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Neonatal infections: Case definition and guidelines for data collection, analysis, and presentation of immunisation safety data☆

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ABSTRACT

Maternal vaccination is an important area of research and requires appropriate and internationally comparable definitions and safety standards. The GAIA group, part of the Brighton Collaboration was created with the mandate of proposing standardised definitions applicable to maternal vaccine research. This study proposes international definitions for neonatal infections.

The neonatal infections GAIA working group performed a literature review using Medline, EMBASE and the Cochrane collaboration and collected definitions in use in neonatal and public health networks. The common criteria derived from the extensive search formed the basis for a consensus process that resulted in three separate definitions for neonatal blood stream infections (BSI), meningitis and lower respiratory tract infections (LRTI). For each definition three levels of evidence are proposed to ensure the applicability of the definitions to different settings.

Recommendations about data collection, analysis and presentation are presented and harmonized with the Brighton Collaboration and GAIA format and other existing international standards for study reporting.

1. Preamble

1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for neonatal infections as an adverse event following immunisation

Considering the enormous public health benefit that can potentially be derived by vaccinating women in pregnancy to protect their newborns against specific infections, it is now imperative to establish safety and efficacy standards in this area. This includes the need to develop definitions for neonatal infections. Such definitions need to be flexible enough to reflect changes in the pattern of infections that may occur following vaccination and to include infections as possible adverse events [1,2]. Considering that vaccination may delay the onset of infections from the neonatal period to later in infancy, the definitions also need to be applicable to the young infant.

Providing standardised definitions of neonatal infections is equally relevant for global efforts to address child mortality since the majority of deaths in children less than five years now occur in the neonatal period and neonatal infections are the third most common cause of death in newborns [3]. The majority of deaths occur in low and middle-income countries (LMIC) and therefore standardised definitions for global use must specifically reflect the needs of LMICs. Global deaths from neonatal sepsis and other infections were estimated to be 328,000 and 342,000 in 1990 and 2013, respectively (age-standardised death rates 4.7 and 4.9 per 100,000, respectively) [4]. The other most common types of fatal neonatal infections in 2013 were lower respiratory infections (196,500 deaths), diarrhoeal diseases (44,800), tetanus (26,000), meningitis (20,600), and malaria (16,800) [4].

A variety of definitions for neonatal infections have been proposed and applied in both community and hospital studies (for example from the Young Infant Clinical Study Group (YICSG)) [5], or as part of verbal autopsy studies [6].

In high-income countries, neonatal intensive care has advanced dramatically over the last decades. Neonatal infections cause a significant burden of morbidity and mortality in the extremely preterm population in these settings. As a result, neonatal networks around the world have produced many case definitions for infections, especially focusing on preterm infants. The better known case definitions are from the National Institute of Child Health and Human Development Neonatal Research Network (NICHD) [7], Australian and New Zealand Neonatal Network (ANZNN) (https://npesu.unsw.edu.au/data-collection/australian-new-zealand-neonatal-network-anznn), European Neonatal Network (ENN) [8], the Vermont-Oxford-Network (VON) (https://public.vtoxford.org) and the neonatal infection network (neonIN; www.neonin.org.uk). Some infectious disease networks have focused specifically on healthcare-associated infections, such as neoKISS [9]. With a similar drive to monitoring hospital associated infections, other organisations such as the Centers for Diseases Control (CDC) [10], the European Centre for Disease Control (ECDC) (http://ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/point-prevalence-survey/Pages/Point-prevalence-survey.aspx) and the European Medicine Agency (EMA) (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/12/WC500100199.pdf) have proposed yet more neonatal infection definitions.

In the neonatal period, the immaturity of the immune system, particularly in premature infants, confers distinctive clinical, physical and outcome characteristics to infections compared with other age groups: neonates are more vulnerable to a broad range of pathogens, including those of generally low virulence such as *Listeria*, paraechoviruses or *Candida*. Different pathogens such as bacteria, viruses, fungi or parasites often present in a clinically indistinguishable pattern in neonates, and localised infections may present with systemic signs making the clinical diagnosis difficult and often impossible without imaging confirmation and/or laboratory support. Moreover, a number of non-infectious syndromes, such as respiratory distress syndrome in the premature infant, inborn errors of metabolism and congenital malformations such as serious cardiac anomalies, have initial clinical presentations similar to severe infections [11].

Even when laboratory tests are available, diagnostic tools to guide clinicians are limited. Traditional blood culture methods lack sensitivity, particularly in neonates where only small samples can be obtained. This leads to a high number of negative results, leaving a large percentage of bacterial infections microbiologically unconfirmed [12]. Whilst the diagnosis of some entities such as HIV and CMV has benefited from the use of novel PCR-based molecular diagnostic tools, this has not happened for all neonatal infections. Interpretation of molecular results from non-sterile samples, such as nasopharyngeal aspirates, can be problematic [13].

The lack of a standardised clinical or laboratory diagnosis for neonatal infections explains the heterogeneity in the neonatal infection definitions in current use, particularly for probable bloodstream infections [14].

There is currently no uniformly accepted definition of neonatal infections following immunizations. However, the development of standardised definitions is now essential in order to facilitate comparability of data and outcomes across clinical trials and epidemiological surveillance studies in which women have received vaccines in pregnancy as well as other clinical trials and interventions aimed at reducing neonatal morbidity and mortality.

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