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Improving management of neonatal infections

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Infections causing sepsis, meningitis, or pneumonia contributed directly to around 0·6 million neonatal deaths worldwide in 2016,[1] and indirectly to many more through pathways leading to preterm birth and neonatal encephalopathy. Despite this knowledge, understanding of the causes of neonatal infection, particularly in resource-poor settings, is limited. Treatment in these settings usually relies on the sensitive but non-specific clinical diagnosis of possible serious bacterial infection (pSBI),[2] made by front-line health-care workers and defined according to set criteria. Of the almost 7 million neonates needing treatment worldwide each year based on this diagnosis,[3] most are not tested for specific infectious causes and many are likely to have non-infectious conditions (figure).

In *The Lancet*, Samir Saha and colleagues report the Aetiology of Neonatal Infection in South Asia (ANISA) study,[4] which is an important step forward in understanding the infectious causes of neonatal pSBI. The community-based study design is an advance on previous studies, which have been mostly facility-based, and often performed limited microbiological investigations. ANISA enrolled 84 971 mothers antenatally across five sites in Bangladesh, India, and Pakistan, and used community health-care workers to follow up neonates after birth. Antenatal recruitment of mothers meant that neonates who died shortly after birth were counted and that pSBIs were quickly identified by community health-care worker follow-up. Systematic sampling and testing with conventional and molecular laboratory methods maximised pathogen detection. Reductions in specificity of diagnosis and identification of multiple organisms by molecular diagnostics were mitigated by use of control data and Bayesian partially latent class modelling to estimate attributable proportions for specific infectious causes.

Saha and colleagues' findings for the causes of pSBIs and the non-specificity of this classification as a diagnosis are important. Of 6022 pSBI episodes, only 16% had attributed bacterial causes, and 102 (2%) of 4859 tested blood samples had clinically

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significant pathogens isolated by culture. More specific clinical algorithms and point-of-care diagnostics are needed to direct antibiotic treatment to those who need it, especially as antibiotic treatment for neonatal pSBI is scaled up; WHO guidelines recommend that when referral to hospital is not possible, antibiotic treatment should be given to outpatients to expand access to care.[5] Of note, however, this recommendation was informed by pragmatic antibiotic trials that used pSBI as a clinical diagnosis and tested equivalence of regimens.[6–8] The ANISA study findings add to concerns about the use of non-specific clinical diagnoses for such trials[9] and underscore the uncertainty in their findings.

As well as what it found, ANISA is important for what it did not find. Among 71 361 livebirths, 3061 (4%) babies died by the end of follow-up, most of these soon after birth. Despite active follow-up by community health-care workers, only 689 (23%) babies who died were assessed by a physician before death, and only 349 (11%) had samples taken in the 7 days before death.[4] Under-representation of deaths is a limitation in terms of attributing infectious causes, but showing how many neonates who die and who are not seen or investigated for infection is important. These data are often not captured, or are not reported, and the extent to which the sickest neonates in the community, in research or in clinical practice, are not seen is unknown in many resource-poor settings. Improving understanding of the causes of these deaths is crucial. Infection is likely to be an important direct and indirect contributor, as are preterm birth and neonatal encephalopathy. In ANISA, the number of attributed infections was nearly double that among babies who died than among those who survived, and more than 90% of the infectious causes in those who died were bacterial.[4]

Further development of the evidence base to better direct interventions towards the highest burden of neonatal mortality at and in the few days after birth will need new approaches. One such approach is post-mortem investigation with minimally invasive tissue sampling, which may be more acceptable than complete diagnostic autopsy and could allow investigation of stillbirths and neonates not seen or assessed before death.[10] The Child Health and Mortality Prevention Surveillance study aims to use such techniques.[11] Another potential approach is the use of maternal vaccines in the context of trials, and surveillance after implementation, to determine the contributions of specific infectious causes. Maternal vaccines are being developed for various pathogens, such as respiratory syncytial virus and group B streptococcus.[12]

The ANISA study has advanced understanding of neonatal infection and highlighted the limitations of current management strategies. Ways to address these issues must be urgently sought, and it must be remembered that the neonates not seen matter as much as those that are.

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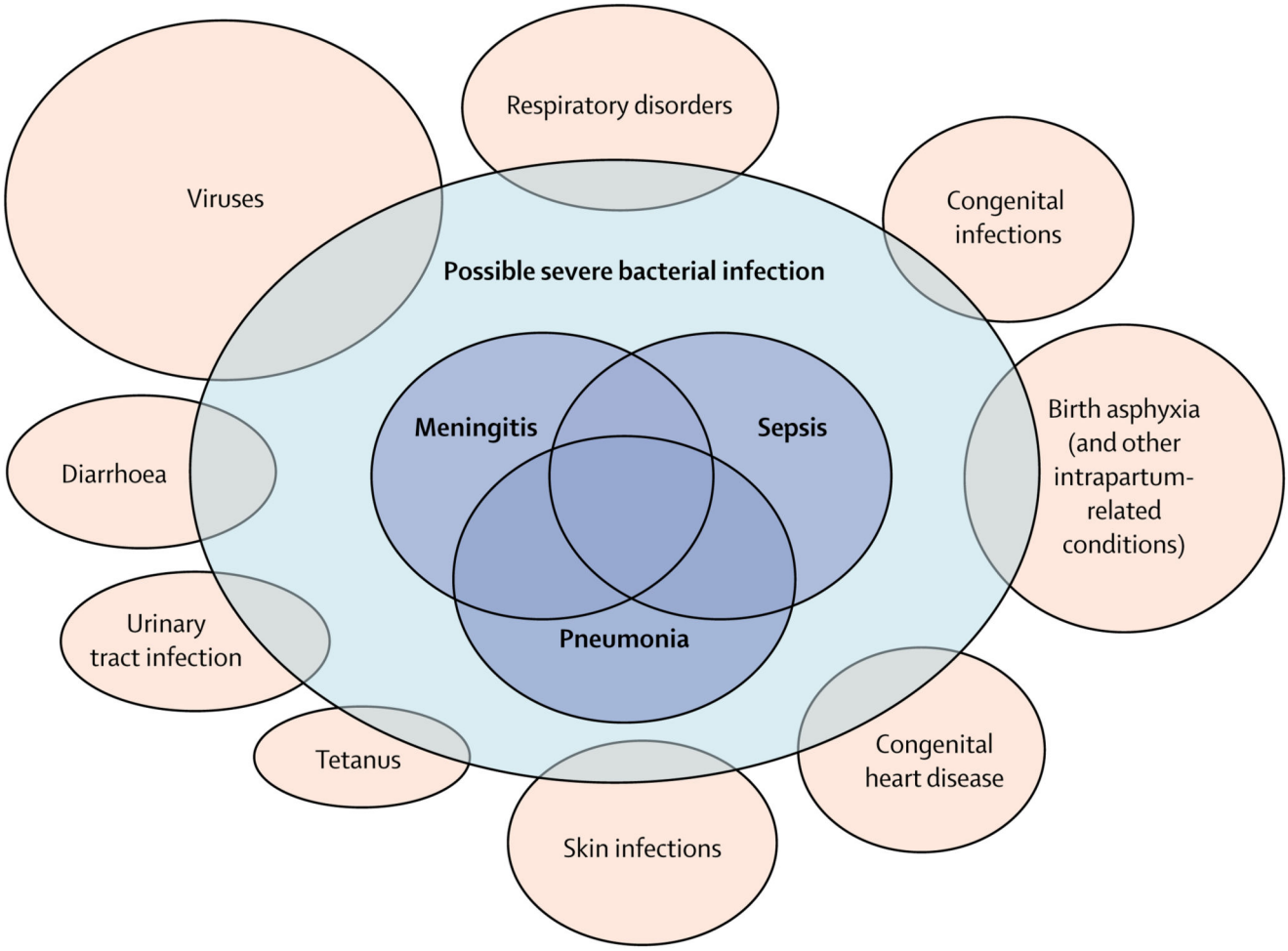

Figure. Overlap between possible serious bacterial infections and other clinical syndromes
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