Neonatal vaccination of low birthweight infants in Ghana

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ABSTRACT

Objectives Global vaccination policy advocates for identifying and targeting groups who are underserved by vaccination to increase equity and uptake. We investigated whether birth weight and other factors are determinants of neonatal BCG vaccination in order to identify infants underserved by vaccination.

Methods We used logistic regression to calculate adjusted ORs (AORs) for the association between birth weight (categorised as non-low birth weight (NLBW) (≥2.50 kg) and low birth weight (LBW) (2–2.49 kg, 1.50–1.99 kg and <1.50 kg)) and non-vaccination with BCG at the end of the neonatal period (0–27 days). We assessed whether this association varied by place of delivery and infant illness. We calculated how BCG timing and uptake would improve by ensuring the vaccination of all facility-born infants prior to discharge.

Results There was a strong dose–response relationship between LBW and not receiving BCG in the neonatal period (p-trend<0.0001). Infants weighing 1.50– 1.99 kg had odds of non-vaccination 1.6 times (AOR 1.64; 95% CI 1.30 to 2.08), and those weighing <1.50 kg 2.4 times (AOR 2.42; 95% CI 1.50 to 3.88) those of NLBW infants. Other determinants included place of delivery, distance to the health facility and socioeconomic status. Neither place of delivery nor infant illness modified the association between birth weight and vaccination (p-interaction all >0.19). Facility-born infants were vaccinated at a mean of 6 days, suggesting that they were not vaccinated in the facility at birth but were referred for vaccination.

Conclusions LBW is a risk factor for neonatal undervaccination, even for facility-born infants. Ensuring vaccination at facility births would substantively improve timing and equitable BCG vaccination.

What is already known on this topic?

▸ Delayed BCG vaccination was associated with low birth weight (LBW) among primarily facility-born infants in urban slums in Kenya.

▸ Undernourishment (caused by LBW, illness and feeding practices) was also associated with delayed BCG vaccination in urban Nigeria.

What this study adds?

▸ This large, generalisable prospective population-based cohort study in rural Ghana demonstrates lower compliance with the BCG vaccination schedule among LBW compared with non-LBW infants.

▸ LBW is a strong determinant of neonatal BCG vaccination, with a dose–response relationship between birth weight and vaccination.

▸ The association persists even for facility-born LBW infants, suggesting a lack of compliance with policy to vaccinate prior to discharge from the facility.

INTRODUCTION

Approximately 3 in 10 deaths among children aged 1–59 months are vaccine preventable,1 and 1 in 5 infants is not fully vaccinated by age 52 weeks. Substantive socio-demographic inequities in vaccination remain.2 Many infants are vaccinated late.3 4 The latest global vaccination policy highlights the need to identify and target those underserved by vaccination in order to increase equity and uptake.2 Using data from a large prospective population based trial of neonatal vitamin A supplementation in Kintampo in rural Ghana (Neovita), we previously reported that low birthweight (LBW) infants are more likely to be delayed in their DTP1 and DTP3 vaccination.5 For postneonatal vaccines, the onus is on the caretaker to bring the infant for vaccination at scheduled times. Any vaccination delay may be partly due to caretaker hesitancy to bring infants for vaccination, possibly due to their fragility or illness.6 This may not be the case for neonatal vaccinations as the large proportion of facility-born infants automatically have opportunities for vaccination. Consequently, vaccine determinants may differ in these periods. In an effort to identify further those underserved by vaccination, we investigated birth weight and other factors as determinants of neonatal vaccination.

In countries with a high prevalence of tuberculosis, the WHO recommends 'BCG be given to all healthy neonates, or as soon as possible after birth'.7 In addition to BCG, in Ghana, a birth dose of polio (OPVB) is recommended at a maximum age of 2 weeks8 as part of a four-dose schedule. Hepatitis B is not recommended in the schedule. The WHO recommends BCG vaccination by intradermal injection to the arm,7 whereas OPVB is given orally.9 We selected BCG as an indicator for neonatal vaccination due to its longer recommended window for administration (throughout the neonatal period) and on the basis that any hesitancy relating to the vaccination of fragile infants would be more evident for injected vaccines.

LBW is not a contraindication to BCG vaccination.7 The WHO advises that infants should receive all due vaccines prior to discharge from health facilities.10 Therefore, infants born in health facilities should be vaccinated prior to discharge home.

Infant illness has been cited as a reason for non-vaccination by both caregivers and vaccine providers.6 Given this and the opportunities for vaccination associated with being born in a facility, as secondary objectives we investigated whether the association between birth weight and neonatal BCG vaccination varied by place of delivery and infant illness.

MATERIALS AND METHODS

Neovita was undertaken at the Kintampo Health Research Centre (KHRC) in rural Ghana. Trial methods have been described in detail elsewhere.11 12

In Ghana, neonatal vaccines are given either at the health facility following delivery or at child health clinics in health facilities or community health planning system (CHPS) compounds in the community. Monthly mobile outreach clinics target areas lacking health facilities or CHPS compounds. Following vaccination, the vaccine provider records (on a vaccination card or, less commonly, in the mother's antenatal card) the administrated vaccine, the batch number, date and clinic name.

Infants who were up to three days of age at screening, who could suckle or feed and who were staying in the study area for at least six months after enrolment were included in the trial.

Trained field workers used a prospective surveillance system (that monitored registered women aged 15–49 years for pregnancies and deliveries) to ascertain all births in the study area between August 2010 and November 2011. They enrolled eligible infants of consenting mothers in the trial and weighed them using calibrated electronic (38%) or spring (62%) scales. They recorded birth weights to the nearest 0.1 kg (electronic scales) or 0.2 kg (spring scales). All but five infants (0.2%) were weighed within 72 hours of delivery. At enrolment, field workers collected data on infant, maternal and household characteristics. Data on vaccination status (written record and maternal recall) were collected at monthly follow-up visits.

Infants were categorised as (1) vaccinated, known vaccination date (if they had a plausible vaccination date on their vaccination card); (2) vaccinated, unknown vaccination date (if they had an unknown or implausible date on their card); and (3) unvaccinated (if either (a) their card was viewed and had no evidence of vaccination or (b) their card was not viewed (possibly because they did not have a card) but their caretaker consistently reported that they had never been vaccinated). In addition, infants whose card was never viewed and whose mothers reported they were vaccinated, but did not report which vaccine they received, were categorised as vaccination status unknown as were those infants never seen in follow-up, with no information on their vaccination status.

We categorised infants as either non-low birth weight (NLBW) (weighing ≥2.50 kg) or LBW (2.00–2.49 kg, 1.50– 1.99 kg and <1.50 kg). Neonatal illness was a health facility admission in the neonatal period (0–27 days of age).

Infants with known vaccination status, in follow-up at the end of the neonatal period and having complete covariate data were eligible for inclusion in the analyses.

Analytical methods

We conducted all analyses using STATA V.14.1 (StataCorp, 2015). As neonatal BCG vaccination is a frequent event, we calculated adjusted ORs (AORs) for the less frequent outcome of non-vaccination (rather than for vaccination) using multivariable logistic regression. The resulting AORs for this less frequent outcome thus approximated more closely to risk or rate ratios. Model building was informed by a hierarchical framework5 of the determinants of vaccination identified a priori.3 4 13 14 We initially fit a model comprising distal determinants (religion, ethnicity, socioeconomic status (SES), maternal occupation, maternal education, vaccine due in wet season, infant sex); then added intermediate determinants (maternal age/family size, maternal illness in the year before delivery, distance to the nearest health facility, place of delivery, multiple birth), followed by birth weight and, finally, infant illness, a possible mediator of the association between birth weight and vaccination. We

used likelihood ratio tests and 95% CIs to assess statistical associations between each explanatory variable and vaccination.

We fitted interaction terms of birth weight and (1) place of delivery, and (2) neonatal illness to the final model to assess whether either of these modified the association between birth weight and vaccination.

For all infants, irrespective of place of birth, we calculated BCG uptake rates at the end of the neonatal period and at 8, 12 and 52 weeks of age, stratified by birth weight, to examine variation by time since the due date. To assess how ensuring vaccination of facility-born infants prior to discharge would affect vaccination, we calculated 'theoretical' proportions vaccinated by assigning these infants as vaccinated in the neonatal period. We calculated the proportional increase in vaccination by dividing the theoretical proportion by the actual proportion for each time period.

RESULTS

Of 22 955 infants enrolled in Neovita, 22 217 (96.8%) were included in the analyses. Among 738 excluded, 362 were BCG vaccination status unknown, 242 were BCG vaccinated with an unknown date, 88 were lost to follow-up in the neonatal period and 46 were missing covariate data. Of those excluded, 275 died in the neonatal period. Table 1 shows that excluded infants were more likely to have LBW, to live further from a health facility, to be a multiple birth and to have poorer mothers.

Infants were BCG vaccinated at a median of 8 days; 77% were vaccinated by the end of the neonatal period. Uptake decreased with declining birth weight and was lowest (60%) among infants weighing <1.50 kg. There was a strong dose– response relationship between LBW and the odds of non-vaccination in the neonatal period (p-trend<0.0001) after adjustment for other variables (table 2). Infants weighing 1.50– 1.99 kg (AOR 1.64; 95% CI 1.30 to 2.08) and those weighing <1.50 kg (AOR 2.42; 95% CI 1.50 to 3.88) had odds of non-vaccination 1.6 times and 2.4 times those of NLBW infants.

Not being born in a health facility (compared with being born in a health facility), living ≥5 km from the nearest health facility (compared with living within 1 km of a health facility) and being in the lowest quintile of SES (compared with the highest) were all strongly associated with not receiving BCG in the neonatal period (table 2). Almost 40% of home-born infants were BCG unvaccinated, and their odds of non-vaccination were 1.82 times those of facility-born infants (AOR 1.82; 95% CI 1.69 to 1.98; p≤0.0001). Infants living >5 km from a health facility had odds of non-vaccination 1.37 times those of infants living within 1 km (AOR 1.37; 95% CI 1.25 to 1.49; p≤0.0001) even after adjusting for place of birth and other factors. A strong dose–response relationship was observed between SES and neonatal BCG vaccination (p-trend <0.0001), with infants from the poorest quintile of SES having odds of

Table 1 Baseline characteristics of infants included in the analyses of determinants of neonatal BCG vaccination

	Excluded	Included
Variable	Total=738	Total=22 217
Distal determinants		
Religion of head of household		
Christian	471 (63.8)	15 508 (69.8)
Muslim	201 (27.2)	5310 (23.9)
None/traditional/other	66 (8.9)	1399 (6.3)
Ethnicity		
Akan	317 (43.0)	10 376 (46.7)

Non-Akan	421 (57.0)	11 841 (53.3)
Socioeconomic status		
1 (poorest)	185 (25.1)	4325 (19.5)
2	174 (23.6)	4376 (19.7)
3	150 (20.3)	4433 (20.0)
4	125 (16.9)	4519 (20.3)
5 (richest)	103 (14.0)	4564 (20.5)
Missing values	1 (0.1)	
Maternal occupation		
Government/private/other	31 (4.2)	1194 (5.4)
Self-employed	232 (31.4)	8714 (39.2)
Farming	251 (34.0)	6420 (28.9)
Does not work	224 (30.4)	5889 (26.5)
Maternal education		
None	264 (35.8)	6863 (30.9)
Primary school	138 (18.7)	4098 (18.5)
Secondary/tertiary	322 (43.6)	11 256 (50.7)
Missing values	14 (1.9)	
Vaccine due in wet season	461 (62.5)	14 494 (65.2)
Sex, female	340 (46.1)	10 966 (49.4)
Intermediate determinants		
Maternal age (years)/family size		
<20	114 (15.4)	2531 (11.3)
20–29; 1–3 children	263 (35.6)	7815 (35.2)
20–29; ≥4 children	120 (16.3)	3843 (17.3)
≥30; 1–3 children	29 (3.9)	1108 (5.0)
≥30; ≥4 children	182 (24.7)	6920 (31.2)
Missing values	30 (4.1)	
Maternal illness in year before delivery	32 (4.3)	1091 (4.9)
Distance (km)		
<1.00	409 (55.5)	13 471 (60.6)
1.00-4.99	152 (20.6)	5133 (23.1)
≥5.00	174 (23.6)	3613 (16.3)
Missing values	2 (0.3)	
Facility delivery	517 (70.1)	17 064 (76.8)
Multiple birth	52 (7.1)	795 (3.6)
Proximal variables		
Birth weight (kg)		
≥2.5	520 (70.5)	18 841 (84.8)
2.00-2.49	121 (16.4)	2910 (13.1)
1.50-1.99	59 (8.0)	385 (1.7)
<1.50	36 (4.8)	81 (0.4)
Missing values	2 (0.3)	
Mediating variables		
Neonatal illness	31 (4.2)	426 (1.9)

non-vaccination 2.7 times greater than those from the wealthiest quintile (AOR 2.69; 95% CI 2.34 to 3.08) even after adjustment for all other explanatory variables.

Being a farmer or unemployed (compared with being self-employed), having primary school education or no education (compared with secondary/tertiary education) and being aged <20 years of age (compared with being aged ≥30 with four or more children) were associated with an increased odds of non-vaccination in the final model. Conversely, female infants had lower odds of non-vaccination (table 2).

There was little variation in the effect size for the distal factors, after adjustment for intermediate and proximal mediating variables, and in the effect size for intermediate-level factors, after adjustment for birth weight. Illness did not appear to mediate the effect of birth weight or any other determinants of vaccination (table 2).

There was little evidence that either place of delivery or infant illness modified the association between birth weight and vaccination (p value for interaction all >0.2).

Additional analyses of the vaccination of facility-born infants

As a post hoc analysis, we further explored the vaccination of facility-born infants. We analysed their age at vaccination and analysed their determinants of vaccination.

Facility-born infants were vaccinated at a median age of 6 days (IQR 17). The effect estimates for the determinants of vaccination were very similar to those for the entire study population. The most important effect was for infants living >5 km from a health facility (AOR 1.60; 95% CI 1.41 to 1.81) (table 2).

Impact of vaccinating all facility-born infants before discharge

Overall BCG uptake was 77.1% (95% CI 76.5 to 77.6) by the end of the neonatal period, 91.8% (95% CI 91.4 to 92.1) by 8 weeks of age, 95.9% (95% CI 95.6 to 96.1) by 12 weeks of age and 98.7% (95% CI 98.5 to 98.8) by 52 weeks of age (table 3). At each of these time points, uptake declined with decreasing birth weight, although there was little difference at age 52 weeks (table 3). We calculated that 91.0% (95% CI 90.6 to 91.3) of all infants, 91.2% (95% CI 87.9 to 93.6) of infants weighing 1.50–1.99 kg and 88.9% (95% CI 79.9 to 94.1) of infants weighing <1.50 kg may have been vaccinated in the neonatal period if all facility-born infants were vaccinated prior to discharge. This represented a respective 18%, 31% and 47% increase in vaccine uptake by the end of the neonatal period. Similar smaller gains in vaccine uptake would have occurred for the other categories of birth weight (table 3).

DISCUSSION

Our analyses indicate that LBW infants are at high risk of missing BCG vaccination in the neonatal period. There appears to be a dose–response relationship between vaccination and birth weight; vaccination declines with decreasing birth weight, regardless of place of birth.

We excluded sicker weaker infants who were unable to feed at enrolment, as well as those who died during the neonatal period. The LBW infants included in our analyses were probably well, and illness was probably not a contraindication to vaccination. Our finding that neonatal illness did not appear to mediate the association between birth weight and vaccination, overall or when stratified by place of delivery, supports this. LBW is not a contraindication to vaccination, and LBW infants are recommended to be vaccinated at the same chronological age as NLBW infants;15 however, our results indicate that this recommendation is not being optimally adhered to in Ghana. We identified

a number of additional determinants of neonatal BCG vaccination, including place of delivery, distance to health facility, SES, and maternal education, occupation and age.

Table 2 Determinants of non-vaccination with BCG in the neonatal period

	Not vaccinated/ total	Proportion not vaccinated (95% CI)	Unadjusted ORs OR (95% CI) (p value)	Adjusted for distal determinants AOR (95% CI) (p value)	Adjusted for distal and intermediate determinants AOR (95% CI) (p value)	Adjusted for distal, intermediate and proximal determinants (final model) AOR (95% CI) (p value)	Final model adjusted for mediating effects of infant illness AOR (95% CI) (p value)	Final model; among infants born in a health facility AOR (95% CI) (p value)
Distal variables Religion of head of household Christian	3387/15 508	21.8 (21.2–22.5)	Ref	Ref	Ref	Ref	Ref	Ref
Muslim	1310/5310	24.7 (23.5–25.8)	1.17 (1.09–1.26)	1.04 (0.95–1.13)	1.01 (0.93–1.10)	1.01 (0.93–1.11)	1.01 (0.93–1.11)	1.00 (0.89–1.11)
None/traditional/ other	392/1399	28.0 (25.7–30.4)	1.39 (1.23–1.58) (<0.0001)	0.96 (0.85–1.09) (0.5416)	0.90 (0.79–1.03) (0.2438)	0.90 (0.79–1.03) (0.2445)	0.90 (0.79–1.03) (0.2439)	0.86 (0.72–1.03) (0.2440)
Ethnicity Akan	1891/10 376	18.2 (17.5–19.0)	Ref	Ref	Ref	Ref	Ref	Ref
Non-Akan	3198/11 841	27.0 (26.2–27.8)	0.60 (0.56–0.64) (<0.0001)	0.91 (0.84–0.99) (0.0320)	0.94 (0.86–1.02) (0.1381)	0.93 (0.86–1.02) (0.1112)	0.93 (0.86–1.02) (0.1099)	0.96 (0.87–1.06) (0.4092)
Socioeconomic status 1 (poorest)	1618/4325	37.4 (36.0–38.9)	5.19 (4.63–5.82)	3.90 (3.42–4.44)	2.70 (2.35–3.10)	2.69 (2.34–3.08)	2.68 (2.33–3.08)	2.98 (2.53–3.50)
2	1271/4376	29.0 (27.7–30.4)	3.56 (3.17–3.99)	2.91 (2.57–3.29)	2.33 (2.05–2.65)	2.32 (2.04–2.64)	2.32 (2.04–2.64)	2.34 (2.03–2.71)
3	1020/4433	23.0 (21.8–24.3)	2.60 (2.31–2.92)	2.27 (2.01–2.57)	1.98 (1.75–2.24)	1.98 (1.74–2.24)	1.98 (1.74–2.24)	1.98 (1.72–2.26)
4	709/4519	15.7 (14.7–16.8)	1.62 (1.43–1.83)	1.50 (1.32–1.70)	1.42 (1.25–1.61)	1.41 (1.24–1.60)	1.41 (1.24–1.60)	1.47 (1.28–1.68)
5 (richest)	471/4564	10.3 (9.5–11.2)	Ref (<0.0001)	Ref (<0.0001)	Ref (<0.0001)	Ref (<0.0001)	Ref (<0.0001)*	Ref (<0.0001)
Maternal occupation								
Government/ private/other	158/1194	13.2 (11.4–15.3)	0.73 (0.61–0.87)	0.89 (0.75–1.07)	0.92 (0.76–1.10)	0.91 (0.76–1.09)	0.91 (0.76–1.10)	0.92 (0.75–1.12)
Self-employed	1500/8714	17.2 (16.4–18.0)	Ref	Ref	Ref	Ref	Ref	Ref
Farming	2082/6420	32.4 (31.3–33.6)	2.31 (2.14–2.49)	1.33 (1.22–1.46)	1.21 (1.11–1.33)	1.21 (1.11–1.33)	1.21 (1.11–1.33)	1.24 (1.11–1.39)
Does not work	1349/5889	22.9 (21.9–24.0)	1.43 (1.32–1.55) (<0.0001)	1.19 (1.09–1.30) (<0.0001)	1.13 (1.03–1.24) (0.0001)	1.13 (1.03–1.24) (0.0001)	1.13 (1.03–1.24) (0.0001)	1.18 (1.06–1.32) (0.0001)
Maternal education								

None	2032/6863	29.6 (28.5–30.7)	1.95 (1.81–2.09)	1.13 (1.03–1.24)	1.15 (1.05–1.26)	1.15 (1.05–1.27)	1.15 (1.05–1.27)	1.13 (1.01–1.27))
Primary school	1057/4098	25.8 (24.5–27.2)	1.61 (1.48–1.75)	1.18 (1.08–1.29)	1.17 (1.07–1.28)	1.17 (1.06–1.28)	1.17 (1.06–1.28)	1.17 (1.05–1.31)
Secondary/tertiary	2000/11 256	17.8 (17.1–18.5)	Ref (<0.0001)	Ref (0.0013)	Ref (0.0013)	Ref (0.0015)	Ref (0.0015)	REF0.0138
Vaccine due in wet season								
Yes	3272/14 494	22.6 (21.9–23.3)	Ref	Ref	Ref	Ref	Ref	Ref
No	1817/7723	23.5 (22.6–24.5)	1.06 (0.99–1.13) (0.1082)	1.04 (0.97–1.11) (0.2274)	1.04 (0.97–1.12) (0.2284)	1.04 (0.97–1.12) (0.2353)	1.04 (0.97–1.12) (0.2402)	1.05 (0.97–1.15) 0.2121
Sex								
Male	2701/11 251	24.0 (23.2–24.8)	Ref	Ref	Ref	Ref	Ref	Ref
Female	2388/10 966	21.8 (21.0–22.6)	0.88 (0.83–0.94) (0.0001)	0.87 (0.82–0,93) (<0.0001)	0.86 (0.80–0.92) (<0.0001)	0.85 (0.80–0.91) (<0.0001)	0.85 (0.80–0.91) (<0.0001)	0.83 (0.77–0.90) (<0.0001)
Intermediate variables								
Maternal age (years)/family size								
<20	650/2531	25.7 (24.0–27.4)	1.10 (98.8–1.22)		1.22 (1.07–1.39)	1.19 (1.04–1.35)	1.19 (1.04–1.35)	1.27 (1.09–1.48)
20–29; 1–3 children	1601/7815	20.5 (19.6–21.4)	1.10 (98.8–1.22)		1.22 (1.07–1.39)	1.19 (1.04–1.35	1.19 (1.04–1.35)	1.27 (1.09–1.48)
20–29; ≥4 children	1008/3843	26.2 (24.9–27.6)	1.13 (1.03–1.24)		1.11 (1.01–1.22)	1.11 (1.10–1.22)	1.11 (1.01–1.22)	1.14 (1.01–1.29)
≥30; 1–3 children	173/1108	15.6 (13.6–17.9)	0.59 (0.50–0.70)		0.93 (0.77–1.11)	0.92 (0.76–1.10)	0.92 (0.76–1.10)	0.97 (0.78–1.19)
≥30; ≥4 children	1657/6920	23.9 (23.0–25.0)	Ref (<0.0001)		Ref (0.0080)	Ref (0.0186)	Ref (0.0191)	Ref (0.0194)
Maternal illness in year before delivery								
No	4840/21 126	22.9 (22.3–23.5	Ref		Ref	Ref	Ref	Ref
Yes	249/1091	22.8 (20.4–25.4)	1.00 (0.86–1.15) (0.9468)		0.94 (0.80–1.09) (0.3866)	0.93 (0.80–1.08) (0.3568)	0.93 (0.80–1.08) (0.3545)	0.92 (0.76–1.11) (0.3764)
Distance from health facility (km)								
<1.00	2570/13 471	19.1 (18.4–19.8)	Ref	Ref	Ref	Ref	Ref	Ref
1.00–4.99	1146/5133	22.3 (21.2–23.5)	1.22 (1.13–1.32)		1.06 (0.98–1.16)	1.06 (0.98–1.15)	1.06 (0.98–1.15)	1.06 (0.96–1.17)

≥5.00	1373/3613	38.0 (36.4–39.6)	2.60 (2.40–2.82) (<0.0001)		1.37 (1.25–1.50) (<0.0001)	1.37 (1.25–1.49) (<0.0001)	1.37 (1.25–1.49) (<0.0001)	1.60 (1.41–1.81) (<0.0001)
Place of birth								
Facility	3079/17 064	18.0 (17.5–18.6)	Ref		Ref	Ref	Ref	
39.0 (37.7–40.3)	2010/5153	39.0 (37.7–40.3)	2.90 (2.71–3.11) (<0.0001)		1.83 (1.69–1.98) (<0.0001)	1.82 (1.69–1.98) (<0.0001)	1.83 (1.69–1.98) (<0.0001)	
Multiple birth								
No	4898/21 422	22.9 (22.3–23.4)	Ref		Ref	Ref	Ref	Ref
Yes	191/795	24.0 (21.2–27.1)	1.07 (0.90–1.26) (0.4468)		1.08 (0.91–1.29) (0.3692)	0.93 (0.78–1.13) (0.4742)	0.93 (0.78–1.13) (0.4747)	1.00 (0.81–1.23) (0.9889)
Proximal variables								
Birth weight (kg)								
≥2.5	4204/18 841	22.3 (21.7–22.9)	Ref			Ref	Ref	Ref
2.00–2.49	737/2910	25.3 (23.8–26.9)	1.18 (1.08–1.29)			1.08 (0.98–1.19)	1.08 (0.98–1.19)	1.12 (0.99–1.27)
1.50–1.99	116/385	30.1 (25.7–34.9)	1.50 (1.20–1.87)			1.64 (1.30–2.08)	1.64 (1.30–2.08)	1.69 (1.28–2.22)
<1.50	32/81	39.5 (29.4–50.6)	2.27 (1.45–3.55) (<0.0001)			2.41 (1.50–3.88)) (<0.0001)	2.42 (1.51–3.89) (<0.0001)*	2.29 (1.35–3.90 (0.0001)
Mediating variable								
Neonatal illness								
No	5009/21 791	23.0 (22.4–23.5)	Ref				Ref	Ref
Yes	80/426	18.8 (15.3–22.8)	0.77 (0.61–0.99) (0.0363)				0.91 (0.71–1.17) (0.4627)	0.89 (0.66–1.20) (0.4542)

*p trend ≤0.0001.

Table 3 BCG uptake rates at 4, 8, 12 and 52 weeks of age by birth weight and rates that could be achieved if all those born in a facility had been vaccinated prior to discharge from the facility

BCG uptake rates			
Birth weight (kg)	Actual	Theoretical	% increase in vaccine uptake
Age 4 weeks	77.7 (77.1–78.3)	91.2 (90.8–91.6)	17.4
≥ 2.00–2.49	74.7 (73.1–76.2)	89.4 (88.2–90.5)	19.7
1.50–1.99	69.9 (65.1–74.3)	91.2 (87.9–93.6)	30.5
<1.50	60.5 (49.4–70.6)	88.9 (79.9–94.1)	46.9
Overall	77.1 (76.5–77.6)	91.0 (90.6–91.3)	18.0
Age 8 weeks	92.1 (91.7–92.5)	96.7 (96.4–96.9)	5.0
≥ 2.00–2.49	90.4 (89.3–91.4)	95.7 (94.9–96.4)	5.9
1.50–1.99	87.5 (83.8–90.5)	97.9 (95.9–99.0)	11.9
<1.50	72.8 (62.1–81.4)	91.4 (82.9–95.8)	25.5
Overall	91.8 (91.4–92.1)	96.5 (96.3–96.8)	5.1
Age 12 weeks	96.1 (95.8–96.4)	98.2 (98.1–98.4)	2.2
≥ 2.00–2.49	95.1 (94.2–95.8)	97.8 (97.2–98.2)	2.8
1.50–1.99	93.8 (90.9–95.8)	98.4 (96.6–99.3)	4.9
<1.50	88.9 (79.9–94.1)	97.5 (90.6–99.4)	9.7
Overall	95.9 (95.6–96.1)	98.2 (98.0–98.4)	2.4
Age 52 weeks	98.8 (98.6–98.9)	99.5 (99.4–99.6)	0.1
≥ 2.00–2.49	98.1 (97.5–98.5)	99.1 (98.7–99.4)	1.0
1.50–1.99	97.4 (95.2–98.6)	99.5 (97.9–99.9)	2.2
<1.50	96.3 (89.1–98.8)	98.8 (91.7–99.8)	2.6
Overall	98.7 (98.5–98.8)	99.4 (99.3–99.5)	0.7

These were also identified as determinants in our analyses of postneonatal vaccination 5 and other analyses,16 and reflect broader inequities in access to care in our study population.

In our study area, >20% of the 77% of facility-born infants were unvaccinated at the end of the neonatal period, demonstrating a lack of compliance with the routine schedule. This was double for infants weighing <1.5 kg at birth.

Vaccination was even lower among home-born infants, suggesting parental delay in accessing vaccination services, or for those living far from a facility, the monthly scheduling of mobile outreach clinics. The fact that home-born LBW infants are even more delayed may reflect parental reluctance to bring fragile infants for vaccination, as previously documented in a review of unpublished surveys.6

Facility-born infants were vaccinated at a median age of 6 days, suggesting that many are unvaccinated at discharge following delivery; they may instead be referred to the child health clinic for vaccination. This would explain why birth weight and other maternal and household factors remain as vaccine determinants among facility-born infants. If true, then this practice is allowing inequities in vaccination to persist. A single phial of BCG vaccinates 20 infants. Fear of wastage has previously been cited as a reason for missing opportunities for vaccination17 and may be a motivation for referring facility-born infants to the child health clinic for vaccination.

Overall uptake of BCG vaccination at age 52 weeks was high; however, many infants were vaccinated late, including a higher proportion of LBW infants. BCG vaccination is known to have an important protective effect against tuberculous meningitis in the first five years of life.18 Timely vaccination is important so as not to prolong the risk of infection. Furthermore, timeliness of vaccination is increasingly recognised as an important indicator of the overall quality of vaccination programmes,19 and our finding that LBW infants were less likely to be in compliance with the routine schedule highlights them as a group who are underserved by vaccination. The Global Vaccine Action Plan2 advocates for identifying groups who are underserved by routine vaccination services so that they can be targeted for vaccination, and so that inequities in the delivery of the vaccination programme can be reduced. Ensuring vaccination of facility born infants prior to discharge would optimise compliance with the recommended schedule and the timeliness of BCG vaccination.

Our finding of reduced vaccination of LBW infants is consistent with our previous finding of delayed postneonatal vaccination (with DTP1 and DTP3) of LBW infants.5 It also supports recent findings20 from Nairobi, Kenya, that infants weighing <2.00 kg living in informal urban settlements took nine times longer to be vaccinated in the first 90 days of life than NLBW infants. The difference in the magnitude of the association between our study and the Kenyan study may be due to the exclusion of unvaccinated infants, the lower prevalence of LBW (6%), the higher proportion of facility-born infants (96%) and the higher proportion of private facility-born infants (67%) in the Kenyan study.

Data from Guinea-Bissau21 also suggested lower BCG vaccination among LBW infants. As there was reportedly a national policy of delaying vaccination of LBW infants until they had gained weight or attended for DTP vaccination, these results are not generalisable to countries, such as Ghana, where no such policy exists.

A study from Nigeria22 reported delayed vaccination of undernourished children. This study provides indirect evidence of the effect of birth weight, in addition to infant feeding and illness (the causes of undernourishment23) on BCG vaccination.

Strengths

Our study was strengthened by low loss to follow-up rates (<3%), by the population-based nature of the sample and by the collection of high-quality data on both birth weight and vaccination.

Limitations

We lacked qualitative data on the practices associated with vaccination following delivery, including the reasons why infants born in health facilities were not getting vaccinated, and why LBW infants born in health facilities were less likely to be vaccinated. This limits our understanding of the barriers to neonatal vaccination (among both facility-born and home-born infants) and to the vaccination of LBW infants.

A large number of variables were included in our models, thus increasing the possibility of type 1 errors. Due to small numbers, our study was underpowered to detect differences in analyses where birth weight was stratified by factors such as infant illness. Although we demonstrated that vaccinating all facility-born infants prior to discharge could substantively improve the timing and equity of delivery of BCG vaccination, this finding may not be generalisable to settings where most infants are born at home.

CONCLUSIONS

Our analyses indicate that LBW is a risk factor for not being vaccinated with BCG in the neonatal period, even for facility-born LBW infants. Efforts to improve neonatal vaccination, especially for LBW infants, are warranted, regardless of where they are born. For LBW infants born in facilities, vaccination prior to discharge is recommended. Qualitative studies to understand the reasons for non-vaccination with BCG in the neonatal period are needed. In particular, studies are needed to understand why infants, including LBW infants born in health facilities, are not getting vaccinated.

Acknowledgements Our thanks to the mothers and infants who participated in the study, and to the staff of the KHRC and WHO for their help with the implementation of the project. Thanks also to Robin Nesbitt for providing data on distance to health facility.

Contributors MOL drafted the report, and it was reviewed by all authors. MOL, ST, SF and KE designed the study and analyses. KE, BK and SN designed the trial. CS, MOL, GT, SN, LH and KE were responsible for trial conduct. GT coordinated the fieldwork. MOL and CS managed the database. MOL undertook the statistical analyses with input from ST and SF.

Funding The Bill and Melinda Gates Foundation funded the Neovita trial.

Competing interests None declared.

Ethics approval The ethics committees of the WHO, the London School of Hygiene & Tropical Medicine (LSHTM) and the KHRC granted approval for the

Neovita trial.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 World Health Organization (WHO). United Nations Children's Fund (UNICEF). Global immunization data. Geneva: WHO; 2014. http://www.who.int/immunization/ monitoring_surveillance/global_immunization_data.pdf?ua51 (accessed 6 Oct 2015). 2 World Health Organisation (WHO). The global vaccine action plan 2011-2020. Geneva: WHO, 2013. http://www.who.int/immunization/global_vaccine_action_ plan/GVAP_doc_2011_2020/en/ (accessed 04.08.2015).

3 Gram L, Soremekun S, ten Asbroek A, et al. Socio-economic determinants and inequities in coverage and timeliness of early childhood immunisation in rural Ghana. Trop Med Int Health 2014;19:802–11.

4 Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet 2009;373:1543–9.

5 O'Leary M, Thomas S, Hurt L, et al. Vaccination timing of low-birth-weight infants in rural Ghana: a population based, prospective cohort study. Bull World Health Organ 2016;94:442–451D.

6 Favin M, Steinglass R, Fields R, et al. Why children are not vaccinated: a review of the grey literature. Int Health 2012;4:229–38.

7 World Health Organization. BCG vaccine. WHO position paper. Wkly Epidemiol Rec 2004;79:27–38.

8 Ministry of Health—Ghana. Immunisation Programme Comprehensive Multi-year Plan (2010-2014). http://www.gavi.org/…/Ghana/…/Comprehensive-multi-yearplan-for-2010-2014 (accessed 7 Mar 2016).

9 Polio vaccines: WHO position paper, January 2014. Wkly Epidemiol Rec 2014;89:73–92.

10 World Health Organisation. Pocket book of hospital care for children: Second edition. guidelines for the management of common childhood illnesses. Geneva: WHO, 2013. http://www.who.int/maternal_child_adolescent/documents/child_ hospital_care/en/ (accessed 5 Sep 2014).

11 Edmond KM, Newton S, Shannon C, et al. Effect of early neonatal vitamin A supplementation on mortality during infancy in Ghana (Neovita): a randomised, double-blind, placebo-controlled trial. Lancet 2015;385:1315–23.

12 Bahl R, Bhandari N, Dube B, et al., NEOVITA Study Author Group. Efficacy of early neonatal vitamin A supplementation in reducing mortality during infancy in Ghana, India and Tanzania: study protocol for a randomized controlled trial. Trials 2012;13:22.

13 Moisi JC, Kabuka J, Mitingi D, et al. Spatial and socio-demographic predictors of time-to-immunization in a rural area in Kenya: Is equity attainable? Vaccine 2010;28:5725–30.

14 Dayan GH, Shaw KM, Baughman AL, et al. Assessment of delay in age-appropriate vaccination using survival analysis. Am J Epidemiol 2006;163:561–70.

15 Saari TN, American Academy of Pediatrics Committee on Infectious Diseases. Immunization of preterm and low birth weight infants. American Academy of Pediatrics Committee on Infectious Diseases. Pediatrics 2003;112(Pt 1):

193–8.

16 Rainey JJ, Watkins M, Ryman TK, et al. Reasons related to non-vaccination and under-vaccination of children in low and middle income countries: findings from a systematic review of the published literature, 1999-2009. Vaccine 2011;29:8215–21.

17 Hutchins SS, Jansen HA, Robertson SE, et al. Studies of missed opportunities for immunization in developing and industrialized countries. Bull World Health Organ 1993;71:549–60.

18 Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet 2006;367:1173–80.

19 Dombkowski KJ, Lantz PM, Freed GL. The need for surveillance of delay in ageappropriate immunization. Am J Prev Med 2002;23:36–42.

20 Mutua MK, Ochako R, Ettarh R, et al. Effects of low birth weight on time to BCG vaccination in an urban poor settlement in Nairobi, Kenya: an observational cohort study. BMC Pediatr 2015;15:45.

21 Roth A, Jensen H, Garly ML, et al. Low birth weight infants and Calmette-Guerin bacillus vaccination at birth: community study from Guinea-Bissau. Pediatr Infect Dis J 2004;23:544–50.

22 Olusanya BO. Pattern and determinants of BCG immunisation delays in a subSaharan African community. Health Res Policy Syst 2010;8:1.

23 Christian P, Lee SE, Donahue Angel M, et al. Risk of childhood undernutrition related to small-for-gestational age and preterm birth in low- and middle-income countries. Int J Epidemiol 2013;42:1340–55.