our knowledge, only one study has used longitudinal data to investigate the question: it found that out of 1824 Indian children, those vaccinated against Hib were

**Table 2.** Propensity score matching–based estimates (ATT) of the associations of Hib vaccination

	Model (1)		Model (2)	
	ATT	P value	ATT	P value
2013 Survey (11–12 year olds):				
Height-for-age Z-score (HAZ)	0.25	0.00	0.22	0.00
BMI-for-age Z-score (BMIZ)	−0.05	0.48	−0.03	0.71
English percentage score (0–100)	4.09	0.00	4.01	0.00
PPVT percentage score (0–100)	−0.56	0.44	−0.52	0.56
Language percentage score (0–100)	1.63	0.10	−0.01	0.99
Mathematics percentage score (0–100)	4.78	0.00	3.70	0.01
Highest schooling grade attained	0.16	0.02	0.14	0.11
2016 survey (14–15 year olds):				
Height-for-age Z-score (HAZ)	0.18	0.00	0.17	0.01
BMI-for-age Z-score (BMIZ)	0.07	0.35	0.11	0.20
PPVT percentage score (0–100)	−0.21	0.77	0.14	0.87
Reading percentage score (0–100)	3.63	0.00	2.67	0.02
Mathematics percentage score (0–100)	3.22	0.00	2.76	0.01
Highest schooling grade attained	0.15	0.02	0.15	0.07

NOTE: Data are from 2013 and 2016 rounds of the Young Lives Survey, comprising 1824 children in the younger cohort in India. ATT denotes the propensity score matching estimator (kernel) of the associations of Hib vaccination. Model (1) excluded public healthcare access indicators from propensity score estimation, while Model (2) included them.

24% less likely to be stunted and 21% less likely to be underweight at ages 4–6 years.<sup>25</sup> The authors did not examine the nutritional status of children beyond this age, or their cognitive development or schooling outcomes at any age. The study also did not account for possible confounding effects from other vaccines.

In this study, we used longitudinal data from India and employed a quasiexperimental methodology that enabled us to address some of the shortcomings of the existing literature. We investigated the associations of Hib vaccination in early childhood with anthropometric, cognitive functioning, and schooling attainment outcomes for children at ages 11–12 and 14–15 years.

## Materials and methods

### *Young lives survey data*

We used data from the Young Lives Survey (YLS), an international study of the determinants and consequences of childhood poverty.<sup>26</sup> In 2002, the study enrolled a “younger cohort” of approximately 2000 children aged 6–18 months and an “older cohort” of approximately 1000 children aged 7.5–8.5 years in four countries—Ethiopia, India, Peru, and Vietnam—for a total enrollment of approximately 12,000 children. The children and their

households were resurveyed in 2006, 2009, 2013, and 2016.

We analyzed the younger-cohort data from India in this study. In India, six districts from three agro-climatic regions in the formerly undivided state of Andhra Pradesh (presently divided into Andhra Pradesh and Telangana) were selected for YLS.<sup>27</sup> Twenty sentinel sites (subdistrict) were selected, and in each site, 100 households with one child in the younger cohort were chosen for the survey. At the 2002 baseline, 2011 children and their households were enrolled. A comparison based on the National Family Health Survey of India (1998–1999) shows that the YLS households were slightly wealthier and had better access to services as compared with the average household in these states, although secular trends may explain such differences.<sup>28,29</sup> Sample attrition between the baseline and the 2016 follow-up surveys was 3%.

In 2006, when the younger cohort was 4–6 years old, the survey collected data on whether a child had received Hib vaccination within the past 4 years (as reported by the mother or primary caregiver). Vaccination card was reported to be available for 47% of children. Considering that the Hib vaccine was not included in the national child immunization program at that time, whether the card listed the

**Table 3.** Comparison with BCG and measles vaccines

	BCG-vaccinated children				Measles-vaccinated children			
	Model (1)		Model (2)		Model (1)		Model (2)	
	ATT	P value	ATT	P value	ATT	P value	ATT	P value
2013 survey (11–12 year olds):								
Height-for-age Z-score (HAZ)	0.21	0.00	0.18	0.00	0.15	0.01	0.15	0.03
BMI-for-age Z-score (BMIZ)	−0.04	0.58	−0.01	0.88	−0.04	0.62	−0.02	0.79
English percentage score (0–100)	3.49	0.00	3.35	0.01	4.05	0.00	4.13	0.00
PPVT percentage score (0–100)	−0.61	0.39	−0.78	0.36	−0.34	0.66	−0.01	0.99
Language percentage score (0–100)	1.69	0.08	0.93	0.42	1.66	0.13	1.07	0.40
Mathematics percentage score (0–100)	4.02	0.00	3.30	0.02	3.42	0.01	2.38	0.13
Highest schooling grade attained	0.12	0.07	0.10	0.20	0.06	0.44	0.10	0.28
2016 survey (14–15 year olds):								
Height-for-age Z-score (HAZ)	0.17	0.00	0.16	0.01	0.12	0.04	0.12	0.08
BMI-for-age Z-score (BMIZ)	0.09	0.22	0.11	0.19	0.10	0.23	0.10	0.27
PPVT percentage score (0–100)	−0.20	0.78	−0.12	0.90	−0.85	0.30	−0.69	0.47
Reading percentage score (0–100)	3.52	0.00	2.69	0.01	3.84	0.00	3.05	0.01
Mathematics percentage score (0–100)	3.15	0.00	2.54	0.01	2.95	0.00	2.12	0.07
Highest schooling grade attained	0.12	0.06	0.12	0.12	0.10	0.17	0.13	0.13

NOTE: Data are from 2013 and 2016 rounds of the Young Lives Survey's younger cohort in India. Only children who were reported as BCG-vaccinated or measles-vaccinated in 2002 were included. ATT denotes the propensity score matching estimator (kernel) of the associations of Hib vaccination. Model (1) excluded public healthcare access indicators from propensity score estimation, while Model (2) included them.

vaccine is unknown. The survey also did not collect data on the whether the vaccine receipt information was cross-validated with the card.

We combined the vaccine receipt information with household socioeconomic characteristics and child anthropometric, cognition, and schooling data from the 2013 and 2016 surveys. Community-level information on access to public healthcare, such as the availability of health centers (which could affect vaccination rates), was available for 88% of children in 2002. We used these data for additional analyses, as discussed later.

Using the 2013 survey data, we examined the following anthropometric indicators of 11- to 12-year-old children: height-for-age Z-scores (HAZ) and body-mass-index-for-age Z-scores (BMIZ). We excluded children with outlier values of the indicators ( $HAZ < -6$  or  $HAZ > 6$  and  $BMIZ < -5$  or  $BMIZ > 5$ ).

We evaluated cognition indicators, which were based on percentage scores, from the following standardized assessments: an English language test, the Peabody Picture Vocabulary Test (PPVT), a local language test, and a mathematics test.<sup>30,31</sup> The English and local language tests involved answer-

ing questions based on words and passages. The mathematics test consisted of number recognition and basic operations, and the PPVT included a set of age-appropriate questions that were adapted for India. The psychometric validity of these tests has been discussed in a previous YLS study.<sup>30</sup> We also examined a schooling indicator: highest grade attained by the child, which ranged from 0 to 11 in the 2013 data.

Using the 2016 survey data—when the children were 14–15 years old—we examined the same indicators, with the exception of the English and local language test scores, which were not administered. Instead, we included the percentage score of a reading test, which was available in the 2016 data. In this survey round, the highest grade attained ranged from 1 to 12.

### Analysis

Childhood vaccination rates vary widely across regions and socioeconomic groups in India.<sup>32–34</sup> Standard of living, access to postnatal care and subsidized vaccines, maternal schooling, and health insurance coverage have all been linked positively to vaccination rates.<sup>35,36</sup> These factors could

**Table 4. Model (1)—tests of matching quality**

	Mean % bias in unmatched data	Mean % bias after PSM	Pseudo- $R^2$ before matching	Pseudo- $R^2$ after matching	$P$ value for $\chi^2$ before matching	$P$ value for $\chi^2$ after matching
Analysis of 2013 survey (11–12 year olds):						
Height-for-age Z-score (HAZ)	11.6	2.6	0.079	0.003	0	1
BMI-for-age Z-score (BMIZ)	11.6	2.6	0.079	0.003	0	1
English percentage score (0–100)	11.6	2.5	0.079	0.003	0	1
PPVT percentage score (0–100)	11.6	2.5	0.079	0.003	0	1
Language percentage score (0–100)	11.6	2.5	0.079	0.003	0	1
Mathematics percentage score (0–100)	11.6	2.5	0.079	0.003	0	1
Highest schooling grade attained	11.6	2.6	0.079	0.003	0	1
Analysis of 2016 survey (14–15 year olds):						
Height-for-age Z-score (HAZ)	11.5	2.9	0.072	0.003	0	1
BMI-for-age Z-score (BMIZ)	11.5	2.8	0.072	0.003	0	1
PPVT percentage score (0–100)	11.5	2.9	0.072	0.003	0	1
Reading percentage score (0–100)	11.5	2.8	0.072	0.003	0	1
Mathematics percentage score (0–100)	11.5	2.8	0.072	0.003	0	1
Highest schooling grade attained	11.5	3	0.072	0.003	0	1

NOTE: Bias is measured as the standardized percentage difference in the average value of the variable between the Hib-vaccinated and -unvaccinated samples. Matching was based on propensity scores, using the kernel (Epanechnikov) matching method. Model (1) excluded public healthcare access indicators from propensity score estimation.

make Hib-vaccinated and -unvaccinated children systematically different, potentially biasing least squares regression-based estimates of the associations of the vaccine with our outcomes of interest because such differences may also be linked to these outcomes.

We used a quasiexperimental methodology of propensity score matching (PSM) to reduce the differences in the characteristics of the two groups of children.<sup>37–40</sup> Separately for the 2013 and 2016 survey rounds, we first regressed the Hib-vaccinated status of each child on the following characteristics: age of child in months, squared value of age in months, whether child is female, whether child was born prematurely, rural household indicator, number of household members, and indicators of caste groups (scheduled caste, scheduled tribe, or other backward classes) and religion (Muslim, Christian, or Buddhist). We also included covariates for the characteristics of the household head: whether female, age in years, and indicators of schooling level (<6 years,  $\geq 6$  years but  $\leq 11$  years, and  $\geq 12$  years of schooling). Mother's age in years and schooling indicators (same categories as listed) are also included.

We measured the household standard of living through a composite YLS index of durable assets, such as television, radio, and bicycle ownership, along with housing conditions, such as indicators of construction quality and access to drinking water and toilets.<sup>41</sup> We divided the wealth index into quintiles and included binary indicators of second to fifth quintiles in the regression.

Using the predicted probability (propensity score) of Hib vaccination from this probit model, we matched Hib-vaccinated children with similar Hib-unvaccinated children. We used a kernel (Epanechnikov) matching algorithm and only considered the observations with overlapping propensity scores (known as the “common support”). After matching, differences in child outcomes between the Hib-vaccinated and matched Hib-unvaccinated groups could be attributed to the Hib vaccine. This difference is known as the *average treatment effect on treated* (ATT).

In additional analyses, we estimated the ATT associations of the Hib vaccine by including the following public healthcare indicators in the probit model of propensity scores: availability of a public hospital, a public health post, and a public health

**Table 5.** Model (2)—tests of matching quality

	Mean % bias in unmatched data	Mean % bias after PSM	Pseudo- $R^2$ before matching	Pseudo- $R^2$ after matching	$P$ value for $\chi^2$ before matching	$P$ value for $\chi^2$ after matching
Analysis of 2013 survey (11–12 year olds):						
Height-for-age Z-score (HAZ)	19.9	4.2	0.171	0.008	0	0.986
BMI-for-age Z-score (BMIZ)	19.9	4.2	0.171	0.008	0	0.987
English percentage score (0–100)	19.9	4.3	0.171	0.008	0	0.985
PPVT percentage score (0–100)	19.9	4.2	0.171	0.008	0	0.986
Language percentage score (0–100)	19.9	4.3	0.171	0.008	0	0.981
Mathematics percentage score (0–100)	19.9	4.3	0.171	0.008	0	0.983
Highest schooling grade attained	19.9	4.2	0.171	0.008	0	0.986
Analysis of 2016 survey (14–15 year olds):						
Height-for-age Z-score (HAZ)	18.6	4.7	0.162	0.011	0	0.890
BMI-for-age Z-score (BMIZ)	18.6	4.7	0.162	0.011	0	0.889
PPVT percentage score (0–100)	18.6	4.7	0.162	0.010	0	0.915
Reading percentage score (0–100)	18.6	4.8	0.162	0.011	0	0.865
Mathematics percentage score (0–100)	18.6	4.7	0.162	0.011	0	0.888
Highest schooling grade attained	18.6	5	0.162	0.012	0	0.826

NOTE: Bias is measured as the standardized percentage difference in the average value of the variable between the Hib-vaccinated and -unvaccinated samples. Matching was based on propensity scores, using the kernel (Epanechnikov) matching method. Model (2) included public healthcare access indicators in propensity score estimation.

center. We considered  $P < 0.05$  for statistical significance in all models.

### *Comparison with other vaccines, matching quality tests, and additional matching algorithms*

We examined the associations of Hib vaccination vis-à-vis two other vaccines: the 2002 YLS collected information on the administration of bacillus Calmette–Guérin (BCG) and measles vaccines to the child (reported by the mother and cross-validated with vaccination card). We estimated the ATT associations of Hib vaccine only within the subsample of children who had received BCG vaccine (92%). We repeated a similar analysis among measles-vaccinated children (73%).

We also used multiple tests to check whether the kernel PSM algorithm was valid, that is, if it reduced the initial differences between the Hib-vaccinated and -unvaccinated groups. First, we calculated the mean standardized percentage bias, that is, the average percentage difference in the values of PSM probit model covariates between Hib-vaccinated and -unvaccinated groups before matching. We then compared it with the mean standardized bias calculated from the Hib-vaccinated and matched Hib-unvaccinated (after matching) groups. A valid PSM

would reduce the mean bias substantially pre- to post-matching.

Second, we reestimated the PSM probit model using the Hib-vaccinated and matched Hib-unvaccinated samples. If PSM successfully reduced the differences between the two groups, the pseudo- $R^2$  statistic from this regression should be substantially smaller than the pseudo- $R^2$  in the original model.

Third, we conducted a likelihood ratio test of the joint significance of the probit covariates before and after matching. In the matched Hib-vaccinated and -unvaccinated sample, failure to reject the null hypothesis of joint significance would indicate that the quality of matching was high, that is, the covariates could no longer explain the Hib-vaccination status of a child in the combined matched data.

Finally, we tested the sensitivity of our results by repeating the analysis under two other matching algorithms: one-to-one nearest neighbor matching with replacement and within a probability radius of 0.01 and one-to-three nearest neighbors matching.

## **Results**

Our sample included 1824 younger-cohort children, of whom 42.9% were reported as



**Table 6.** Model (1)—standardized percentage bias before and after matching

	2013 Survey (11–12 year olds)		2016 Survey (14–15 year olds)	
	% bias before matching	% bias after matching	% bias before matching	% bias after matching
Age of child in months	−5.1	−2.4	−7.6	−0.7
Squared age of child in months	−5.1	−2.4	−7.6	−0.7
Whether child was born premature	10	1.1	10	4.5
Whether child is female	9.9	−1.8	9.3	−0.3
Rural household	−41.4	−5.3	−34.1	−2.6
Household size	−7	4	−14.8	2.6
Whether scheduled caste (SC)	−12.2	0.4	−12.2	−0.2
Whether scheduled tribe (ST)	13.3	−5.8	13.3	−4.2
Whether other backward classes (OBCs)	−4	2.2	−4	3.3
Whether Muslim	7.5	−0.8	7.5	−4.4
Whether Christian	−9	0.6	−9	0.6
Whether Buddhist	6.3	3.5	6.3	1.8
Whether household head is female	3.4	−2.6	8.7	−2.7
Age of household head in years	−4	2.5	−5.1	2.3
Head's schooling: <6 years	−13.8	−0.9	−12.7	−4.6
Head's schooling: ≥6 years but ≤11 years	−4.9	0.8	1.5	−0.7
Head's schooling: ≥12 years	19.7	3.5	20.3	7.3
Mother's schooling: <6 years	−4.1	−4.8	−5.9	−5.6
Mother's schooling: ≥6 years but ≤11 years	34.9	4.5	31.4	4.3
Mother's schooling: ≥12 years	−0.4	3.9	5.4	4.2
Mother's age in years	−11.8	2	−10.6	2.9
Household belongs to wealth quintile 2	−24.5	0.4	−12	−2.2
Household belongs to wealth quintile 3	1	−2.1	2.6	−2
Household belongs to wealth quintile 4	4.4	−1.6	1.9	−2.6
Household belongs to wealth quintile 5	32.9	4.6	33.8	5.6

NOTE: Bias is measured as the standardized percentage difference in the average value of the variable between the Hib-vaccinated and -unvaccinated samples. Results from the analysis of height-for-age Z score (HAZ) are shown. Matching was based on propensity scores, using the kernel (Epanechnikov) matching method. Model (1) excluded public healthcare access indicators from propensity score estimation.

Hib-vaccinated. Table 1 presents the summary statistics of the study sample by Hib vaccination status. As compared with Hib-unvaccinated children, Hib-vaccinated children were more likely to be younger, female, from smaller and wealthier families, from urban areas, and have younger mothers and household heads.

#### *Outcomes at ages 11–12 years (2013 YLS)*

Table 2 presents estimates of the ATT associations of Hib vaccination. When public healthcare access indicators were excluded from propensity score estimation (Model 1), Hib-vaccinated children had 0.25 (95% CI: 0.14–0.35;  $P < 0.001$ ) higher HAZ, scored 4.09 (95% CI: 2.02–6.15;  $P < 0.001$ ) percentage points (pp) higher on the English test and 4.78 pp (95% CI: 2.41–7.15;  $P < 0.001$ ) higher on the math-

ematics test, and attained 0.16 (95% CI: 0.03–0.3;  $P < 0.05$ ) more schooling grades than matched Hib-unvaccinated children.

After including public healthcare access indicators, which were available for 88% of the sample (Model 2), Hib-vaccinated children had 0.22 (95% CI: 0.09–0.34;  $P < 0.01$ ) higher HAZ and scored 4.01 pp (95% CI: 1.48–6.53;  $P < 0.01$ ) higher on the English test and 3.7 pp (95% CI: 0.77–6.62;  $P < 0.05$ ) higher on the mathematics test than matched Hib-unvaccinated children.

#### *Outcomes at ages 14–15 years (2016 YLS)*

In Model (1), Hib-vaccinated children had 0.18 (95% CI: 0.08–0.28;  $P < 0.001$ ) higher HAZ, scored 3.63 pp (95% CI: 1.81–5.44;  $P < 0.001$ ) higher on the reading test and 3.22 pp (95% CI: 1.49–4.96;



**Table 7. Model (2)—standardized percentage bias before and after matching**

	2013 Survey (11–12 year olds)		2016 Survey (14–15 year olds)	
	% bias before matching	% bias after matching	% bias before matching	% bias after matching
Age of child in months	−6.1	−5.5	−6.3	−5.2
Squared age of child in months	−6.1	−5.5	−6.3	−5.1
Whether child was born premature	8.9	2	7.7	0.2
Whether child is female	10.7	3.1	11.3	4.7
Rural household	−52.7	−6.9	−47.4	−9.1
Household size	−7.3	1.4	−16.7	1.3
Whether scheduled caste (SC)	−11.7	−0.8	−14.2	−0.7
Whether scheduled tribe (ST)	16.4	−16.6	16.1	−16.5
Whether other backward classes (OBCs)	−9.4	9.7	−7.5	10.9
Whether Muslim	14.3	−2.2	16.7	−4.2
Whether Christian	−9.6	−3.5	−9.8	−5.7
Whether Buddhist	5.3	2.6	3.7	2.9
Whether household head is female	1.7	−2.7	10.1	−0.8
Age of household head in years	−6.5	6.3	−3	6
Head's schooling: <6 years	−14.3	−4.9	−11.2	−3.6
Head's schooling: ≥6 years but ≤11 years	−7.1	−0.5	3	−2.3
Head's schooling: ≥12 years	21.3	7.6	21	10.7
Mother's schooling: <6 years	−0.4	−2.6	−2.7	−3.4
Mother's schooling: ≥6 years but ≤11 years	33.2	1.7	30	2.6
Mother's schooling: ≥12 years	1.2	6.3	5.7	7.8
Mother's age in years	−10.6	3.1	−11	3.6
Household belongs to wealth quintile 2	−24.2	−1.4	71.5	4.7
Household belongs to wealth quintile 3	−30.8	0.5	64.9	3.5
Household belongs to wealth quintile 4	7.6	2.2	61.8	4.5
Household belongs to wealth quintile 5	47.8	8.3	−16.3	−1.7
Public hospital available in community	67.5	4	5.2	−1.7
Public health post available in community	62.4	2.7	4.3	5.8
Public health center available in community	60.5	3.8	34.6	2

NOTE: Bias is measured as the standardized percentage difference in the average value of the variable between the Hib-vaccinated and -unvaccinated samples. Results from the analysis of height-for-age Z score (HAZ) are shown. Matching was based on propensity scores, using the kernel (Epanechnikov) matching method. Model (2) included public healthcare access indicators in propensity score estimation.

$P < 0.001$ ) higher on the mathematics test, and attained 0.15 (95% CI: 0.02–0.28;  $P < 0.05$ ) more schooling grades than matched Hib-unvaccinated children.

In Model (2), Hib-vaccinated children had 0.17 (95% CI: 0.05–0.3;  $P < 0.01$ ) higher HAZ and scored 2.67 pp (95% CI: 0.45–4.89;  $P < 0.05$ ) higher on the reading test and 2.76 pp (95% CI: 0.65–4.87;  $P < 0.05$ ) higher on the mathematics test than matched Hib-unvaccinated children.

### Results from comparison with BCG and measles vaccines

Table 3 presents results from the BCG-only and measles-only analyses. Among BCG-vaccinated 11-

to 12-year-old children in Model (1), children who also received the Hib vaccine had 0.21 (95% CI: 0.1–0.31;  $P < 0.001$ ) higher HAZ and scored 3.49 pp (95% CI: 1.51–5.46;  $P < 0.001$ ) higher on the English test and 4.02 pp (95% CI: 1.73–6.32;  $P < 0.001$ ) higher on the mathematics test than matched children who had received the BCG vaccine but not Hib. At age 14–15 years, these Hib-vaccinated children had 0.17 (95% CI: 0.07–0.27;  $P < 0.001$ ) higher HAZ and scored 3.52 pp (95% CI: 1.76–5.28;  $P < 0.001$ ) and 3.15 pp (95% CI: 1.44–4.87;  $P < 0.001$ ) higher on the reading and mathematics tests, respectively, than their matched counterparts.

**Table 8. Alternative matching algorithms**

	One-to-one neighbor matching				One-to-three neighbor matching			
	Model (1)		Model (2)		Model (1)		Model (2)	
	ATT	P value	ATT	P value	ATT	P value	ATT	P value
2013 survey (11–12 year olds):								
Height-for-age Z-score (HAZ)	0.20	0.00	0.18	0.05	0.22	0.00	0.22	0.01
BMI-for-age Z-score (BMIZ)	−0.04	0.66	−0.09	0.41	−0.02	0.80	−0.03	0.73
English percentage score (0–100)	3.48	0.01	1.49	0.25	3.71	0.00	3.79	0.00
PPVT percentage score (0–100)	−1.02	0.32	−0.65	0.57	−0.74	0.40	−0.72	0.47
Language percentage score (0–100)	1.07	0.35	−0.77	0.62	1.26	0.22	0.46	0.72
Mathematics percentage score (0–100)	5.82	0.00	2.33	0.16	4.90	0.00	3.03	0.04
Highest schooling grade attained	0.18	0.04	0.18	0.06	0.14	0.07	0.13	0.11
2016 survey (14–15 year olds):								
Height-for-age Z-score (HAZ)	0.16	0.02	0.13	0.09	0.17	0.01	0.17	0.01
BMI-for-age Z-score (BMIZ)	0.04	0.68	0.19	0.07	0.02	0.79	0.19	0.05
PPVT percentage score (0–100)	0.50	0.64	1.75	0.23	0.32	0.69	0.79	0.49
Reading percentage score (0–100)	4.20	0.00	3.62	0.03	4.01	0.00	2.46	0.05
Mathematics percentage score (0–100)	4.71	0.00	3.63	0.01	2.98	0.00	3.05	0.01
Highest schooling grade attained	0.22	0.05	0.14	0.37	0.16	0.03	0.14	0.05

NOTE: Data are from 2013 and 2016 rounds of the Young Lives Survey, comprising 1824 children in the younger cohort in India. ATT denotes the propensity score matching estimator of the associations of Hib vaccination. One-to-one nearest neighbor matching with replacement and within a radius of 0.01 and one-to-three nearest neighbor matching were used. Model (1) excluded public healthcare access indicators from propensity score estimation, while Model (2) included them.

Among measles-vaccinated children of age 11–12 years in Model (1), those who were also vaccinated with Hib had 0.15 (95% CI: 0.03–0.26;  $P < 0.05$ ) higher HAZ and scored 4.05 pp (95% CI: 1.8–6.3;  $P < 0.001$ ) and 3.42 pp (95% CI: 0.79–6.04;  $P < 0.05$ ) higher on the English and mathematics tests, respectively, than matched children who had received the measles vaccine but not Hib. At age 14–15 years, these Hib-vaccinated children had 0.12 (95% CI: 0–0.23;  $P < 0.05$ ) higher HAZ and scored 3.84 pp (95% CI: 1.86–5.82;  $P < 0.001$ ) and 2.95 pp (95% CI: 1–4.9;  $P < 0.01$ ) higher on the reading and mathematics tests, respectively, than matched Hib-unvaccinated children.

Results from Model (2) were similar to Model (1) for both the BCG-only and measles-only analyses. They are presented in Table 3 but not discussed here separately.

### Results from matching quality tests and alternative matching algorithms

Tables 4 and 5 present results from the tests of matching quality under the original kernel PSM Model (1) and Model (2), respectively. The mean standardized percentage bias declined by more than

74%, while pseudo- $R^2$  declined by more than 95% from pre- to post-matching in Model (1). Similarly, mean bias and pseudo- $R^2$  declined by at least 73% and 93%, respectively, after matching in Model (2). In all models, the  $P$  value of the likelihood ratio  $\chi^2$  was higher than 0.05 after matching. This implies that the null hypothesis of joint significance of covariates in the propensity score estimation using the matched sample could not be rejected. Additional results presented in Tables 6 and 7 show that the standardized percentage bias reduced substantially from pre- to post-matching for almost all individual covariates of the models.

Table 8 presents results from PSM using alternative matching algorithms. The associations of Hib vaccination in these additional analyses were similar in magnitude and statistical significance as in the original kernel PSM, with some minor variations.

### Discussion and conclusion

Indian children who received the Hib vaccine in early childhood were found to be taller than similar Hib-unvaccinated children at ages 11–12 and 14–15 years by 11–16%. Hib-vaccinated children

also scored 7–12% higher on English and mathematics tests at age 11–12 years and 7–10% higher on reading and mathematics tests at age 14–15 years and attained more schooling (by 11–12%) at both ages as compared with their unvaccinated counterparts. The estimates were smaller, and no statistically significant association of Hib vaccine receipt with schooling grade attainment was evident in the subsample of children with data on access to public healthcare facilities. Overall, our findings were not sensitive to the choice of matching algorithm and were statistically significant, even after accounting for possible confounding effects from BCG and measles vaccinations.

The burden of Hib disease in India was high in 2000—the only year during early life of the YLS cohort for which such data are available. Estimates from two modeling studies and the World Health Organization range from 2 to 4.5 million Hib cases in India in 2000, most of which were Hib pneumonia.<sup>3,24,42</sup> Two-thirds of Hib cases are known to occur in children under the age of 2 years, implying that a substantial proportion of the under-2 cohort of 36.2 million Indian children at that time was affected.<sup>43</sup> However, the burden of Hib meningitis may have been substantially underestimated in these models, as it was estimated from small surveillance studies which are known to capture such data inadequately.<sup>24</sup> Hib nonpneumonia and nonmeningitis disease burden, which was calculated based on meningitis burden, was also likely underestimated.<sup>24</sup>

The positive association between Hib vaccination and anthropometric outcomes in our study could be mediated largely by pneumonia risk factors. In LMICs, stunted and underweight children are known to be at a higher risk of pneumonia.<sup>44,45</sup> The Hib-unvaccinated children in our study were from lower-income families and may have had higher rates of undernutrition before the 2006 survey, as compared with the Hib-vaccinated children. As a result, they may have been predisposed to higher rates of pneumonia. With respect to cognitive test and schooling grade outcomes of children, the estimated positive associations of Hib vaccination could be mediated by worse nutritional status preschool and school absenteeism due to pneumonia among control group children.<sup>12–14</sup>

Our findings contribute substantially to the scant literature on the potential long-term benefits of

childhood vaccines in LMICs. In addition to the aforementioned study of Hib vaccination and anthropometric outcomes of Indian children aged 4–6,<sup>25</sup> other studies have demonstrated commensurate benefits: measles vaccination was associated with 7.4% higher schooling enrollment among 8- to 16-year-old children in Bangladesh and 0.2 more schooling grades attained by 6- to 11-year-old children in South Africa,<sup>46,47</sup> and full immunization with 0.5 standard deviation higher cognitive test scores of 10- to 11-year-old Filipino children.<sup>48</sup> In India, a study has linked the national immunization program with reduction in height-for-age deficit of under-4 children by up to 25% and weight-for-age deficit by up to 15%.<sup>49</sup>

The findings have important policy implications. Worldwide, 191 countries had adopted the Hib vaccine by 2017, with an estimated 72% of Hib third dose (Hib3)—which promotes durability following the immune response built by the first two doses—coverage among 12- to 23-month-old children.<sup>5,50</sup> However, coverage varied widely, from 94% in high-income countries to 81%, 77%, and 41%, respectively, in lower-middle-, low-, and upper-middle-income countries,<sup>50</sup> and 975,000 cases and 29,800 deaths from Hib still occurred among 1- to 59-month-old children worldwide in 2015.<sup>3</sup> India's Hib3 coverage rates among children under the age of 2 years increased from 20% in 2013 to 88% in 2017,<sup>5</sup> but its burden of disease remains the highest in the world.<sup>3</sup> Funding for India's national immunization program remains inadequate. During 2013–2017, the estimated annual budgetary shortfall for the program increased from \$8.6 to \$544.2 million (in 2013 US\$), primarily because of the introduction of pentavalent and other new vaccines.<sup>51,52</sup>

The economic viability of publicly funded vaccines is traditionally evaluated using cost-effectiveness analysis (CEA). However, CEAs that use disability-adjusted life years (DALYs) to measure health gains have many methodological shortcomings, chief among them being that DALYs do not account for potential nonhealth benefits of vaccines and ignore any equity aspects of benefits across population subgroups. Therefore, alternative methodologies, such as benefit–cost analysis or multicriteria decision analysis, which incorporate various health and nonhealth metrics, have gained prominence in recent years.<sup>53–55</sup> Our findings

show that the Hib vaccine could rank highly in the context of multicriteria-based resource allocation.

Our analysis has some limitations. Although we included an extensive set of child, household, and healthcare access covariates in our PSM, unobserved heterogeneity may be present that could bias the results. For example, parents may have vaccinated children based on their health (i.e., perceived likelihood of survival, susceptibility to infections, and growth), which was unobserved in the data. Also, if Hib vaccination of a child was associated positively with other human capital investments that also affect long-term outcomes (e.g., nutrition or healthcare resources), our estimates may be inflated. PSM would not mitigate any possible biases arising from such unobserved differences between Hib-vaccinated and Hib-unvaccinated children.

Whether the reported receipt of Hib vaccine in YLS was cross-validated with vaccination cards is unknown, making it susceptible to measurement errors. Some Hib-unvaccinated children may have been categorized as vaccinated, making our estimates of positive associations conservative. The survey also did not collect information on age at vaccination or the number of Hib doses administered to children. The 2006 YLS asked about the receipt of Hib vaccine (without specifying dose) in the 4 years preceding the interview date; considering that the children were 4–6 years old in 2006, the survey may have missed Hib vaccinations during the first 2 years of life of some children. Because these children would have been improperly categorized as Hib-unvaccinated, our estimates of the positive associations of the vaccine may be conservative.

Large regional disparities exist in India with respect to socioeconomic indicators, access to and quality of healthcare and schooling infrastructure, and disease burden. For example, children from the northern Indian states, such as Uttar Pradesh, Bihar, and Madhya Pradesh, have higher rates of undernutrition and incidence of childhood diseases. Therefore, our findings from Andhra Pradesh may not be generalizable to other parts of India.

Further, owing to a lack of data, we could not capture any secondary immunity provided by the Hib vaccine to Hib-unvaccinated children who might have been in contact with Hib-vaccinated children. The 2013 and 2016 YLS surveys also could not capture data on children who had died since 2006.<sup>28</sup>

These may have made our estimates of the associations of the vaccine conservative.

Notwithstanding these limitations, our findings do suggest that Hib vaccination not only reduces the immediate burden of Hib diseases, but may also be associated with improved adolescent height, cognitive functioning, and schooling attainment in India. These positive health and social outcomes are strongly associated with positive economic outcomes, implying that the benefits of Hib vaccination for LMICs could reverberate throughout multiple domains of society. India has made great strides in its struggle against Hib, but our analysis suggests the need to continue, indeed accelerate, efforts to expand Hib vaccination.

### Acknowledgments

This work was supported by the Bill & Melinda Gates Foundation (OPP1183738). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. D.B. thanks the Bill & Melinda Gates Foundation for supporting his work on this article through the Value of Vaccination Research Network.

### Author contributions

A.N. and R.L. designed the study. A.N. collected the data, conducted the analysis, and wrote the first version of the manuscript. All authors interpreted the findings and critically evaluated and edited the manuscript. All authors approved the final draft for publication.

### Competing interests

D.B. has previously received research support or personal fees from GlaxoSmithKline plc, Merck, Pfizer, and Sanofi-Pasteur related generally to value-of-vaccination research, but not for this study. All other authors declare no competing interests.

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