National active surveillance to understand and inform neonatal care in COVID-19

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The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and has spread rapidly. COVID-19 was declared a pandemic by the WHO on 12 March 2020. Robust, population-based data describing COVID-19 during pregnancy and the neonatal period are critical to understand and manage this global threat in these groups.

There are three key ways that SARS-CoV-2 could affect neonates:

1. Vertical transmission of SARS-CoV-2 from mother to infant, which may lead to neonatal COVID-19.
2. Horizontal transmission of SARS-CoV-2 in the neonatal period, potentially leading to neonatal COVID-19; this may occur from family contacts or nosocomial transmission in healthcare settings, such as neonatal units.
3. Indirect effects on the newborn following maternal COVID-19 that impact pregnancy or labour and birth, leading to complications, such as preterm birth. This will include situations where the neonate is affected by, but does not contract, SARS-CoV-2.

The impact of COVID-19 on neonates, as well as the importance of these different potential mechanisms of exposure, remains unclear. Vertical transmission of SARS-CoV-2 has yet to be definitively established; neonatal infection with the virus has been detected in the first days after birth to mothers with COVID-19[1]; however, this could represent early horizontal transmission. Support for vertical transmission comes from serological testing following maternal COVID-19, which found SARS-CoV-2 IgM in umbilical cord blood[2]; however, SARS-CoV-2 viral RNA was not detected in these newborns, and the validity of current serological tests remains to be established.[3] Nevertheless, neonates can be symptomatic with COVID-19 regardless of the mechanism of transmission. Although initial data indicated that the disease was less severe in children,[4] approximately 10% of neonates and infants with COVID-19 develop severe or critical disease, a higher proportion than that in any other paediatric age group.[5] The wider impact of maternal COVID-19 on the offspring is even less well understood. Several hundred cases of COVID-19 and asymptomatic SARS-CoV-2 infection[6] have been reported in pregnancy, and while the majority of newborns were asymptomatic, cases of preterm birth and one neonatal death (a preterm infant negative for SARS-CoV-2) have been reported.[7] Higher rates of stillbirth and preterm delivery were found in women affected by the 2009/H1N1 influenza pandemic.[8] A similar pattern, if seen in SARS-CoV-2, may result in higher requirements for neonatal cots and additional morbidity and mortality.

Measuring the incidence of neonatal complications of COVID-19 accurately and comprehensively is therefore critical to provide optimal advice and care. Understanding rates of vertical and perinatal horizontal transmission is essential to inform newborn care following birth to an affected mother, where current UK practice—keeping mother and newborn together and encouraging breastfeeding—differs from countries affected earlier in the pandemic. Data describing the neonatal impact of maternal management of COVID-19 are vital to inform maternity care and neonatal service delivery. Moreover, information describing both the severity of COVID-19 and current management is key to informing treatment, ideally in the context of randomised trials. Large, national, adaptive trials have been rapidly developed, including the Randomised Evaluations of COVID-19 Therapy Trial (www.recoverytrial.net), comparing multiple potential treatments for COVID-19. Although this trial predominantly targets adults, pregnant women and children (including neonates) are eligible, and enrolment should be considered in severe disease.

Given the critical relevance of incidence data, it is important to note that much currently available information comes from limited case series or single-centre studies rather than population-based surveillance, which is more robust, objective and less likely to be biased by local practices and protocols. Accurate population-level incidence data are essential, and acquisition of such data requires *active population surveillance*; this differs from generally unrepresentative data collected through registries that are unable to inform incidence or complication rates at population level. The British Paediatric Surveillance Unit (BPSU) has pioneered active surveillance for rare diseases in the UK and internationally since 1985. The *orange card* system developed by the BPSU has been an exemplar for the development of national surveillance in other specialties (such as UK Obstetric Surveillance System (UKOSS)) and internationally. Crucially, BPSU contacts paediatricians and neonatologists across the UK and Ireland every month and asks them to report whether they have managed a case of any condition under active BPSU surveillance. A response is requested even if no cases were encountered; this ensures high case ascertainment with more than 90% of paediatrician and neonatologists responding to the BPSU every month. This methodology enables accurate estimation of regional and national incidence, clinical and outcome data in rare diseases in children.

A BPSU study on neonatal complications of COVID-19 has been developed to perform active surveillance to address key uncertainties related to COVID-19 in neonates. Any neonate that meets the surveillance case definition (box 1) in the UK should be reported to the BPSU. For

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Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2020-319372 on 14 June 2020. Downloaded from http://fn.bmj.com/ on April 16, 2024 by guest. Protected by copyright.

Box 1 British Paediatric Surveillance Unit surveillance case definition for neonatal complications of COVID-19

Any baby or infant

1. That has a diagnosis of COVID-19 made on a sample taken before 29 days of age and receives inpatient care for COVID-19 (this includes postnatal ward, neonatal unit, paediatric inpatient wards and paediatric intensive care units) or
2. Where the mother had confirmed COVID-19 at the time of birth or suspected COVID-19 at the time of birth that has subsequently been confirmed, and the baby was admitted for neonatal care.

the first time, the BPSU is asking for cases of neonatal complications of COVID-19 to be reported weekly to capture more timely data to inform clinical care; this will be reviewed as the pandemic evolves (data collection form: online supplementary file 1). For more complete case ascertainment, this BPSU surveillance will link with other related data sources, including ongoing UKOSS surveillance of COVID-19 in pregnancy for maternal cases, Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK), for neonatal deaths and stillbirths, and Public Health England (PHE), Health Protection Scotland, Public Health Wales and the Health and Social Care Public Health Agency in Northern Ireland. To limit reporting burden during a period of increased healthcare activity and to further ensure complete case ascertainment, this BPSU surveillance will also link with routinely recorded neonatal and paediatric intensive care data held in the National Neonatal Research Database (NNRD) and the Paediatric Intensive Care Audit Network (PICANet). The resulting UK population-level incidence data will be used to inform clinical care, advice to pregnant women and service provision, and will be shared with global registries for international comparisons, further reducing reporting burden for clinicians.

The BPSU surveillance focuses on symptomatic cases that require hospital admission and the neonatal impact of maternal COVID-19. Similar surveillance of children older than 28 days of age who test positive for SARS-CoV-2 is being undertaken through PHE, and cases can be reported directly to phe.paedcovid@nhs.net. To better understand the vertical and horizontal transmission following SARS-CoV-2 infection in pregnancy, including asymptomatic transmission, the periCOVID study (www.pericovid.com) has been established at St Georges Hospital in collaboration with PHE. This seeks to recruit pregnant women with COVID-19 to collect antenatal, perinatal and postnatal samples for viral and serological testing. Further initiatives are seeking to understand the impact of COVID-19 on neonatal services (https://public.vtoxford.org/covid-19/).

Available data suggest that most infants and children with COVID-19 develop mild to moderate illness only. However, there remains considerable uncertainty about the burden of disease in higher-risk groups, such as neonates, especially those born preterm, the wider impact of COVID-19 in pregnancy on neonatal outcomes and the influence of different models of postnatal care on neonatal disease. Active surveillance through established national systems such as the BPSU and UKOSS with very high population-based case ascertainment is among the simplest, quickest and most efficient way to obtain the accurate population level incidence data and to determine true infection rates, clinical characteristics and outcomes, which are needed to inform optimal perinatal and neonatal care.

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Contributors All authors conceived the manuscript. CG drafted the initial version, and all authors contributed to subsequent drafts and reviewed the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests All authors are investigators on the BPSU Neonatal Complications of COVID-19 study.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2020-319372).

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To cite Gale C, Knight M, Ladhani S, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2020;**105**:F346–F347.

Received 14 April 2020
Revised 7 May 2020
Accepted 14 May 2020
Published Online First 14 June 2020

Arch Dis Child Fetal Neonatal Ed 2020;**105**:F346–F347. doi:10.1136/fetalneonatal-2020-319372

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