Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

before COVID-19 vaccine can be rolled out in younger children. Given the distinct immunogenicity profile and development stage of children, post-marketing surveillance of the vaccine safety should be done and maintained for a longer period than that in adults.

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How reliable are COVID-19 burden estimates for India?

With nearly 31 million reported COVID-19 cases and 410 000 deaths,[1] India is one of the countries with the heaviest burden of COVID-19 cases and deaths. There is near-universal consensus that the country's reported morbidity and mortality data are substantial underestimates. The majority of the morbidity and mortality in India are a consequence of the second wave, which started in March, 2021,[1] and which is attributable largely to the delta SARS-CoV-2 variant. There is some suggestion that India was largely spared from the COVID-19 disease burden in the first wave of the pandemic that began in June, 2020.[1] In the absence of good vital registration data and electronic health records that are available in more well resourced countries, good-quality surveillance data are relied upon to estimate disease burden. In this context, the study by Ramanan Laxminarayan and colleagues[2] in *The Lancet Infectious Diseases* makes a valuable contribution by reporting results from a large-scale active SARS-CoV-2 surveillance programme in Madurai, Tamil Nadu, during the first wave of the pandemic. In this study, prospective testing through RT-PCR was done from May 20, 2020, to Oct 31, 2020, for individuals with fever or acute respiratory symptoms as well as selected groups of individuals at high risk of COVID-19, including returning travellers, frontline workers, contacts of laboratory-confirmed COVID-19 cases, residents of containment zones, and patients having medical procedures. The authors also report data from a cross-sectional serosurvey done from Oct 19, 2020, to Nov 5, 2020.

On the basis of this surveillance, Laxminarayan and colleagues[2] report that the proportion of individuals who tested positive after RT-PCR was 3·6% overall (5·4% among symptomatic individuals and 2·5% among asymptomatic individuals). Although the number of males and females who received RT-PCR tests was broadly similar among symptomatic individuals, more males were tested than females among asymptomatic individuals. Adjusted odds of symptomatic SARS-CoV-2 infection were 21% higher among males than females, although this difference was reversed for asymptomatic infection. The case-fatality ratio among RT-PCR-confirmed cases was 2·4%. Although these findings are important for understanding the risk profile of symptomatic and asymptomatic infections at the population level, interpretation of these findings should be made in the context of several potential


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biases. First, the surveillance case definition for symptomatic individuals, which only considered fever and respiratory symptoms, was not comprehensive; other common COVID-19 symptoms, such as loss of smell and taste,[3] were not considered, which could lead to both selection and misclassification biases. Second, testing among asymptomatic individuals was not random but targeted, and thus could lead to selection bias. Third, misclassification bias could also occur through comorbidity status (given that this was self-reported), which could bias the association between SARS-CoV-2 infection and risk factors towards null. Fourth, although the surveillance system in Madurai allowed 13·5 diagnostic tests per 100 inhabitants to be done, almost twice the national average for this period, the number of tests done per day was not uniform across the study period, which probably contributed to ascertainment bias. Lastly, socioeconomic deprivation and occupation were not considered in the analysis, which could confound the aforementioned association.

The Article from Laxminarayanan and colleagues[2] appears to suggest that cases and deaths were substantially underestimated. The authors report an overall weighted seroprevalence of 40·1% in their study population, whereas of the 440 253 RT-PCR tests that were done, only 15 781 were positive, thus indicating an infection-case ratio (ICR) of about 67. This is substantially higher than previously reported seroprevalence estimates of 18·4% (with an ICR of about 20) by Selvaraju and colleagues[4] for Chennai, Tamil Nadu, in July, 2020. Another nationwide serosurvey done between August, 2020, and September, 2020, by Murhekar and colleagues[5] reported a weighted nationwide seroprevalence of 6·6% (with an ICR of about 30), with an unweighted seroprevalence of 33·5% in Chennai. Laxminarayanan and colleagues[2] also report an overall infection-fatality ratio (IFR) of 0·043% from the serosurvey, a figure that is broadly similar to the nationwide study by Murhekar and colleagues[5] in India (0·1%) but substantially lower than nationwide studies in England[6] (0·9%), France[7] (0·8%), and Spain[8] (0·8%) during the first wave of the pandemic. The authors claim that only one SARS-CoV-2 death was reported for every 9·1 deaths expected to occur, which is a cause for concern; this estimate should be interpreted with caution—the expected deaths were crudely estimated by applying the external age-specific IFR estimates from a meta-analysis[9] of studies from Spain, Geneva, New York City, England, Italy, Kenya, Portugal, and Sweden. Laxminarayan and colleagues[2] have made a courageous assumption that the difference in IFRs between Madurai, India, and other countries is entirely attributable to underreporting, although it is probable that several factors other than age could have contributed to variations in IFR, such as comorbidity,[10] socioeconomic status, and occupation.[11] Nevertheless, this study serves as a call to action for substantial investments in developing good data systems to gather accurate data on COVID-19 morbidity and mortality, to inform policy decisions both for India specifically and low-income and middle-income countries in general. In the absence of good vital registration data, this type of data system would require strengthening existing demographic and health-surveillance systems with the addition of high-quality mortality surveillance, collection of nasal swabs twice per week even in the absence of symptoms and repeated serosurveys, and linking these results to clinic and hospital records. Such data systems would also support national burden estimates for other respiratory infections such as influenza, and close the data gaps for future pandemics.

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Antibiotics for neonatal sepsis in low-income and middle-income countries—where to go from here?

The 2017 Global Burden of Disease study[1] reported that sepsis results in 2·9 million deaths in children younger than 5 years, with the highest incidence and mortality rates observed in neonates.[2,3] Neonatal sepsis leads to excess infant mortality even after hospital discharge,[4] and survivors might develop neurocognitive sequelae affecting later growth and development.[5] By striking contrast with most neonatal trials done in high-income regions and countries such as Europe, Canada, Australia, and the USA, high-quality, large neonatal sepsis cohort studies in low-income and middle-income countries (LMICs), where sepsis disproportionally affects maternal and child health, are much less common.[6] This challenge is further potentiated by the rapid emergence of drug-resistant organisms globally, which increasingly jeopardise the effectiveness of antimicrobials, the most effective therapy for sepsis since the discovery of penicillin by Alexander Fleming in 1928.

In neonatal intensive care units (NICUs), antimicrobial use is extremely common even in the absence of robust signs and laboratory markers of infection. In the no-more-antibiotics and resistance (NO-MAS-R) point prevalence study[7] done across 84 NICUs from 29 high-income countries and LMICs, one in four neonates admitted to a NICU was treated with antibiotics. In the NeoPInS trial[8] of procalcitonin-guided antimicrobial treatment for early-onset neonatal sepsis, fewer than one in 50 neonates treated with antibiotics had proven sepsis. However, this scenario might not reflect the day-to-day reality in certain LMIC settings, where presentations during an advanced, sometimes moribund stage of infection occur more frequently. Several international initiatives have been launched to address WHO's Global Action Plan on Antimicrobial Resistance,[9] such as the Global Antibiotic Research and Development Partnership (GARDP)[10] whose mission is "to ensure that everyone who needs antibiotics receives effective and affordable treatment."

In this context, the Article by Kathryn M Thomson and colleagues[11] published in *The Lancet Infectious Diseases*, which reports results from a substudy of the Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) study, led by an international consortium including sites in south-east Asia and Africa, addresses a key knowledge gap of relevance for clinicians, researchers, and stakeholders in public health. The main BARNARDS study enrolled neonates aged 0–60 days presenting with suspected sepsis at BARNARDS hospital sites in Bangladesh, Ethiopia, India, Pakistan, Nigeria, Rwanda, and South Africa between Nov 1, 2015, and March 31, 2018. 1019 had culture-proven sepsis and antibiotic data available, and had been treated with one of the four most commonly prescribed antibiotic combinations: ampicillin–gentamicin, ceftazidime–amikacin, piperacillin–tazobactam–amikacin, or amoxicillin–clavulanate–amikacin. In the substudy, Thomson and coworkers[11] analysed data from 442 of these neonates, for whom whole genome sequencing data for 457 isolates were available.

Although the 2016 update by WHO[12] on empiric antibiotics for neonatal sepsis recommends the use of ampicillin plus gentamicin as first-line therapy, in the substudy[11] only 28·5% of Gram-negative isolates (111 of 390) were found to be susceptible to this regimen. Other combinations such as ceftazidime–amikacin had three times higher susceptibility rates. Additionally, treatment with ceftazidime–amikacin was associated with lower mortality than treatment with ampicillin–gentamicin (adjusted hazard ratio 0·316, 95% CI 0·139–0·718; p=0·006), although the mortality


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