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Effect of *Helicobacter pylori* infection on growth trajectories in young Ethiopian children: a longitudinal study



Bineyam Taye^{a,b,*}, Fikre Enquselassie^b, Aster Tsegaye^c, Alemayehu Amberbir^d, Girmay Medhin^e, Andrew Fogarty^f, Karen Robinson^g, Gail Davey^h

^a Colgate University, Department of Biology, 214 Olin Hall, 13 Oak Dr, Hamilton, NY, 13346, USA

^b School of Public Health, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

^c School of Allied Health Sciences, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

^d Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

^e Akllilu Lemma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia

^f Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK

^g Nottingham Digestive Diseases Biomedical Research Unit, School of Medicine, University of Nottingham, Nottingham, UK

^h Wellcome Trust Centre for Global Health Research, Brighton and Sussex Medical School, Brighton, UK

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SUMMARY

Background: *Helicobacter pylori* infection has been associated with early childhood growth impairment in high- and middle-income countries; however, few studies have examined this relationship within low-income countries or have used a longitudinal design. The possible effects of *H. pylori* infection on growth trajectories were examined in a cohort of young Ethiopian children.

Methods: In 2011/12, 856 children (85.1% of the 1006 original singletons in a population-based birth cohort) were followed up at age 6.5 years. An interviewer-led questionnaire administered to mothers provided information on demographic and lifestyle variables. Height and weight were measured twice, and the average of the two measurements was used. Exposure to *H. pylori* infection was assessed using a rapid *H. pylori* stool antigen test. The independent associations of positive *H. pylori* infection status (measured at ages 3 and 6.5 years) with baseline height and weight (age 3 years) and height and weight growth trajectory (from age 3 to 6.5 years) were modelled using hierarchical linear models.

Results: At baseline (age 3 years), the children's mean height was 85.7 cm and their mean weight was 11.9 kg. They gained height at a mean rate of 8.7 cm/year, and weight at a mean rate of 1.76 kg/year. *H. pylori* infection was associated with lower baseline measurements and linear height trajectory ($\beta = -0.74$ cm and -0.79 cm/year, respectively), after controlling for demographics and markers of socio-economic status. However, the positive coefficient was associated with quadratic growth in height among *H. pylori*-infected children ($\beta = 0.28$, 95% confidence interval 0.07 to 0.49, $p < 0.01$), and indicated an increase in height trajectory as the child increased in age. A non-significant difference in baseline and trajectory of weight was observed between *H. pylori*-infected and non-infected children.

Conclusions: These findings add to the growing body of evidence supporting that *H. pylori* infection is inversely associated with childhood growth trajectory, after controlling for a range of factors associated with reduced growth and *H. pylori* status. Further follow-up will be important to confirm possible catch-up in height trajectory among *H. pylori*-infected children as they grow older.

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1. Introduction

There is now good evidence that infection with *Helicobacter pylori* is the principal cause of acute and chronic gastritis and

atrophic gastritis.^{1–3} More recently, however, there has been interest in the effects of *H. pylori* in extra-gastrointestinal diseases.^{4–7} This interest has led researchers to investigate the effects of *H. pylori* in a wide range of growth outcomes. Evidence for an association between *H. pylori* and childhood growth impairment has arisen from a range of epidemiological studies.^{8–12} Delayed growth,^{11,12} short stature,¹³ and growth retardation^{8,9,12,14} appear to be related to *H. pylori* infection.

* Corresponding author. Tel.: +1 315 228 7398.
E-mail address: btaye@colgate.edu (B. Taye).

Several mechanisms by which *H. pylori* infection causes growth impairment have been proposed.^{15,16} One hypothesis that has attracted attention is that since infection with *H. pylori* is accompanied by hypochlorhydria, this facilitates the acquisition of other enteropathogens due to impairment of the gastric acid barrier. This then results in diarrheal disease, iron-deficiency anaemia, and growth impairment.^{15,16} This is likely to occur most frequently in developing regions where the prevalence of *H. pylori* infection is disproportionately high and multiple enteric co-infections are common.^{15,17} *H. pylori* infection has also been associated with impaired absorption of nutrients and vitamins,¹⁸ and reduced food intake as a result of dyspepsia,¹⁹ which in turn impairs childhood growth. Although these hypotheses seem biologically plausible, whether growth impairment occurs as a direct effect of the *H. pylori*-induced inflammation, or as a consequence of indirect effects (such as infection-induced anorexia,²⁰ *H. pylori*-associated intestinal permeability changes,²¹ and/or malabsorption or diarrheal disease²²) is unclear. It has been suggested that direct and indirect effects may both contribute to growth impairment.⁴

Whilst the role of *H. pylori* in childhood growth impairment is intriguing, possible bias due to potential confounding variables such as socio-economic status, which may contribute both to occurrences of childhood growth impairment and to *H. pylori* infection, are difficult to exclude. If *H. pylori* can be proved to negatively affect childhood growth, it can then be considered a treatable cause of diminished growth and a potential target for nutritional intervention. In Ethiopia, childhood undernutrition continues to be a major public health problem,²³ and is associated with complex socio-demographic and economic factors.²⁴ Few studies have examined the possible link between *H. pylori* infection and childhood growth outcomes within low-income countries or have used a longitudinal design. It appears that no study has attempted to investigate this relationship in Ethiopia. In this study, data from a detailed Ethiopian birth cohort were used to assess the effect of *H. pylori* infection on growth trajectories, using two-level hierarchical linear models.

2. Methods

2.1. Study setting and design

A detailed description of the original Butajira Birth Cohort study has been published.^{25,26} Briefly, the birth cohort is nested within the Butajira Demographic Surveillance Site,²⁷ which covers a sample of nine rural and one urban administrative units in and around the town of Butajira in southern Ethiopia,²⁴ with a total population of approximately 33 393 in 2007. Of the 1234 women eligible in 2005–2006, 1065 were recruited (86% of those eligible); all live singleton babies born to these women ($n = 1006$) were followed-up as a birth cohort (Figure 1).

2.2. Measurement and data collection

After informed consent was given by the mothers, information on demographic and selected lifestyle factors was collected via an interviewer-administered questionnaire during pregnancy, at birth, and during the follow-up visits.

During follow-up visits at ages 3, 5, and 6.5 years, mothers were also asked to collect a faecal sample from their child using a leak-proof plastic container. The samples were then transported to the Butajira Health Centre laboratory for analysis, to ascertain the child's *H. pylori* and intestinal parasite infection status.

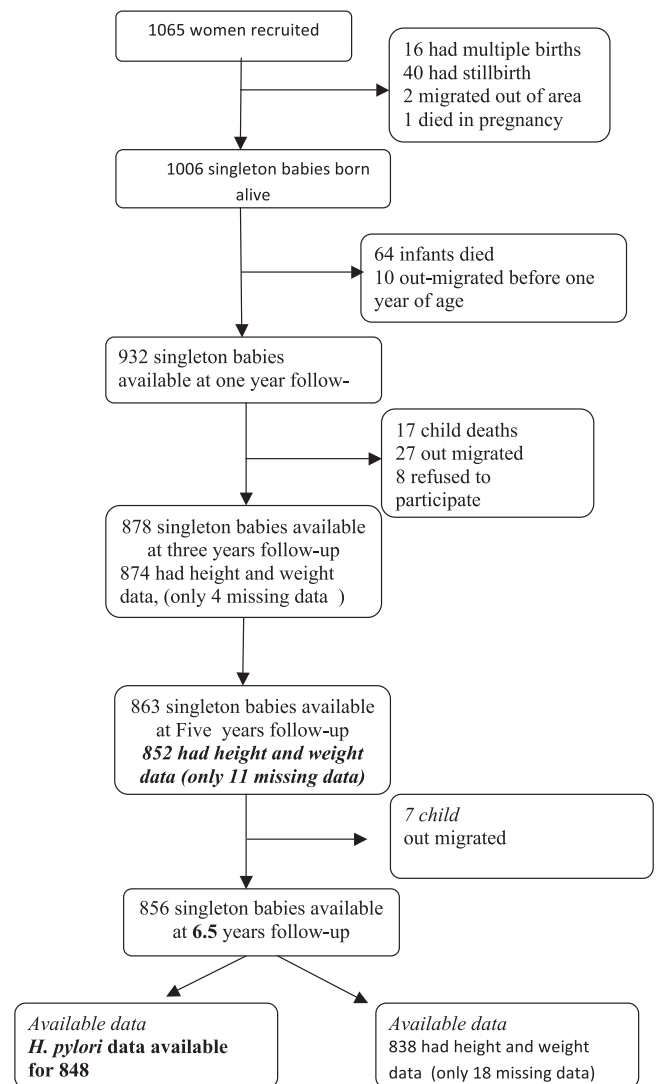


Figure 1. Butajira birth cohort followed at age 6.5 years.

2.3. Laboratory analyses

H. pylori status was determined using an *H. pylori* stool antigen test (SD Bioline; Standard Diagnostics, Inc., South Korea). *H. pylori* stool antigen (HP Ag) testing is rapid, non-invasive, easy to perform, and can be used to detect a current infection; it can also be used to monitor the effectiveness of eradication therapy. Tests were performed in accordance with the manufacturer's instructions. A portion of faeces (approximately 50 mg) was swirled with assay diluent solution at least 10 times, until it dissolved. It was then allowed to settle for 5 min at room temperature. One hundred microlitres of the prepared sample was placed on the HP Ag test strip, and the test results were read 15 min later. One red line indicated a negative result, and a double red line indicated a positive result.

All faecal samples were also examined qualitatively using the modified formol–ether concentration method to ascertain the child's intestinal parasite infection status.

2.4. Anthropometric measurements

At each follow-up visit, the child's height and weight were measured in duplicate, and the average of the two measurements

was used. Height and weight were recorded for children without shoes and wearing light clothes, standing straight, with their weight distributed uniformly on both feet and their arms hanging freely at their sides. An easy-glide bearing wall stadiometer with a reading precision of 1 mm was used to measure height. For weight measurement, a digital scale with reading precision of 50 g for weights up to 50 kg and of 100 g for greater weights was used. The accuracy of this scale was maintained using calibration weights.

2.5. Growth outcome

The growth trajectory was defined using the change in height (in cm) and weight (in kg) per year from baseline at age 3 years to 6.5 years.

2.6. Statistical analysis

Growth curve analyses were conducted to examine the trajectory of the children's height and weight from age 3 to 6.5 years using hierarchical linear modelling.^{28,29} Growth curve models belong to a general class of mixed models that take into consideration the clustering of observations within persons and also have the capacity to handle unbalanced designs (such as an inconsistent number of observations per person).²⁸ Such models allow for change in scale and variance of height or weight over time and use all available data from all eligible children under a 'missing-at-random' assumption.

Age was used as the indicator of time. In order to facilitate parameter interpretation, age was centred on the initial point of data collection on *H. pylori* infection status at age 3 years, since this was the main exposure of interest for the analysis presented here. Following the guidelines of Singer and Willett,²⁹ unconditional and conditional growth modelling was applied. Further details of the statistical analysis and modelling strategies, with consideration of potential confounders including child-, maternal-, household-, and community-related variables, are given in the **Supplementary Material** (Annex 1 and 2).

All data analyses were performed using the MIXED procedure in IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA), with maximum likelihood estimation and an unstructured covariance matrix.

2.7. Ethical approval

The study was approved by the Institutional Review Board (IRB) of the College of Health Sciences, Addis Ababa University, Ethiopia. Written, informed consent was obtained from the mothers after they had been clearly informed about the study. In keeping with the requirements of the College of Health Sciences IRB, all women and their children were reimbursed for health care costs.

3. Results

3.1. Description of the cohort participants from 3 to 6.5 years of age

At recruitment in 2005–2006, a total of 1006 singleton babies made up the initial birth cohort. Of these infants, 64 (6.4%) had died and 10 (0.9%) had migrated from the study area before their first birthday. A detailed description of the cohort at years 1, 3, and 5 is reported elsewhere.^{24,26,30} At 6.5 years, a total of 856 singleton children were successfully followed-up (85.1% of the original cohort at birth). Complete height and weight measurements were available for 99.5% (874/878) at age 3 years and 97.9% (838/856) at age 6.5 years (Figure 1).

3.2. Baseline demographic characteristics of the study subjects

Socio-demographic characteristics of the study sample at baseline (age 3 years) are presented in Table 1. At age 3 years, 50.6% (441/874) were male, and the majority (87.2%, 761/874) were living in a rural area. Maternal demographic characteristics showed that 47.4% (402/848) of the mothers belonged to the Meskan ethnic group, 78.1% (683/874) were Muslim, 80.0% (701/874) did not have a formal education, and 83.8% (709/848) were housewives (Table 1).

3.3. Relationship between potential confounders and child growth parameters

On univariate analysis, maternal age, history of breastfeeding, reported illness, diarrhoea, antibiotics use, history of vaccination, history of vitamin A supplementation at 1 year, insanitary conditions, and crowdedness of housing showed no statistically significant associations with height or weight. However, significant associations with both height and weight were found with the child's sex, place of residence, religion, birth weight category, and relative wealth. Maternal occupation, intestinal parasite infection, and feeding problems were also associated with the mean difference in height at age 3 years (Table 2).

Table 1

Baseline demographic characteristics of children followed at age 3 years—Butajira Birth Cohort, Ethiopia

Variables	Number (%)
Sex	
Female	431 (49.4)
Male	441 (50.6)
Place of residence	
Urban	111 (12.7)
Rural	761 (87.3)
Ethnicity	
Meskan	402 (47.4)
Mareko	111 (13.1)
Silti	200 (23.6)
Other	135 (15.9)
Religion	
Muslim	683 (78.1)
Christian	193 (22.0)
Maternal education	
No formal	701 (80.0)
Formal	171 (19.5)
Maternal occupation	
Housewife	733 (83.7)
Farming and related	21 (2.4)
Trading and related	101 (11.5)
Other	21 (2.4)
Maternal age, years	
15–24	332 (37.9)
25–34	412 (47.0)
35–44	132 (15.1)
Water sources	
Piped water	725 (83.1)
Other	147 (16.9)
History of vaccination ^a	
Not vaccinated	361 (41.7)
Vaccinated	511 (58.3)
Birth weight (n = 544)	
Low (<2.5 kg)	45 (8.3)
Normal	498 (91.7)
Vitamin A supplementation ^b	
Yes	99 (11.8)
No	743 (88.2)
<i>Helicobacter pylori</i> positivity	
Age 3 years, n = 616	253 (41%)
Age 5 years, n = 857	377 (44%)
Age 6.5 years, n = 848	88 (10.4%)

^a Measured at 2 months.

^b Measured at 1 year.

Table 2
Distribution of potential confounders and associations with anthropometric indicators (outcomes) among children followed at age 3 years—Butajira Birth Cohort, Ethiopia

Variables	Overall n (%)	Height (n=876) Mean (SD)	Weight (n=876) Mean (SD)	Mean difference (95% CI) ^a	Mean difference (95% CI) ^b
Sex					
Male	441 (50.6)	86.2 (4.5)	12.1 (1.43)	1	1
Female	431 (49.4)	85.5 (4.2)	11.7 (1.32)	-0.71 (-1.29 to -0.13) ^c	-0.39 (-0.57 to -0.20) ^c
Place of residence					
Urban	111 (12.7)	88.8 (4.0)	12.4 (1.32)	1	1
Rural	761 (87.3)	85.5 (4.3)	11.8 (1.40)	-3.35 (-4.20 to -2.50) ^c	-0.53 (-0.81 to -0.25) ^c
Ethnicity					
Meskan	402 (47.4)	85.7 (4.59)	11.8 (1.47)	-1.51 (-2.41 to -0.61) ^c	-0.28 (-0.58 to 1.33)
Mareko	111 (13.1)	85.6 (3.76)	12.1 (1.23)	-1.60 (-2.74 to -0.46) ^c	0.04 (-0.33 to 0.40)
Silti	200 (23.6)	85.8 (4.27)	11.8 (1.25)	-1.38 (-2.39 to -0.37) ^c	-0.24 (-0.56 to 0.08)
Other	135 (15.9)	87.2 (4.17)	12.1 (1.47)	1	1
Religion					
Muslim	683 (78.0)	85.6 (4.44)	11.8 (1.40)	1	1
Christian	193 (22.0)	87.0 (3.95)	12.3 (1.30)	1.39 (0.63 to 2.14) ^c	0.41 (0.17 to 0.64) ^c
Maternal education					
No formal	701 (80.5)	85.5 (4.39)	11.8 (1.38)	-1.67 (-2.41 to -0.95) ^c	-0.52 (-0.75 to -0.29) ^c
Formal	171 (19.5)	87.2 (4.23)	12.3 (1.39)	1	1
Maternal occupation					
Housewife	733 (83.7)	85.9 (4.29)	11.9 (1.38)	-2.72 (-5.03 to -0.41) ^c	0.11 (-0.62 to 0.85)
Farming and related	21 (2.4)	85.5 (4.28)	11.6 (1.45)	-3.17 (-6.02 to -0.31) ^c	-0.19 (-1.11 to 0.72)
Trading and related	101 (11.5)	85.2 (4.54)	11.7 (1.39)	-3.50 (-5.97 to -1.03) ^c	-0.06 (-0.85 to 0.73)
Other	21 (2.4)	88.7 (5.78)	11.8 (1.63)	1	1
Maternal age, years					
15–24	332 (37.9)	86.4 (4.58)	12.0 (1.46)	0.64 (-0.31 to 1.6)	0.47 (-0.26 to 0.35)
25–34	412 (47.0)	85.6 (4.28)	11.8 (1.36)	-0.07 (-0.99 to 0.85)	-0.17 (-0.47 to 1.21)
35–44	132 (15.1)	85.7 (4.25)	11.9 (1.31)	1	1
Water source					
Piped water	725 (83.1)	86.0 (4.32)	11.9 (1.38)	0.76 (-0.02 to 1.54) ^d	0.37 (0.12 to 0.62) ^c
Other	147 (16.9)	85.2 (4.76)	11.5 (1.50)	1	1
History of vaccination ^e					
Not vaccinated	361 (41.7)	85.9 (4.2)	11.8 (1.34)	1	1
Vaccinated	511 (58.3)	85.7 (4.5)	11.9 (1.43)	-0.12 (-0.76 to 0.53)	0.05 (-0.17 to 0.23)
Birth weight (n=544)					
Low (<2.5 kg)	45 (8.3)	83.6 (4.23)	11.2 (1.50)	-1.92 (-3.22 to -0.63) ^c	-0.65 (-1.11 to -0.19) ^c
Normal	498 (91.7)	85.5 (4.31)	11.8 (1.38)	1	1
Vitamin A supplementation ^f					
Yes	99 (11.8)	86.4 (5.2)	12.0 (1.42)	0.02 (-0.18 to 0.23)	0.15 (-0.21 to 0.40)
No	743 (88.2)	85.8 (4.2)	11.9 (1.38)	1	1
Availability of latrine					
Yes	627 (81.6)	85.9 (4.56)	11.9 (1.38)	0.02 (-0.59 to 0.63)	0.36 (-0.47 to 1.19)
No	241 (18.4)	85.8 (3.97)	11.8 (1.42)	1	1
Number at home					
1–3	58 (6.6)	86.7 (5.07)	11.8 (1.41)	1	-0.34 (-0.69 to 0.01)
4–6	501 (57.2)	85.7 (4.50)	11.9 (1.33)	-0.92 (-2.12 to 0.29)	-0.29 (-0.65 to 0.07)
7+	317 (36.2)	85.9 (4.12)	12.2 (1.50)	-0.69 (-1.94 to 0.55) ^d	
Any intestinal parasitosis					
Yes	291 (33.4)	85.7 (4.43)	11.9 (1.42)	-0.62 (-1.24 to -0.01) ^c	-0.08 (-0.32 to 0.14)
No	579 (66.6)	86.3 (4.27)	12.0 (1.32)	1	1
Still breastfeeding					
Yes	93 (10.7)	86.2 (4.69)	11.7 (1.51)	0.25 (-0.72 to 1.23)	-0.19 (-0.50 to 0.12)
No	779 (89.3)	85.9 (4.40)	11.9 (1.40)	1	1
Any illness in the past					
Yes	540 (61.6)	85.9 (4.35)	11.9 (1.42)	0.14 (-0.47 to 0.75)	0.09 (-0.13 to 0.26)
No	336 (39.3)	85.8 (4.52)	11.8 (1.38)	1	1
Diarrhoea					
Yes	325 (38.5)	85.7 (4.39)	11.8 (1.40)	-0.29 (-0.90 to 0.31)	-0.08 (-0.27 to 0.12)
No	547 (61.5)	86.0 (4.41)	11.9 (1.41)	1	1
Fever					
Yes	462 (57.7)	85.9 (4.42)	11.9 (1.42)	0.14 (-0.45 to 0.75)	0.07 (-0.11 to 0.26)
No	414 (43.3)	85.8 (4.40)	11.8 (1.41)	1	1
Feeding problem					
Yes	24 (2.8)	87.8 (3.82)	11.8 (1.15)	1.94 (0.15 to 3.72) ^c	-0.13 (-0.71 to 0.44)
No	848 (97.2)	85.8 (4.41)	11.9 (1.41)	1	1
Child received antibiotics					
Yes	249 (26.6)	85.7 (4.36)	11.9 (1.46)	-0.19 (-0.45 to 0.85)	-0.06 (-0.26 to 0.15)
No	623 (73.4)	85.9 (4.54)	11.8 (1.38)	1	1
Availability of soap					
Yes	557 (63.8)	86.2 (4.46)	11.9 (1.42)	0.71 (0.10 to 1.32) ^c	0.13 (-0.06 to 0.33)
No	315 (43.2)	85.4 (4.28)	11.8 (1.37)	1	1
Family had debts					
Yes	52 (5.9)	85.3 (3.58)	12.0 (1.19)	-0.67 (-1.72 to 0.34)	-0.05 (-0.35 to 0.44)
No	820 (94.1)	85.9 (4.45)	11.9 (1.42)	1	1
Relative wealth					
Less	402 (46.3)	85.5 (4.40)	11.7 (1.40)	-1.02 (-1.63 to -0.43) ^c	-0.27 (-0.46 to -0.08) ^c
More	43 (4.9)	85.9 (3.91)	12.0 (1.23)	-0.48 (-1.86 to 0.89)	0.00 (-0.44 to 0.43)

Table 2 (Continued)

Variables	Overall n (%)	Height (n = 876) Mean (SD)	Weight (n = 876) Mean (SD)	Mean difference (95% CI) ^a	Mean difference (95% CI) ^b
The same	423 (48.7)	86.4 (4.24)	12.0 (1.42)	1	1

SD, standard deviation; CI, confidence interval.

^a Mean difference (95% CI) calculated by independent *t*-test for height and covariates.

^b Mean difference (95% CI) calculated by independent *t*-test for weight and covariates.

^c *p*-Value < 0.2.

^d Borderline significant.

^e Measured at 2 months.

^f Measured at 1 year.

3.4. Unconditional growth model

3.4.1. Unconditional mean model

Table 3 presents the results for the unconditional mean without any person-level covariates. Model 1 estimated a mean height of 98.8 cm (standard error (SE) 0.14, *p* < 0.001) and a mean weight of 14.8 kg (SE 0.04, *p* < 0.001) averaged across all children and time points. A significant unconditional mean model suggests that examining predictors in the subsequent model is warranted.

3.4.2. Unconditional growth model

Fitting the basic model gives the estimated parameters of the growth curve; the fixed- and random-effects results are reported in Table 3. Results indicated a typical pattern of growth amongst the children in the Butajira Birth Cohort from age 3 to 6.5 years. The values for the intercepts, 85.7 cm and 11.9 kg, represent the average height and weight at age 3 years, respectively. Growth increased by 8.7 cm in height ($\beta = 8.7$, SE 0.141, *p* < 0.01) and 1.76 kg in weight ($\beta = 1.76$, SE 0.043, *p* < 0.01) per unit increase in age. However, a second-order polynomial (quadratic term; Table 3) indicated that both height and weight decelerate as the child increases in age, as indicated by the negative sign in the quadratic term (acceleration) (Table 3).

Table 3 shows additional information on the variance-covariance matrix of the random-effects for height and weight,

respectively. The significant variance terms indicated that there is a substantial amount of variation in growth among children over time, and additional person-level variables may explain this variation in subsequent conditional models.

3.5. Conditional growth model

For growth as a function of *H. pylori* infection status, three conditional growth models (level 2) are presented in Table 4. For model 4, the inclusion of *H. pylori* exposure status (*H. pylori*-infected, *H. pylori* non-infected) in the conditional quadratic model improved overall model fit compared to the unconditional quadratic model (height: $\Delta -2 \log$ likelihood (LL) = 12 669, Chi-square (3) = 1433.5, *p* < 0.001; weight: $\Delta -2LL = 777.13$, *p* < 0.001).

3.6. Association of exposure to *H. pylori* with height and weight at baseline (age 3 years)

The adjusted mean height at baseline (age 3 years) was significantly lower amongst the *H. pylori*-infected children than amongst the non-infected children (adjusted $\beta = -0.74$, 95% confidence interval (CI) -1.27 to -0.22 , *p* < 0.001). Similarly, there was a non-significant difference in baseline weight measurements between the *H. pylori*-infected and non-infected children (Tables 4 and 5).

Table 3

Summary of level 1 (unconditional) models

Variables	Model 1: Intercept only	Model 2: Linear	Model 3: Quadratic
Fixed-effects	Parameter estimates (SE)		
Intercept	98.8 (0.141) ^a	86.1 (0.158) ^a	85.7 (0.160) ^a
Linear	-	7.1 (0.040) ^a	8.7 (0.141) ^a
Quadratic	-	-	-0.49 (0.039) ^a
Random-effects	Covariance estimates (SE)		
Within-person	112.59 (1.132) ^a	8.65 (0.298) ^a	7.93 (0.273) ^a
Intercept	11.28 (0.841) ^a	14.2 (0.828) ^a	14.41 (0.825) ^a
Goodness-of-fit statistics			
Model fit (-2LL)	19542.008	14249.157	14102.558
Number of parameters	3	4	5
Chi-square	-	5292.851 ^a	146.599 ^a
Degrees of freedom	-	1	1
Fixed-effects	Weight Parameter estimates (SE)		
Intercept	14.8 (0.049) ^a	11.94 (0.054) ^a	11.90 (0.055) ^a
Linear	-	1.58 (0.104) ^a	1.76 (0.043) ^a
Quadratic	-	-	-0.05 (0.012) ^a
Random-effects	Covariance estimates (SE)		
Within-person	7.87 (0.221) ^a	0.76 (0.026) ^a	0.75 (0.026) ^a
Intercept	1.82 (0.103) ^b	1.92 (0.104) ^a	1.91 (0.105) ^a
Goodness-of-fit statistics			
Model fit (-2LL)	12485.522	8379.896	8362.876
Number of parameters	3	4	5
Chi-square	-	1	1
Degrees of freedom	-	4105.626 ^a	17.02 ^a

SE, standard error, *t*-statistic; LL, log likelihood.

^a *p* < 0.001

^b *p* < 0.005, Wald Z.

Table 4
Repeated-measures mixed model results for height in relation to *Helicobacter pylori* infection status from 3 to 6.5 years—Butajira Birth Cohort, Ethiopia

Fixed-effects	Model 4 (Unadjusted model)		Model 5 (Partially adjusted)		Model 6 (Partially adjusted)		Model 7 (Fully adjusted)	
	β^a	95% CI	β^b	95% CI	β^c	95% CI	β^d	95% CI
Mean height at age 3 years, (intercept)	86.08	85.66 to 86.50 ^e	86.30	85.56 to 86.04 ^e	88.38	86.13 to 90.63 ^e	88.87	86.53 to 91.22 ^e
Linear change in height, cm/year	9.04	8.63 to 9.45 ^e	8.90	8.45 to 9.35 ^e	9.01	8.60 to 9.41 ^e	9.02	8.62 to 9.43 ^e
Quadratic change in height, cm/year ²	-0.61	-0.72 to -0.49 ^e	-0.56	-0.69 to -0.43 ^e	-0.59	-0.70 to -0.49 ^e	-0.59	-0.71 to -0.49 ^e
<i>Helicobacter pylori</i> infection status								
Infected \times intercept (initial, cm)	-0.73	-1.26 to -0.19 ^e	-0.87	-1.45 to -0.29 ^e	-0.76	-1.28 to -0.23 ^e	-0.74	-1.27 to -0.22 ^e
Infected \times linear growth, cm/year	-0.79	-1.49 to -0.01 ^f	-0.70	-1.52 to 0.12	-0.72	-1.40 to -0.03 ^f	-0.72	-1.41 to -0.04 ^f
Infected \times quadratic growth, cm/year ²	0.28	0.07 to 0.49 ^e	0.27	-0.02 to 0.56	0.26	0.05 to 0.47 ^f	0.26	0.05 to 0.47 ^f
Random-effects								
Between individuals								
Intercept (SE)	7.95	(1.032) ^e	7.49	(1.212) ^e	6.78	(0.917) ^e	6.63	(0.924) ^e
<i>H. pylori</i> (SE)	1.67	(1.008)	0.64	(0.000)	1.45	(0.947)	1.43	(0.945)
Within individuals								
Residual (SE)	6.62	(0.344) ^e	6.14	(0.422) ^e	6.24	(0.324) ^e	6.24	(0.324) ^e
Goodness-of-fit statistics								
Model fit (-2LL)	12 669.008		9405.936		12 147.953		12 035.908	
Number of parameters	13		18		23		26	
Chi-square	1433.55 ^e		3263.072 ^e		521.055 ^e		633.100 ^e	
Degrees of freedom	3		5		10		13	

CI, confidence interval; SE, standard error; LL, log likelihood.

^a Values were derived from mixed-effects models and adjusted for within-child correlation.

^b Adjusted for child-related factors: sex, history of vaccination at 2 months, vitamin A supplementation at 1 year, episodes of diarrhoea, and any intestinal parasite infections.

^c Adjusted for household- and maternal-related factors: household size, relative wealth, availability of toilet, availability of soap, maternal height, maternal weight, maternal education, religion, and residence.

^d Adjusted for child-, household-, and maternal-related factors.

^e $p < 0.00$

^f $p < 0.05$, Wald Z.

3.7. Association of exposure to *H. pylori* with height growth trajectory

The results from the fixed- and random-effect models assessing the relationship between change in height and *H. pylori* exposure are presented in Table 4. The first column of Table 4 (model 4) incorporates only *H. pylori* status, the coefficient representing the estimate for the relationship between growth and *H. pylori*

infection. This estimate indicated that growth of the *H. pylori*-infected children was approximately 0.79 cm per year slower than that of non-infected children ($\beta = -0.79$, 95% CI -1.49 to -0.01 , $p < 0.05$). The positive coefficient associated with quadratic growth in height in the *H. pylori*-infected group ($\beta = 0.28$, 95% CI 0.07 to 0.49 , $p < 0.01$), indicated that there were increases in height trajectories as the children increased in age. Compared to

Table 5
Repeated-measures mixed model results for weight in relation to *Helicobacter pylori* infection status from 3 to 6.5 years—Butajira Birth Cohort, Ethiopia

Fixed-effects	Model 4 (Unadjusted model)		Model 5 (Partially adjusted)		Model 6 (Partially adjusted)		Model 7 (Fully adjusted)	
	β^a	95% CI	β^b	95% CI	β^c	95% CI	β^d	95% CI
Mean weight at age 3 years, (intercept), kg	11.93	11.80 to 12.07 ^e	11.84	11.59 to 12.09 ^e	11.09	10.29 to 11.90 ^e	10.61	9.39 to 12.31 ^e
Linear change in height, kg/year	1.71	1.58 to 1.84 ^e	1.65	1.51 to 1.79 ^e	1.71	1.58 to 1.84 ^e	1.67	1.50 to 1.82 ^e
Quadratic change in height, kg/year ²	-0.04	-0.07 to -0.01 ^f	-0.01	-0.05 to 0.03	-0.04	-0.07 to -0.004 ^f	-0.02	-0.06 to -0.02 ^e
<i>Helicobacter pylori</i> infection status								
Infected \times intercept (initial, kg)	-0.02	-0.19 to 0.15	-0.01	-0.18 to 0.17	-0.01	-0.19 to 0.17	-0.002	-0.18 to 0.17
Infected \times linear growth, kg/year	0.09	-0.13 to 0.31	0.11	-1.52 to 0.37	0.12	-0.12 to 0.33	0.13	-0.12 to 0.39
Infected \times quadratic growth, kg/year ²	-0.03	-0.09 to 0.04	-0.04	-0.13 to 0.05	-0.04	-0.11 to 0.03	-0.06	-0.15 to 0.03
Random-effects								
Between individuals								
Intercept (SE)	0.87	(0.090) ^e	0.87	(0.110) ^e	1.06	(0.141) ^e	0.79	(0.112) ^e
<i>H. pylori</i> (SE)	0.14	(0.114)	0.18	(0.132)	0.03	(0.000)	0.17	(0.123)
Within individuals								
Residual (SE)	0.76	(0.036) ^e	0.70	(0.042) ^e	0.75	(0.037) ^e	0.68	(0.041) ^e
Goodness-of-fit statistics								
Model fit (-2LL)	7585.750		5612.941		7257.554		5478.967	
Number of parameters	13		20		23		25	
Chi-square	777.13 ^e		1972.809 ^e		328.196 ^e		2106.783 ^e	
Degrees of freedom	3		7		10		12	

CI, confidence interval; SE, standard error; LL, log likelihood.

^a Values were derived from mixed-effects models and adjusted for within-child correlation.

^b Adjusted for child-related factors: sex, history of vaccination at 2 months, vitamin A supplementation at 1 year, episodes of diarrhoea, episodes of cough, and birth weight.

^c Adjusted for household- and maternal-related factors: household size, relative wealth, availability of toilet, availability of soap, maternal height, maternal weight, maternal education, religion, and residence.

^d Adjusted for child-, household-, and maternal-related factors.

^e $p < 0.00$

^f $p < 0.05$, Wald Z.

the linear change trajectory ($\beta = -0.79$), the rate of quadratic growth ($\beta = 0.28$) was small, suggesting that the height growth trajectory among *H. pylori*-infected children decreased at the beginning, but this trend slowed down later on.

In the subsequent conditional growth models summarized in Table 4, child-related factors (model 5), household- and maternal-related factors (model 6), and all factors (model 7) were included as confounders. All models revealed an identical pattern of results for the association between *H. pylori* status and the linear and quadratic growth trajectory in height. The final model, adjusted for child-, household-, and maternal-related characteristics, did not significantly modify the effect estimate observed in the unadjusted model (*H. pylori*-infected \times linear: $\beta = -0.72$, 95% CI -1.41 to -0.04 , $p < 0.05$; *H. pylori*-infected \times quadratic: $\beta = 0.26$, 95% CI 0.05 to 0.47 , $p < 0.05$) (Table 4).

In analyses stratified by sex, a greater decline in linear growth trajectory in height was observed among *H. pylori*-infected females than non-infected females (only female model: linear growth, $\beta = -0.78$, 95% CI -1.48 to -0.07 , $p < 0.05$). A non-significantly different decrease in linear growth trajectory was observed among infected compared to non-infected males (only male model: linear growth, $\beta = -0.85$, 95% CI -1.87 to 0.17 , $p = 0.1$). Similar analyses relating change in weight (outcomes) to *H. pylori* infection status stratified by sex did not show a significant difference in linear or quadratic weight growth among *H. pylori*-infected and non-infected children of either sex. At baseline, *H. pylori*-infected children were shorter than non-infected children of both sexes (Supplementary Material, Table S1).

3.8. Association of exposure to *H. pylori* with weight growth trajectory

A separate conditional growth model related change in weight (outcomes) to *H. pylori* infection status. This showed no statistically significant difference in intercept (weight at age 3 years: $\beta = -0.02$, 95% CI -0.19 to 0.15 , $p > 0.05$) or linear growth (weight \times age: $\beta = 0.09$, 95% CI -0.13 to 0.04 , $p > 0.05$) between groups; however *H. pylori*-infected children showed a non-significant decline in quadratic weight growth compared with the non-infected group ($\beta = -0.03$, 95% CI -0.09 to 0.04 , $p > 0.05$). The final model adjusted for child-, household-, and maternal-related characteristics did not significantly modify the pattern of the effect estimate observed in the unadjusted model (Table 5).

3.9. Prototypical plot for height and weight in relation to *H. pylori* status

Figures 2 and 3 illustrate the interaction between *H. pylori* status and growth parameters. These plots were created using the equation from the final model (Tables 4 and 5). *H. pylori* status was dummy coded (1 = positive, 0 = negative). These graphs illustrate the effect of *H. pylori* infection on height and weight growth, and revealed that children who were infected with *H. pylori* at age 3 years had a significant decline in their linear height growth (Figure 2) compared to non-infected children; however the reduction in height trajectory growth disappeared with increasing age. A non-significant difference in linear and quadratic weight trajectory (Figure 3) was observed between the *H. pylori*-infected and non-infected children.

4. Discussion

This study adds to the evidence on the influence of *H. pylori* infection on childhood growth trajectory using longitudinal panel data from the Butajira Birth Cohort. The presence of *H. pylori* infection was associated with a decrease in baseline height and

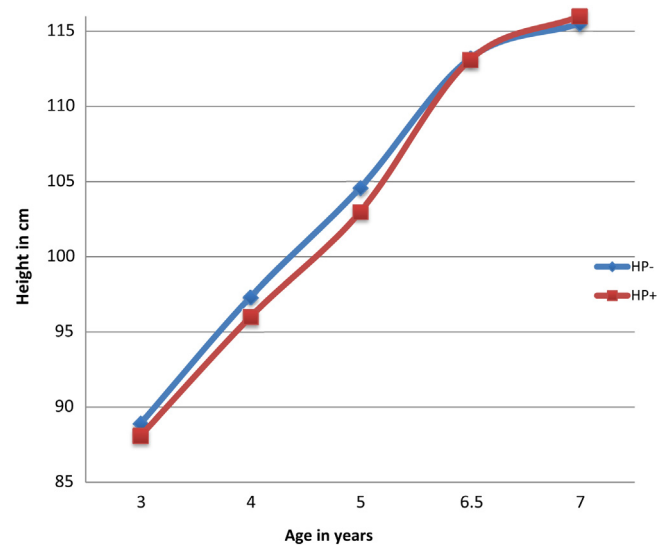


Figure 2. Average fractional polynomial curve of height trajectories for children by *Helicobacter pylori* infection status, age 3 to 6.5 years, adjusted for confounders. Values are predicted from the final models and represent the predicted anthropometry.

linear height trajectory ($\beta = -0.74$ and -0.79 cm/year, respectively). However, the positive coefficient associated with quadratic growth in height ($\beta = 0.28$, 95% CI 0.07 to 0.49 , $p < 0.01$), indicated an increase in height trajectory as a child increases in age. Compared to the linear change trajectory ($\beta = -0.79$), the rate of quadratic growth ($\beta = 0.28$) was small, suggesting that the height trajectory of *H. pylori*-infected individuals decreased at the beginning, but this trend slowed down later on.

The significant association between *H. pylori* infection and decreased linear height growth trajectory in the current study is backed by previous epidemiological studies in different settings. In two prospective cohort studies, Goodman et al.¹⁴ and Bravo et al.⁸ reported a significant association between *H. pylori* infection and reduced growth velocity (on average -0.022 cm/month and 0.5 cm/year) among school-age children (4–8 years and 1–5 years, respectively) in Colombia, after controlling for socio-economic confounders. The present study findings are also consistent with those of another cohort study reported by Thomas et al.⁹ from rural Gambia, who found a lower value for length Z-score (difference -0.35 for length, $p = 0.04$) in infants (age 3 months) infected with *H. pylori*. Additionally, in agreement with the current findings,

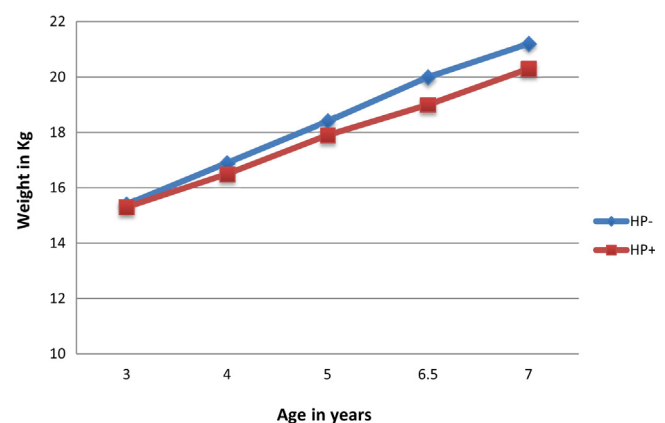


Figure 3. Average fractional polynomial curve of weight trajectories for children by *Helicobacter pylori* infection status, age 3 to 6.5 years, adjusted for confounders. Values are predicted from the final models and represent the predicted anthropometry.

studies, mostly cross-sectional in nature, have reported similar patterns of inverse associations between *H. pylori* infection and growth in height.¹² In rural Germany, a large population-based cross-sectional study ($n = 3315$) in children aged 5–7 years showed a significantly lower height among *H. pylori*-infected children compared to non-infected children (117.6 ± 5.5 cm vs. 118.9 ± 5.7 cm, $p < 0.01$).¹² Another cross-sectional study among children from a low-income country reported a significantly higher number of *H. pylori*-infected children than non-infected children falling below the 5th percentile of height-for-age.³¹ In contrast with these findings, no association between height and *H. pylori* infection was reported in studies of children from Alaska,³² Australia,³³ Iran,³⁴ and Guatemala.³⁵ These inconsistent findings could be due to variations in age, outcome ascertainment, and differences in the method used for the assessment of *H. pylori* status. More importantly, among these studies there were differences in the distribution of factors that affect growth in childhood, and differences in study design, including the timing of measurements and statistical methods used to estimate effects on growth.

In this study, the positive coefficient associated with quadratic growth in height among *H. pylori*-infected children indicates an increase in height trajectory as the child gets older. Similar influences of *H. pylori* on growth were reported in two cohorts of children from Gambia.⁹ There was a reduction in growth velocity in children who acquired *H. pylori* infection early, at 3–6 months of age, but reduced growth velocity was no longer detected when the children were 5 to 8 years old. In contrast with these findings, two cross-sectional studies by Fialho et al.¹⁰ and Perri et al.¹¹ reported a significant reduction in height-for-age among older children (age 8.5 to 14 years) infected with *H. pylori* compared to younger children. These authors concluded that the effects of *H. pylori* on school children's height were more evident in older children with a long-lasting infection than in younger children with a recently-acquired infection. In contrast with this hypothesis, a cohort study among Colombian children demonstrated that the detrimental effect of *H. pylori* infection was most pronounced right after the infection.³⁶ Indeed, it has been argued that chronic infection, as opposed to the initial acute phase when first colonized, might be associated with reduced gastric inflammation, and therefore fewer detrimental effects on growth in children.³⁷ This argument was supported using an animal model, which demonstrated that the development of an anti-*Helicobacter* antibody response, a biomarker for the chronic phase of infection, coincided with reduced gastric inflammation.³⁸ The discovery of catch-up in the height trajectory of *H. pylori*-infected children as they grew older in this study could be partly explained by this latter hypothesis. In addition, growth retardation might be reversed if the infection clears spontaneously (as has been reported to occur in young children³⁹), but might recur upon reinfection. In line with this, the present authors have previously observed a declining pattern of *H. pylori* prevalence from age 3 to 6.5 years in this cohort,⁷ but the short span of the follow-up period (3.5 years) makes it very difficult to test the hypothesis.

In this study, a non-significant difference in baseline and trajectory of weight measurements was found between *H. pylori*-infected and non-infected children. Other studies have also shown no association between *H. pylori* infection and weight or body surface area among infected and non-infected children.^{11,12}

Various biologically plausible mechanisms have been put forward to explain the observed association between *H. pylori* infection and lower height growth trajectory. For instance, infection with *H. pylori* in children might initiate a vicious cycle of events that results ultimately in malnutrition and growth impairment. Infection with *H. pylori* is accompanied by hypochlorhydria, which facilitates the acquisition of other enteropathogens. The resulting diarrheal diseases may lead to further

nutritional problems including iron-deficiency anaemia.⁴⁰ This is likely to occur most frequently in low-income regions where the prevalence of *H. pylori* infection is disproportionately high and multiple enteric co-infections are common.¹⁵ Others have suggested that growth failure in *H. pylori*-infected children could be a combination of a direct effect from *H. pylori*-induced inflammation and indirect effects such as infection-induced anorexia.⁴

The strengths of this study are that the data come from a population-based birth cohort with a high response rate (85.1% of the original cohort at birth were followed up at 6.5 years) and very low missing anthropometric measurements at each follow-up visit, thereby minimizing selection bias. A highly sensitive and specific *H. pylori* stool antigen test was used.⁴¹ In addition, anthropometric measurements were done in duplicate and agreement between the two measurements was monitored for quality control. The statistical method used to generate effect estimates was hierarchical linear modelling, which does not require either the same number of occasions per individual or that measurements are made at equal intervals, since time is modelled as a continuous function.⁴² This means that data from individuals with different measurement patterns, some of whom may only have been measured once and some of whom may have been measured several times at irregular intervals, can be combined.

The results of this study should be interpreted with caution because the study was conducted in Ethiopia, a low-income country in which the causes of poor childhood growth are multifactorial. Demographic variables and markers of socio-economic status have commonly been found to be associated with childhood growth.^{23,24} Several markers of socio-economic status, demographic and lifestyle variables, and both child- and environment-related confounding factors were therefore measured and controlled for, none of which significantly modified the effect estimates. These included markers of socio-economic status (family size, relative wealth, maternal education, maternal occupation, level of household crowding, availability of soap, household water source (piped water or other origin), availability of a latrine, and urban or rural residence), demographic and early life variables (sex, age, birth weight, breastfeeding, gestational age, history of vaccination at 2 months and 1 year, and vitamin A supplementation at 1 year), selected indicators of child health status (episodes of diarrhoea, fever, whether or not the child had a feeding problem), and genetic factors (using maternal height as a proxy), which suggest that the effects seen are unlikely to be caused by residual confounding by markers of socio-economic status, or demographic or lifestyle variables.

The study participants were apparently healthy children and received free medical care due to their enrolment in the cohort; this may account for the low percentage of reported common childhood illness. However, this is unlikely to vary systematically by *H. pylori* infectious status or growth velocity in this cohort, and would therefore tend to attenuate associations toward the null.

Poor nutrition can cause growth failure and potentially increase susceptibility to *H. pylori* infection.⁴³ Data were lacking on direct nutritional indicators such as dietary quality and quantity. However, the most important factors associated with poor nutrition in the literature (i.e., breast feeding, birth weight, maternal occupation, maternal education, and other markers of socio-economic status) were adjusted for.^{23,24,44,45} Given the correlation among these measures, it is likely that they captured the unmeasured influence of other nutritional indicators not included in the models.

Some problems were identified with the data used in the present study. Specifically, the spacing between visits was not uniform, and the time span of the survey was very short (3.5 years). One of the hallmarks of hierarchical linear modelling, however, is

that it can accommodate lack of regularity in study visits.²⁸ Some of the issues related to growth could not be captured due to the short-span of the survey, including the link between early growth retardation and growth during adulthood, the age at which growth reaches its peak, and when growth stops (height growth). Nevertheless, on the basis of the information available, it was possible to draw statistically valid estimates of the childhood growth trajectory from this cohort.

Another limitation of this study was the lack of faecal *Helicobacter* antigen testing in the earliest phases of the birth cohort (0–2 years). Assessment of the timing of *Helicobacter* infection was not possible, and neither was the duration of its effects on growth. The acquisition of *H. pylori* infection in developing countries usually occurs during infancy and very early life,^{22,46} which limits the possibility that growth failure preceded *H. pylori* infection. Furthermore, growth patterns in early childhood (0–2 years) were not investigated in this study; however factors that influence the growth trajectory in the first years of life such as birth weight, maternal height (as a proxy for genetic factors), history of vaccination at 2 months and 1 year, sex, and maternal education were included in the multivariate models. The results were not appreciably altered by adjustment for these early life covariates.

In conclusion, these findings add to the growing body of evidence that *H. pylori* infection is inversely associated with childhood growth trajectory, after controlling for a range of factors associated with reduced growth and *H. pylori* status. From this study, *H. pylori* appears to be a preventable cause of growth trajectory restriction. Further follow-up of these children will enable confirmation of the tendency of catch-up in height trajectory among *H. pylori*-infected children as they grow older.

Author contributions

BT and AA conceived and designed the study. BT collected data in the field, performed the data analysis, and drafted the manuscript. AA and GM participated in data collection, assisted with the design, and performed the analysis, interpretation of data, and critical review of the manuscript. GD, FE, AT, KR, and AF participated in the study design and interpretation of data, helped to draft the manuscript, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Conflict of interest: We declare that we do not have any conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijid.2016.08.005>.

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