Nosocomial SARS-CoV-2 transmission in a neonatal unit in Botswana: chronic overcrowding meets a novel pathogen

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SUMMARY

We describe a cluster of six SARS-CoV-2 infections occurring in a crowded neonatal unit in Botswana, including presumed transmission among mothers, postnatal mother-to-neonate transmission and three neonate-to-healthcare worker transmissions. The affected neonate, born at 25 weeks' gestation weighing 785 g, had a positive SARS-CoV-2 test at 3 weeks of age which coincided with new onset of hypoxaemia and worsening respiratory distress. Because no isolation facility could accommodate both patient and mother, they were separated for 10 days, during which time the patient was switched from breastmilk to formula. Her subsequent clinical course was marked by several weeks of supplemental oxygen, sepsis-like presentations requiring additional antibiotics and bronchopulmonary dysplasia. Despite these complications, adequate growth was achieved likely due to early initiation of nutrition. This nosocomial cluster highlights the vulnerabilities of neonates, caregivers and healthcare workers in an overcrowded environment, and underscores the importance of uninterrupted bonding and breast feeding, even during a pandemic.

BACKGROUND

Current evidence suggests that most neonates and children infected with the novel SARS-CoV-2 are asymptomatic or have mild disease.[1] However, neonates with COVID-19, especially those born prematurely with low birth weight (BW) and low energy stores, may be at higher risk of severe illness than older children, perhaps due to an immature immune response.[2] Symptoms of neonatal COVID-19 may be impossible to distinguish from sepsis, and may include fever, respiratory distress and poor feeding.[3]

There are no specific therapies currently recommended for COVID-19 disease in neonates; treatment is supportive. While best practices for supportive management of hospitalised adults with COVID-19 have emerged (eg, prone positioning during ventilation, use of dexamethasone and targeted use of surfactant), supportive management for neonates with COVID-19 is not well defined. Thus, clinicians must presume that adherence to enduring principles of neonatal medicine, including thermoregulation, optimising nutrition and exclusive breast feeding, is critical when caring for neonates with COVID-19. SARS-CoV-2 antibodies have been identified in breastmilk of mothers with COVID-19 and SARS-CoV-2 infection in either the mother or infant should not interrupt breast feeding and skin-to-skin care.[4 5] Early introduction of nutrition, especially enteral nutrition with human breastmilk, has been associated with enhanced immune health.[6] In addition to achieving adequate growth and better adaptation to postnatal life, optimal nutrition can supplement the immune response with micronutrient cofactors like vitamin A and D, while iron and zinc deficiency can diminish T-cell immune response.[7]

Most neonatal SARS-CoV-2 infections are acquired from the infant's mother, although the risk of transmission is thought to be mitigated by infection control measures, including hand hygiene, breast cleansing and maternal use of a surgical mask.[8] Nosocomial transmission of SARS-CoV-2 is said to be rare, especially with vigilant adherence to evidence-based infection control practices. However, the risk of hospital transmission may be higher in overcrowded and resource-limited settings, as was illustrated by a nosocomial cluster of SARS-CoV-2 infections reported early in the COVID-19 pandemic at a South African hospital where 119 epidemiologically and phylogenetically linked infections occurred in a period of less than 2 months.[9] Little is known about the risk of nosocomial transmission of SARS-CoV-2 either to or from neonates, but one case series carried out in Spain found that 14 out of 40 neonatal SARS-CoV-2 infections were acquired within the hospital.[10] Overcrowding and understaffing remain major drivers of nosocomial infections among neonates in low/middle-income countries (LMICs), and have been linked to outbreaks of neonatal sepsis and even tuberculosis in endemic areas.[11–13] Little is known about drivers of nosocomial transmission of SARS-CoV-2 among neonates in LMICs: overcrowding, understaffing and poor infection prevention practices are likely major contributors.

In Botswana, where this report originates, the direct and indirect effects of the COVID-19 pandemic continue to be felt in every aspect of daily life. As of the date of this report, Botswana had registered 44 075 cases of SARS-CoV-2 infection (18 475 per 1 million population) and 671 COVID-19-associated deaths.[14] In August 2020, when Botswana first documented community SARS-CoV-2 transmission in the second half of 2020, universal SARS-CoV-2 testing on admission was commenced at our tertiary referral hospital
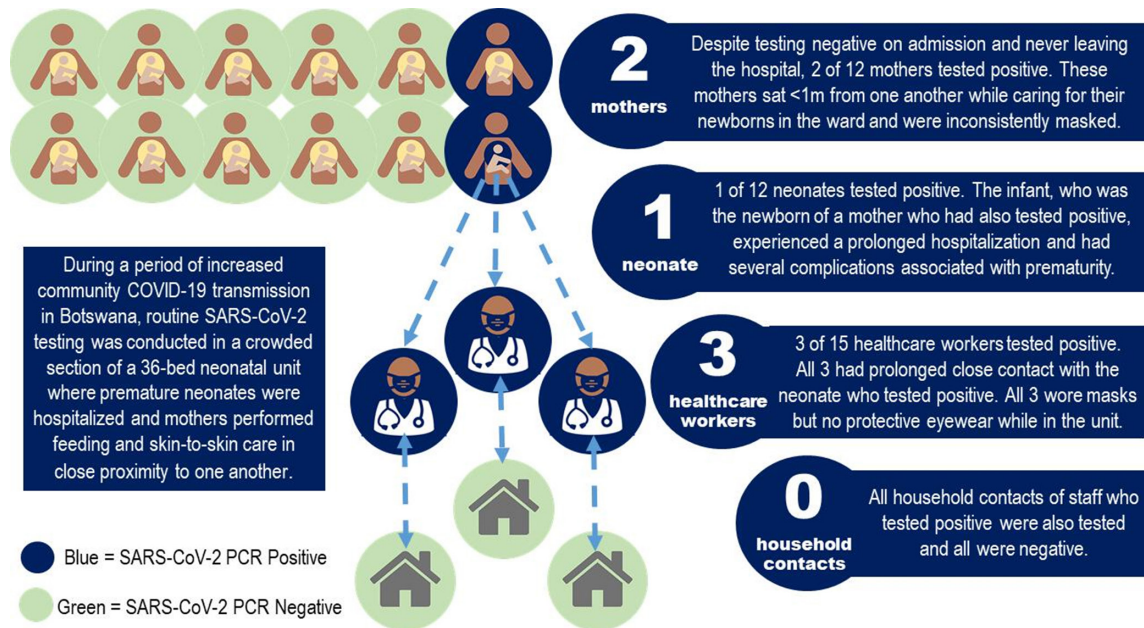
Figure 1 Transmission pathway of a nosocomial SARS-CoV-2 cluster in a neonatal unit in Botswana.

using PCR testing of the nasopharyngeal and oropharyngeal swab samples. Routines for testing all delivering mothers were introduced. However, neonates admitted in our 36-bed neonatal unit were tested only if they had spent time outside the hospital or if their mothers had tested SARS-CoV-2 positive.

According to 2019 statistics, the infant mortality rate in Botswana is approximately 32 per 1000 live births,[15] and the mortality rate in our neonatal unit is approximately 17.5%. Because of limited resources and high mortality among extremely low birthweight (ELBW) neonates, infants weighing less than 900 g are generally provided with supportive care. As in most LMICs, neonatal deaths in Botswana are caused primarily by complications resulting from preterm birth, birth injury and infections.

CASE PRESENTATION
In October 2020, during a period of increased community SARS-CoV-2 transmission in Botswana, routine testing for SARS CoV-2 was performed in our hospital's crowded postpartum ward, where mothers slept, ate and cared for their newborns in close proximity with one another. Masks were worn, but often inconsistently. Despite having tested negative on admission to the hospital, 2 of 12 mothers whose premature infants were hospitalised in a specialised ward for preterm infants tested positive for SARS-CoV-2 on PCR of nasopharyngeal/oropharyngeal swab. Both mothers were asymptomatic and reported having not left the hospital since being admitted. All 12 of the neonates in the preterm ward were tested and 1 was SARS-CoV-2 positive, a neonate of one of the mothers who had also tested positive (figure 1).

The affected neonate was female, HIV unexposed, delivered vaginally at gestational week 25 and at a BW of 785 g, thus categorised as ELBW. Her mother did not receive antenatal steroids. She was admitted to the neonatal unit immediately after birth where she was placed in a temperature-controlled incubator, started on empirical antibiotics (ampicillin and gentamicin) and aminophylline for prevention of apnoea of prematurity. Although she displayed early signs of respiratory distress syndrome (RDS), she did not receive early surfactant therapy or ventilatory support and was initially managed only on supplement oxygen via nasal cannula. She was initiated on minimal enteral feeds (expressed maternal breastmilk) and parenteral nutrition on day of life (DOL) 2. Despite this, she lost 25% of her BW (to a nadir of 595 g on DOL 5). She began gaining weight from DOL 5 for an average daily growth rate of 14 g/kg/day, finally regaining BW at DOL 22. During the first 3 weeks of life, she was visited approximately every 3 hours by her mother who provided her with expressed breastmilk and skin-to-skin kangaroo care, until the mother was proven SARS-CoV-2 positive. In addition, she was provided parenteral nutrition for enhanced nutrition to facilitate adequate growth and development.

On DOL 22, the patient tested positive for SARS-CoV-2 on PCR of nasopharyngeal/oropharyngeal swab. On testing SARS-CoV-2 positive, the neonate was placed in a room with strict isolation precautions. At the time, there was no isolation facility which could accommodate both the infant and her mother, so they were separated for 10 days, during which time the patient was switched from breastmilk to formula. Our unit does not currently have a mechanism for safe storage of expressed breastmilk. Parenteral nutrition was continued until enteral nutrition accounted for about 140 mL/kg/day to ensure adequate nutrition and growth. Two days after testing positive for SARS-CoV-2 and switching to formula, the patient experienced a new onset of hypoxaemia, tachycardia and respiratory distress requiring continuous positive airway pressure (CPAP) support and second-line antibiotics (amikacin and pipercillin–tazobactam). CPAP was introduced, in line with procedures for intensive care and respiratory support in the unit that include intensive care to neonates with gestation of 28 weeks or higher. A chest radiograph taken at the time was normal. A grade 3 systolic murmur detected at the left upper sternal border prompted an echocardiographic evaluation which revealed a persistent ductus arteriosus (PDA). Paracetamol was administered and the PDA spontaneously closed several weeks later. Cranial ultrasounds performed at 3 and 5 weeks of age were normal.

Laboratory evaluation revealed severe anaemia likely due to prematurity, with a haemoglobin level reaching a nadir of 55 g/L at DOL 18. Also, on laboratory evaluation, a
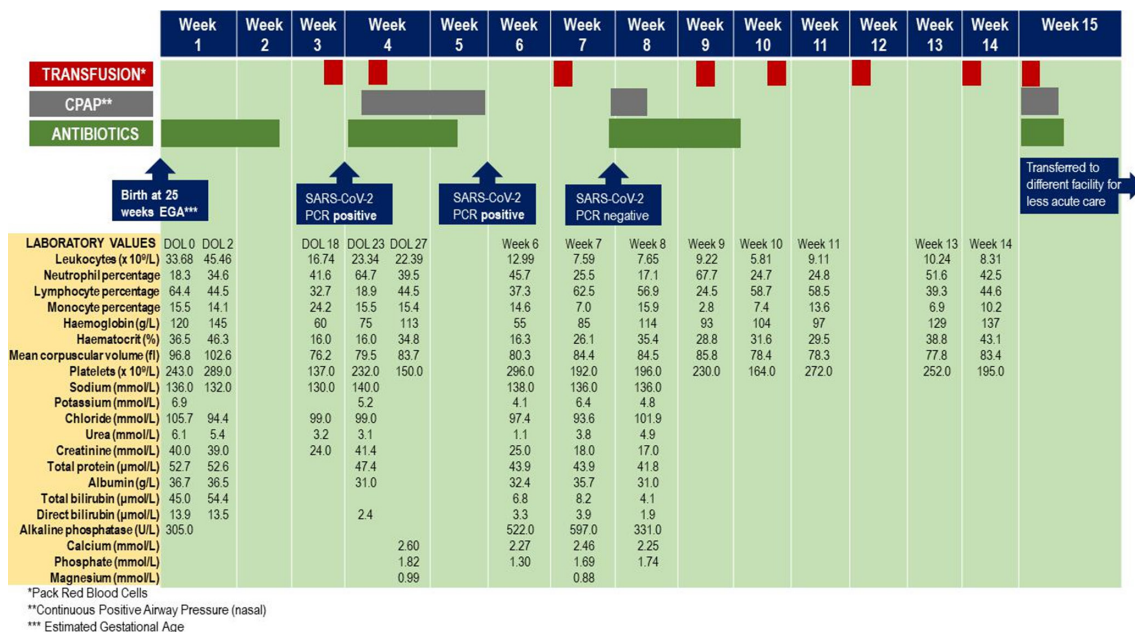
Figure 2 Timeline (Week 1 – Week 15) of clinical interventions:

Intervention	Timing
TRANSFUSION* (Pack Red Blood Cells)	Weeks 3, 4, 7, 9, 10, 12, 13, 15
CPAP**	Weeks 4–5, 8, 15
ANTIBIOTICS	Weeks 1–2, 4–5, 7–8, 14–15

Annotations:
- Birth at 25 weeks EGA*** (Week 1)
- SARS-CoV-2 PCR positive (Week 3)
- SARS-CoV-2 PCR positive (Week 5)
- SARS-CoV-2 PCR negative (Week 7)
- Transferred to different facility for less acute care (Week 15)

LABORATORY VALUES	DOL 0	DOL 2	DOL 18	DOL 23	DOL 27	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 13	Week 14
Leukocytes (x10^9/L)	33.68	45.46	16.74	23.34	22.39	12.99	7.59	7.65	9.22	5.81	9.11	10.24	8.31
Neutrophil percentage	18.3	34.6	41.6	64.7	39.5	45.7	25.5	17.1	67.7	24.7	24.8	51.6	42.5
Lymphocyte percentage	64.4	44.5	32.7	18.9	44.5	37.3	62.5	56.9	24.5	58.7	58.5	39.3	44.6
Monocyte percentage	15.5	14.1	24.2	15.5	15.4	14.6	7.0	15.9	2.8	7.4	13.6	6.9	10.2
Haemoglobin (g/L)	120	145	60	75	113	55	85	114	93	104	97	129	137
Haematocrit (%)	36.5	46.3	16.0	16.0	34.8	16.3	26.1	35.4	28.8	31.6	29.5	38.8	43.1
Mean corpuscular volume (fl)	96.8	102.6	76.2	79.5	83.7	80.3	84.4	84.5	85.8	78.4	78.3	77.8	83.4
Platelets (x10^9/L)	243.0	289.0	137.0	232.0	150.0	296.0	192.0	196.0	230.0	164.0	272.0	252.0	195.0
Sodium (mmol/L)	136.0	132.0	130.0	140.0		138.0	136.0	136.0					
Potassium (mmol/L)	6.9				5.2	4.1	6.4	4.8					
Chloride (mmol/L)	105.7	94.4	99.0		99.0	97.4	93.6	101.9					
Urea (mmol/L)	6.1	5.4	3.2	3.1		1.1	3.8	4.9					
Creatinine (mmol/L)	40.0	39.0	24.0		41.4	25.0	18.0	17.0					
Total protein (µmol/L)	52.7	52.6			47.4	43.9	43.9	41.8					
Albumin (g/L)	36.7	36.5			31.0	32.4	35.7	31.0					
Total bilirubin (µmol/L)	45.0	54.4				6.8	8.2	4.1					
Direct bilirubin (µmol/L)	13.9	13.5			2.4	3.3	3.9	1.9					
Alkaline phosphatase (U/L)	305.0					522.0	597.0	331.0					
Calcium (mmol/L)					2.60	2.27	2.46	2.25					
Phosphate (mmol/L)					1.82	1.30	1.69	1.74					
Magnesium (mmol/L)					0.99		0.88						

*Pack Red Blood Cells
**Continuous Positive Airway Pressure (nasal)
*** Estimated Gestational Age

Figure 2 Summary of clinical course of neonatal patient with COVID-19, including associated laboratory findings and clinical interventions.

lymphocytic-predominant leucocytosis was documented just 2 days after testing SARS-CoV-2 positive (see figure 2). Repeat SARS-CoV-2 testing of the infant 2 weeks after initially testing positive revealed again a positive test with persistently low/borderline cycle threshold values (N gene: 29; ORF gene: 32), suggesting continued viral replication and infectivity. Four weeks later (DOL 42), SARS-CoV-2 PCR was finally negative.

Following deisolation, maternal skin-to-skin care was reinitiated. The infant was not fed breastmilk as the mother's breastmilk production had stopped. Weight gain averaged 16–18 g/kg/day for the remainder of her hospitalisation. The rest of her hospital stay was marked by intermittent episodes of worsening respiratory distress needing CPAP support, likely a sign of evolving bronchopulmonary dysplasia, for which she was treated with dexamethasone and furosemide. Supplemental oxygen was provided through the entire hospitalisation, but very minimal nasal flow in the last 5 weeks. Third-line antimicrobials (meropenem, vancomycin and fluconazole) were initiated during periods of worsening respiratory distress which were indistinguishable from clinical sepsis. In all, she received seven packed red blood cell transfusions and four courses of antimicrobial therapy (cumulatively 40 days), however all blood cultures were negative. She was discharged to a district health facility at 3 months of age, for continued nutritional and oxygen support. At 6 months of age, she was reported to be breathing without supplemental oxygen and with adequate weight gain.

Prior to the detection of SARS-CoV-2, this infant was cared for by several healthcare workers who spent prolonged periods in close proximity with the infant, including several intravenous line changes which were said to be difficult and time-consuming. All healthcare workers were wearing a mask, but face shields/goggles were inconsistently worn when in close proximity with the patient. Three of 15 healthcare workers who had close contact with the patient tested positive for SARS-CoV-2. All three healthcare workers were asymptomatic or minimally symptomatic. Per Botswana Ministry of Health and Welfare protocol, all household members of the healthcare workers who had tested positive were also tested; all household members tested negative on SARS-CoV-2 PCR (figure 1).

Several months after the detection of this cluster, two additional unrelated COVID-19 clusters were detected in the same neonatal unit involving caregivers, staff and patients. Overcrowding and understaffing were again cited as contributing factors to transmission.

GLOBAL HEALTH PROBLEM LIST
- ► Overcrowding is a chronic problem in many neonatal units in LMICs and continues to pose a risk for pathogen transmission, including droplet transmission of SARS-CoV-2.
- ► Facility infection control measures, while aimed at mitigating the risk of hospital transmission, may interrupt mother–neonate bonding and breast feeding, resulting in poor outcomes.
- ► Little is known about SARS-CoV-2 infection in extremely premature neonates and its clinical overlap with sepsis may result in overtreatment with antibiotics. Best practices for supportive care of neonates with COVID-19 are not well defined.

GLOBAL HEALTH PROBLEM ANALYSIS
Overcrowding in neonatal units in LMICs is a problem that predates and will likely outlast the COVID-19 pandemic. Beyond SARS-CoV-2 transmission, overcrowding is a risk for transmission of other infections, including nosocomial sepsis, which is a major contributor to neonatal mortality in our setting.[16] As health systems across the world continue to redirect efforts to controlling COVID-19, tackling the problem of overcrowding is a high-yield effort which is cross-beneficial for both pandemic control and control of other endemic problems. While early pandemic response efforts in many LMICs were thwarted by shortages of personal protective equipment, reducing overcrowding in facilities has become an important tool of COVID-19 prevention and control in these settings. Admittedly, implementation of policies aimed at decongesting hospital units is not always easy and often comes with the need for additional staff. However, healthcare facilities should recognise that additional space and staff is a critical infection prevention and control (IPC) intervention and is likely to be cost-effective in the long run.

Meanwhile, all IPC interventions, whether aimed at COVID-19 or other infections, should be flexible enough to accommodate the standard of care for neonates, especially ELBW infants, particularly to guarantee access to exclusive breast feeding and adequate nutrition by supplemental parenteral nutrition if enteral nutrition cannot be tolerated. In the case of the neonate described, the 10-day period of separation resulted in cessation of breast feeding and she continued with parenteral nutrition since she did not tolerate enteral feeding very well. Due to immune immaturity, neonates may be among those at highest risk of severe COVID-19 disease. Low cycle threshold time values seen in this patient's sample 14 days after the initial positive SARS-CoV-2 test suggest a sluggish immune response. Thus, human breastmilk, which likely contains protective immunoglobulins, may be the nearest equivalent to a life-saving therapeutic. Every effort should be made to avoid interruptions to breast feeding and mother–infant bonding, including and especially among infants born to mothers with COVID-19. Additionally, more guidance is needed for neonatal units in low-resource settings to adhere to best practices which support safe breastmilk storage.

The clinical course of this patient was complicated by an underlying diagnosis of severe RDS for which she was not provided surfactant therapy and ventilatory support per local care guidelines for ELBW neonates. This may have contributed to her persistent dependence on supplemental oxygen throughout most of her hospitalisation. Adding to this, the mother did not receive antenatal steroids, which when provided to a delivering mother shortly before birth, reduce the risk of RDS in the preterm neonate.[17]

Although it is difficult to determine how much of this neonate's clinical course was attributable to SARS-CoV-2, the exacerbating effect of possible SARS-CoV-2 viremia cannot be discounted. We speculate that this patient's acute respiratory decompensation may have been partly due to SARS-CoV-2 viremia, which is supported by the presence of acute lymphocytosis. Because of the clinical overlap with sepsis, this patient received several courses of antibiotics, which highlights the problem of antibiotic overuse in our setting due to limited diagnostic capacity. At one point, necrotising enterocolitis (NEC) was suspected in the patient and enteral feeding stopped for several days accompanied by new courses of empirical antibiotics. Prolonged use of postnatal antibiotics has been shown to increase the risk of NEC, possibly due to perturbations of the developing microbiome.[18 19] The emergence of this novel disease and the antimicrobial courses it elicited underscores the need for greater availability of laboratory biomarkers for sepsis, like C reactive protein and procalcitonin, in low-resource settings.[20] These, together with forthcoming consensus on classic clinical signs of COVID-19 in the neonatal population, may help clinicians distinguish between bacterial, viral and non-infectious aetiologies of sick neonates.

Determining how clinical interventions may have affected this neonatal patient's outcome, whether positively or negatively, is difficult. However, we speculate that early adequate nutrition, both enteral and parenteral, helped support the health of the neonate during a period of infection. This patient's weight gain was anecdotally better than that achieved by other neonates of similar BWs in our unit, and survival among ELBW neonates in our setting is generally very poor. It is unlikely that novel therapies will be available for neonatal COVID-19 in the near future, but adhering enduring principles of neonatal medicine, including optimising nutritional (especially breast feeding and adequate parenteral nutrition if indicated) and thermoregulation, may augment growth and the immune response, and thus should be considered interim cornerstones of supportive care for neonates with COVID-19.

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Learning points

► Hospital overcrowding is likely a major driver of SARS-CoV-2 transmission in hospitals in low/middle-income countries and should be prioritised as a target for infection prevention and control intervention in these locations.

► Every effort should be made to avoid interruptions to breast feeding and mother–infant bonding, including and especially among infants born to mothers with COVID-19.

► Signs of COVID-19 in neonates may be indistinguishable from those of sepsis but greater availability of sepsis biomarkers may help ensure judicious use of antibiotics.

► Early nutrition may play an important role in immune response of neonates and should be considered an important component of supportive care for neonates with COVID-19.

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