Decline in the Incidence of Neonatal Sepsis in Rural Gadchiroli, India During the Twenty-one Years (1998–2019) Following the Home-based Neonatal Care Field-trial

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Background: Sepsis is a leading cause of neonatal mortality globally. The home-based neonatal care (HBNC) field trial (1995–1998) in rural Gadchiroli demonstrated a reduction in the incidence of neonatal sepsis. The current study examines the trend of neonatal sepsis during the twenty-one years (1998–2019) following the trial's completion.

Methods: We conducted a retrospective cohort study based on the HBNC program data in rural Gadchiroli, India, from April 1998 to March 2019. All live-born neonates who spent all or part of the neonatal period in the 39 study villages and received HBNC were eligible for inclusion. Sepsis was diagnosed during regular home visits by trained village health workers if pre-specified clinical criteria were present. Sepsis incidence was computed for seven 3-year periods. Trend analyses were conducted using the Mann-Kendall test.

Results: Of the total 17,289 live births, 16,339 (94.5%) home visited were included. In this cohort, 1069 (65 per 1000 live births) neonates were diagnosed with sepsis. The incidence of neonatal sepsis declined from 111 per 1000 live births in 1998 to 2001 to 19 per 1000 live births in 2016 to 2019, an 82.9% decrease ($P < 0.0001$), mean 4% decrease per year. The incidence of neonatal sepsis declined for early-onset sepsis ($P < 0.0001$), late-onset sepsis ($P < 0.0001$), home births ($P = 0.006$), facility births ($P < 0.0001$), preterm neonates ($P < 0.0001$) and full-term neonates ($P < 0.0001$).

Conclusions: The incidence of neonatal sepsis in rural Gadchiroli has continued to decline during the past twenty-one years. We hypothesize that the decline is due to the ongoing practice of HBNC, improved socioeconomic conditions, and new governmental health policies.

Key Words: neonate, sepsis, rural health, community-health workers, India

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Neonatal sepsis is the third leading cause of neonatal mortality world-wide, accounting for approximately 15% of all neonatal deaths.[1] Those neonates who survive an episode of sepsis are at an increased risk for long-term neurodevelopmental sequelae.[2] Globally, neonatal sepsis accounts for approximately 3% of all disability-adjusted life years.[3]

The burden of neonatal sepsis, including septicemia, meningitis and pneumonia, is highest in resource-poor settings.[4] In these areas, the diagnosis and study of neonatal sepsis are especially challenging due to the lack of microbiologic, biochemical and radiographic investigations. As a result, the diagnosis of neonatal sepsis in resource-poor settings primarily rely on simple and sensitive clinical algorithms given the high case-fatality rate of an untreated serious infection. For example, based on a neonatal cohort in Gadchiroli, a remote and underdeveloped district of India, Bang et al[5] demonstrated that the simultaneous presence of any 2 of 7 clinical signs predicted death from sepsis with 100% sensitivity, 92% specificity.

In 1995, the incidence of clinically diagnosed neonatal sepsis in rural Gadchiroli was extremely high at 170 cases per 1000 live births.[6] The Society for Education, Action and Research in Community Health conducted a field trial of home-based neonatal care (HBNC) interventions for 3 years (1995–1998). HBNC includes home visits by trained female village health workers (VHWs) during pregnancy, delivery and the neonatal period to provide health education for behavior change, neonatal assessments and management of common neonatal problems, including antibiotic therapy for suspected sepsis.[7] Following the introduction of HBNC, the incidence of neonatal sepsis decreased by 51.8%, to 82 per 1000 live births ($P < 0.001$) in 1998.[6]

While the field trial of HBNC concluded in 1998, The Society for Education, Action and Research in Community Health has continued HBNC as a service program and data collection in the 39 villages originally allocated to the intervention arm. The consistent methodologic approach offers a unique opportunity to investigate the longitudinal trend of clinically diagnosed neonatal sepsis in a low-resource, community-based setting. Therefore, we evaluated the 3 yearly incidence of clinically diagnosed neonatal sepsis in Gadchiroli, India, from 1998 to 2019.

MATERIALS AND METHODS

We conducted a retrospective cohort study by analyzing the community-based data from Gadchiroli, India, pertaining to the period of April 1998 to March 2019. The study cohort included the neonates in the 39 villages that were originally allocated to the intervention arm of the HBNC field trial. The setting, study design and results of the HBNC field trial have previously been reported.[7,8] All neonates who spent all or part of the neonatal period in the villages and received HBNC were eligible for inclusion.

VHWs made regularly scheduled home visits to assess the newborn and advise the family. From 1998 to 2002, VHWs visited all neonates on days 1, 2, 3, 5, 7, 15, 21 and 28 after birth. VHWs made additional home visits if the parents reported that their baby was unwell. Since 2002, routine visits on days 5 and 21 were eliminated for healthy neonates because they did not yield new diagnosis of sepsis. On the other hand, since August 1998, high-risk neonates (birthweight < 2000 grams, preterm birth or with difficulty in feeding on day one) received additional visits on days 4, 6, 9, 13, 18 and 24.

Screening for neonatal sepsis occurred at every home visit. Sepsis was defined by the simultaneous presence of 2 or more of the following clinical criteria: (1) weak or absent cry; (2) drowsiness or floppiness or unconsciousness; (3) weak or absent suck;

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(4) cold to touch or fever (> 99 °Fahrenheit); (5) skin pustules or umbilical infection; (6) abdominal distension or vomiting and (7) grunting or chest indrawing.[5] In 2003, skin pustules and grunting were removed from the criteria because they did not add to the clinical algorithm's ability to predict death from sepsis.[5] For neonates diagnosed with clinical sepsis, VHWs advised parents to take the baby to the nearest hospital. If a referral was not feasible, VHWs administered intramuscular gentamicin and oral cotrimoxazole for 7 to 10 days.

In addition to the prospective data collected by the VHWs, vital statistics surveillance was conducted every 6 months by independent field workers to detect any missed births and neonatal deaths in the population. The births and deaths recorded by the female VHWs who provided HBNC combined with this independent surveillance provided the total births and deaths in the area. A verbal autopsy was conducted on all identified neonatal deaths, and the most probable cause of death was assigned. The population-based sepsis-specific neonatal mortality rate (NMR) for the 39 villages was estimated from this.

The incidence of neonatal sepsis was calculated using the number of sepsis episodes diagnosed by computer algorithm using the data collected by VHWs and expressed as episodes per 1000 live births. Incidence trends during the 21-year study period were assessed using the Mann-Kendall test. We performed subgroup trend analyses based on age at diagnosis, gestational age and birth place. All tests were 2-tailed with $P < 0.05$ considered significant. STATA version 15.1 (College Station, TX) was used for all analyses.

RESULTS

Between April 1998 to March 2019, 12,150 live-born neonates were delivered to women in the 39 study villages and 11,276 (92.8%) received home visits from VHWs. An additional 5139 live-born neonates were delivered to women who migrated to the study area after birth, and 5063 (98.5%) of these received home visits from VHWs. Thus, a total of 16,339 (94.5%)neonates received home visits from VHWs and were included in the analysis. The mean number of home visits was 6.64 (SD 2.79) with 92% of all neonates receiving their last home visit on day 28 of life, and there was no difference in the rate of the 28-day follow-up throughout the study period ($P = 0.37$; Table 1). Of the 5063 mothers who migrated to the study area after birth, 4703 (92.9%) received the 28-day follow-up visit.

A total of 1069 neonates were diagnosed with sepsis during the study period (65.4 per 1000 live births). Reduced or absent suck was the most common clinical feature (n = 822, 76.9%), followed by a weak or absent cry (n = 638, 59.7%) and chest in-drawing or grunting (n = 585, 54.7%; Table 2). Skin pustules or signs of an umbilical infection were the least common manifestation (n = 142, 13.3%). The mean number of clinical features per neonate diagnosed with sepsis was 3.3 (SD 1.1).

The incidence of neonatal sepsis consistently declined from 1998 to 2019 ($P < 0.0001$; Fig. 1). From 1998 to 2001, there were 266 episodes of neonatal sepsis (111.2 per 1000 live births), while between 2016 and 2019, there were only 42 episodes of neonatal sepsis (18.6 per 1000 live births). On average, the incidence of neonatal sepsis was reduced by 4% each year of the study period. Of the total number of neonatal sepsis episodes from 1998 to 2019, 277 (25.9%) episodes were due to early-onset sepsis (day 1–4) and 792 (74.1%) episodes were due to late-onset sepsis (day 5–28). From 1998 to 2019, there was a trend toward reduced incidence of both early-onset sepsis ($P < 0.0001$) and late-onset sepsis ($P < 0.0001$; Fig. 1).

Preterm births accounted for 8.4% of all births, and this percentage remained consistent through the study period. The incidence of neonatal sepsis declined in both preterm neonates ($P < 0.0001$) and full-term neonates ($P < 0.0001$) during the study period (Fig. 2). The proportion of women who delivered in a health facility was 11.3% during 1998 to 2001, 45.5% during 2007 to 2010, and 94.6% during 2016 to 2019. For neonates born in a health facility, the first home visit by a VHW occurred on the mean, fourth day-of-life (SD 4.45). When stratified by birth place, the incidence of neonatal sepsis decreased for neonates born at home ($P = 0.006$) as well as neonates born at health facilities ($P < 0.0001$; Fig. 2).

Of the 1069 neonates diagnosed with sepsis during the study period, 102 (9.5%) neonates died. There was no significant change in the case-fatality rate from 1998 to 2019 ($P = 0.74$). The population-based sepsis-specific NMR declined from 13.2 deaths per 1000 live-born neonates (1998–2001) to 3.9 deaths per 1000 live-born neonates (2016–2019; $P = 0.0005$; Fig. 3).

DISCUSSION

In this study, we evaluated the trend in the incidence of clinically diagnosed neonatal sepsis in 39 villages in Gadchiroli, India, from 1998 to 2019. The incidence of neonatal sepsis fell by > 5-fold during these 21 years to a nadir of 19 episodes per 1000 live births. We found a reduction in the incidence of both early-onset and late-onset sepsis in addition to a reduction across many subpopulations. We also observed a nearly 3-fold reduction in the sepsis-specific NMR during this period.

This study has some limitations that need to be considered when interpreting the results. First, our data are limited by the lack of microbiologic confirmation of an infectious etiology. The 2015 Acquired Serious Infections among young children in South Asia (ANISA) study—a multi-center population-based surveillance in India, Bangladesh and Pakistan—found that only 28% of infants with clinically diagnosed sepsis tested positive for a bacterial or viral organism.[8] Because clinical definitions of neonatal sepsis prioritize sensitivity over specificity, it is likely that our diagnosis of sepsis included other neonatal disorders, such as hypoglycemia or hypothermia. However, the over-estimation of neonatal sepsis does not

TABLE 1. Neonatal Home Visit Completion, 1998–2019

Time Period	Number of Live Births Who Received Home Visits	Mean Number of Visits (SD)	Number Visited on 28th Day (%)
April 1998 to March 2001	2393	8.64 (2.51)	2228 (93.1)
April 2001 to March 2004	2213	7.04 (2.88)	2010 (90.8)
April 2004 to March 2007	2299	6.13 (2.80)	2118 (92.1)
April 2007 to March 2010	2235	6.32 (2.74)	2065 (92.4)
April 2010 to March 2013	2476	6.07 (2.63)	2222 (89.7)
April 2013 to March 2016	2461	6.14 (2.45)	2294 (93.2)
April 2016 to March 2019	2262	6.16 (2.51)	2117 (93.6)
Total (1998–2019)	Total: 16,339	Total: 6.64 (2.79)	15,054 (92.1)

TABLE 2. Signs and Symptoms of Neonates Diagnosed With Sepsis

Clinical Feature	Neonates With Sepsis (n = 1069)	
	Number	%
Reduced or absent sucking	822	76.9
Weak or absent cry	638	59.7
Chest in-drawing or grunting*	585	54.7
Cold to touch or fever	526	49.2
Vomiting or abdominal distension	426	39.9
Drowsiness or floppiness or unconsciousness	291	27.2
Umbilical infection or skin pustules*	142	13.3

*Grunting and skin pustules were removed as clinical features in 2003 since these 2 did not increase sensitivity.

negate the reported trend given that the same clinical criteria were used throughout the 21-year period. Moreover, we have previously published the validation of our set of clinical criteria used to diagnose sepsis.[5] Second, our rates of sepsis are based only on those neonates visited by VHWs. The study cohort did not include 5.5% of the total 17,289 neonates in the villages, and within the study cohort, we may have missed cases of sepsis in our primary analysis if they died prior to VHW assessment. However, our sepsis-specific NMR which showed a declining trend was calculated based on all births and deaths in the 39 villages. Given that the case-fatality rate for sepsis remained unchanged, the reduction in the sepsis-specific NMR corroborates with the reported reduction in the incidence of sepsis.

This study includes all cases of neonatal sepsis in Gadchiroli that were diagnosed by a VHW but does not include cases that were diagnosed at a health facility. During the study period, the rate of health facility births increased, and neonates born in health facilities were visited at home by a VHW on the fourth day-of-life, on average. It is possible that the current data missed some cases of early-onset sepsis for those neonates born in health facility which could affect the trend analyses. Nevertheless, throughout the study period, early-onset sepsis represented a much smaller proportion of the total cases of sepsis compared with late-onset sepsis, and the incidence of late-onset sepsis also showed a continued decline. Once neonates are at home, VHWs are the primary health contact for families in Gadchiroli who prefer community-based care over facility-based care. This is best demonstrated by the fact that although VHWs referred all septic neonates to a health facility,

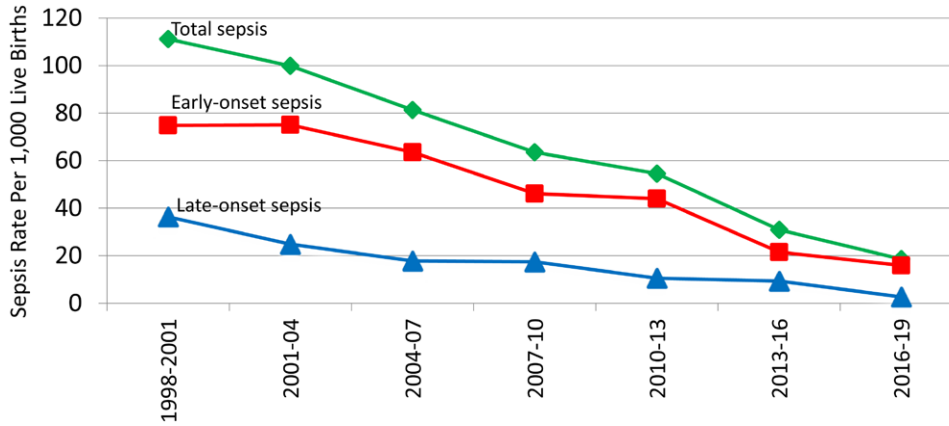

FIGURE 1. Incidence of total neonatal sepsis, early-onset sepsis and late-onset sepsis in 39 villages in Gadchiroli, India, 1998–2019. full color online

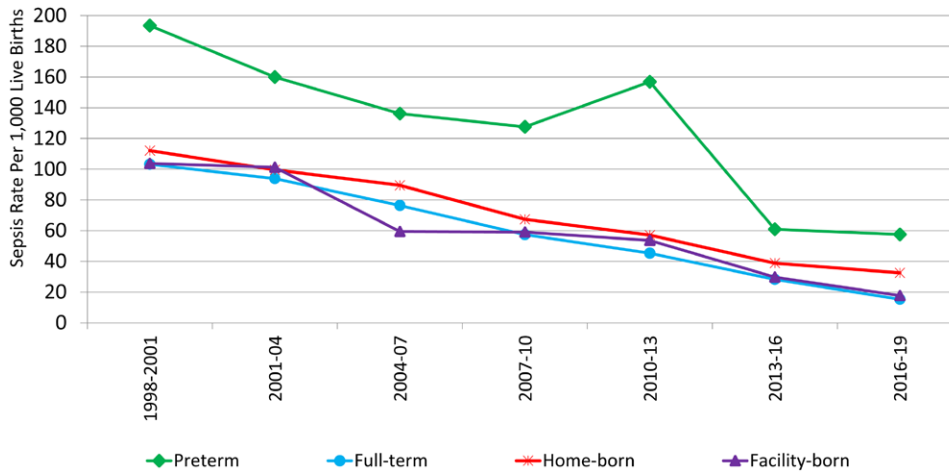

FIGURE 2. Incidence of neonatal sepsis in home-born neonates, facility-born neonates, preterm neonates and full-term neonates in 39 villages in Gadchiroli, India, 1998–2019. full color online

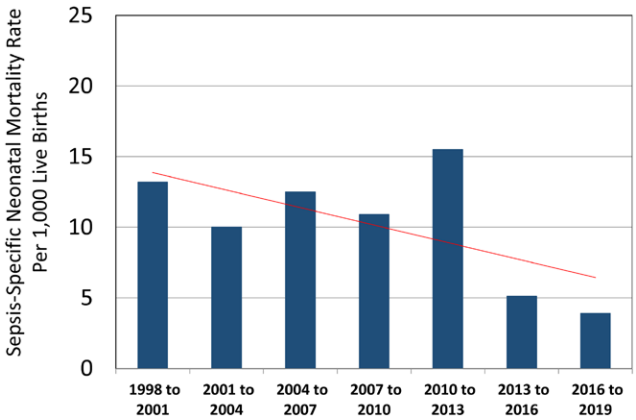

FIGURE 3. Sepsis-specific neonatal mortality rate in 39 villages in Gadchiroli, India, 1998–2019. full color online

very small proportion of families accepted the referral while the remainder chose home-based antibiotic therapy.[7] Therefore, the current study's data on the incidence of late-onset sepsis is likely a true representation of the total cases of clinically diagnosed, late-onset sepsis in Gadchiroli.

The decrease in the incidence of neonatal sepsis may be attributable to several factors. First, the ongoing practice of HBNC following the trial's completion included continuation of many components related to infection prevention, such as hygiene education, clean care of the umbilical cord, ophthalmologic application of tetracycline ointment at birth and exclusive, early breastfeeding.[7] Educational sessions about newborn care for mothers and families only started in the final year (1997–1998) of the HBNC trial and taught infection prevention concepts that were often radically different than traditional practice.[9] As with the spread of any healthcare innovation, the adoption and impact of the new practices were likely gradual based on changing perceptions of the relative benefits.[10]

The second factor that may have contributed to the decline in the incidence of neonatal sepsis is the overall improved socioeconomic status in Gadchiroli. At the start of the HBNC trial (1993–1995), only 29% of homes in the 39 study villages had electricity (a marker of economic status), compared with 68% of rural Gadchiroli homes in the 2011 census.[11] In addition, while the female literacy rate in the study villages was only 38% at the start of the HBNC trial (1993–1995),[7] more than 65% of Gadchiroli women were literate by 2011.[11] Although not causally linked to neonatal sepsis, higher levels of income and maternal education have both been associated with decreased child mortality.[12,13]

The final condition that likely influenced the incidence of neonatal sepsis in Gadchiroli is the introduction of new health policies during the study period. In 2005, the Indian government launched the National Rural Health Mission (NRHM) to improve the health status of under-served rural populations. A major component of the National Rural Health Mission is Janani SurkashaYojana (JSY: 'Safe Motherhood Scheme') which provides monetary incentives to women who give birth in health facilities.[14] JSY started making impact in Gadchiroli since 2009 and it increased the proportion of facility deliveries in this cohort from 45.5% in 2007 to 2010 to 94.6 % in 2016 to 2019. However, the incidence of neonatal sepsis in 2007 to 2010 had already decreased to 67 episodes per 1000 live births, suggesting that the increase in health facility births is not the sole explanatory factor. Also of note, following the introduction of JSY in Gadchiroli, there was a non-statistically significant rise in incidence of sepsis in preterm infants (Fig. 2; $P = 0.40$) and the sepsis-specific NMR (Fig. 3; $P = 0.17$) in 2010 to 2013 compared with 2007 to 2010. This may represent a transition period for both the health facilities and HBNC to adjust their practices to the new reality of increased facility births.

The increase in facility-based births likely contributed to the further decline in neonatal sepsis in Gadchiroli, but it is important to note that facility-based deliveries lower the risk of early-onset sepsis only if infection control measures are superior to those provided at home. In resource-limited settings, facility-based deliveries may not be at a higher standard as home deliveries as demonstrated by the ANISA study which found that 63% of all positive blood cultures were from neonates born in a hospital although only 54% of mothers delivered in a hospital.[8] In 2016, the World Health Organization acknowledged the discordance between the global rise in facility-based births and the persistently high maternal and neonatal mortality rates and published guidelines for improving the quality of maternal and newborn care in hospitals, including infection prevention.[15] Therefore, the effect of increased facility deliveries on the incidence of neonatal sepsis is complex, highly dependent on the care practices at the facility. This might explain the transient rise in the infections and mortality observed during 2010 to 2013.

To our knowledge, this is the first longitudinal, population-based study on neonatal sepsis in a resource-poor setting. Other studies in low- and middle-income countries have examined the incidence of sepsis in infants at specific points in time. A systematic review of cross-sectional studies published from 1999 to 2012 examined the rate of sepsis, as defined by the World Health Organization's criteria for possible serious bacterial infections in infants less than 2 months old (pSBI), in sub-Saharan Africa, South Asia and Latin America and reported a pooled pSBI incidence of 76 per 1000 live births.[4] More recently, the 2015 ANISA study found an overall pSBI incidence of 95 per 1000 live births.[8] In comparison, during the ANISA data collection period (2011–2014), the rate of neonatal sepsis in this cohort in Gadchiroli was 51.5 per 1000 live births.

In conclusion, the incidence of clinically diagnosed neonatal sepsis steadily declined during the 21-year study period in a rural, resource-poor district of India. We hypothesize that the reduction is due to the interaction of the ongoing practice of HBNC, improved socioeconomic conditions, and new governmental health policies. This study also demonstrates the importance of consistent and long-term population-based surveillance of neonatal morbidities. Further research should investigate whether this trend is observed in other resource-poor settings.

REFERENCES

1. United Nations Inter-Agency Group for Child Mortality Estimation. *Levels and Trends in Child Mortality: Report 2019*. UNICEF; 2019.
2. Mwaniki MK, Atieno M, Lawn JE, et al. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. *Lancet.* 2012;379:445–452.
3. Blencowe H, Vos T, Lee AC, et al. Estimates of neonatal morbidities and disabilities at regional and global levels for 2010: introduction, methods overview, and relevant findings from the Global Burden of Disease study. *Pediatr Res*. 2013;74(suppl 1):4–16.
4. Seale AC, Blencowe H, Manu AA, et al.; pSBI Investigator Group. Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, South Asia, and Latin America for 2012: a systematic review and meta-analysis. *Lancet Infect Dis.* 2014;14:731–741.
5. Bang AT, Bang RA, Reddy MH, et al. Simple clinical criteria to identify sepsis or pneumonia in neonates in the community needing treatment or referral. *Pediatr Infect Dis J.* 2005;24:335–341.
6. Bang AT, Bang RA, Reddy HM, et al. Reduced incidence of neonatal morbidities: effect of home-based neonatal care in rural Gadchiroli, India. *J Perinatol.* 2005;25(suppl 1):S51–S61.

7. Bang AT, Bang RA, Baitule SB, et al. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. *Lancet.* 1999;354:1955–1961.
8. Saha SK, Schrag SJ, El Arifeen S, et al. Causes and incidence of community-acquired serious infections among young children in South Asia (ANISA): an observational cohort study. *Lancet.* 2018;392:145–159.
9. Bang AT, Bang RA, Reddy HM, et al. Methods and the baseline situation in the field trial of home-based neonatal care in Gadchiroli, India. *J Perinatol.* 2005;25(suppl 1):S11–S17.
10. Berwick DM. Disseminating innovations in health care. *JAMA.* 2003;289:1969–1975.
11. Government of India. *Census of India 2011: Primary Census Abstract*. Registrar General and Census Commissioner of India, Ministry of Home Affairs. New Delhi, India; 2011.
12. Hales S, Howden-Chapman P, Salmond C, et al. National infant mortality rates in relation to gross national product and distribution of income. *Lancet.* 1999;354:2047.
13. Gakidou E, Cowling K, Lozano R, et al. Increased educational attainment and its effect on child mortality in 175 countries between 1970 and 2009: a systematic analysis. *Lancet.* 2010;376:959–974.
14. Government of India. Janani Suraksha Yojana: Features & Frequently Asked Questions and Answers. Ministry of Health and Family Welfare. New Delhi, India. 2005. Available at: https://nhm.gov.in/WriteReadData/l892s/9782713333152343895 1.pdf. Accessed January 1, 2021.
15. World Health Organization. Standards for improving quality of maternal and newborn care in health facilities. 2016. Available at: https://www.who.int/maternal_child_adolescent/documents/improving-maternal-newborn-care-quality/en/. Accessed January 01, 2021.

Erratum

Pneumococcal Serotype-specific Opsonophagocytic Activity in Interleukin-1 Receptor-associated Kinase 4-deficient Patients: ERRATUM

For the article "Pneumococcal Serotype-specific Opsonophagocytic Activity in Interleukin-1 Receptor-associated Kinase 4-deficient Patients" in the May 2021 issue of *The Pediatric Infectious Disease Journal*, the authors would like to acknowledge the following:

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REFERENCE

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