Ebola-negative neonates born to Ebola-infected mothers after monoclonal antibody therapy: a case series

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For the French translation of the abstract see Online for appendix

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Summary

Background Few fetuses survive childbirth when the mother is positive for Ebola virus, with almost all being miscarried or stillborn, or dying shortly after birth. Before 2019, only two infants had been reported surviving past 28 days, of whom one tested positive for Ebola virus and subsequently received experimental therapies. Little is understood regarding the care of surviving neonates born to Ebola virus-positive mothers in the postnatal period and how novel anti-Ebola virus therapies might affect neonatal outcomes.

Methods In this case series, we report on two neonates liveborn during the 2018–20 North Kivu Ebola epidemic in the Democratic Republic of the Congo who, along with their Ebola virus-positive mothers, received investigational monoclonal antibody treatment (mAB114 or REGN-EB3) as part of a randomised controlled trial (NCT03719586).

Findings Both infants were born Ebola-negative and progressed well while in the Ebola Treatment Centre. Neither neonate developed evidence of Ebola virus disease during the course of the admission, and both were Ebola-negative at 21 days and remained healthy at discharge.

Interpretation To our knowledge these neonates are the first documented as Ebola virus-negative at birth after being born to Ebola virus-positive mothers, and only the third and fourth neonates ever documented to have survived into infancy. Although no conclusions can be drawn from this small case series, and further research is required to investigate the neonatal effects of antibody therapies, these cases warrant review regarding whether post-delivery antibody therapy should be considered for all liveborn neonates of Ebola virus-positive mothers. In the context of a low resource setting, where survival of low-birthweight infants is poor, these cases also highlight the importance of adequate neonatal care.

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Introduction

For the fetuses of pregnant women infected with Ebola virus disease, outcomes are dire.[1] Nearly all die from miscarriage or stillbirth or soon after birth.[2,3] Only 15 babies were reported liveborn to Ebola virus-positive mothers before 2015, but all subsequently died within 28 days.[4,5] In the West African Ebola epidemic (2013–16), published data indicated a neonatal mortality rate of nearly 100% for infants born to Ebola virus-positive mothers.[4,5] Two neonates have been reported as surviving Ebola virus disease: a Guinean neonate born to an Ebola virus-positive mother in 2015 survived after receiving experimental treatments (ZMapp, leukocyte transfusion, and GS-5734 [remdesivir]),[6] and a Congolese baby was born alive and uninfected to a mother who had recovered from Ebola virus disease 3 weeks before delivery in 2019.[7]

Advances in Ebola vaccines and therapies could substantially improve Ebola virus disease response,[8,9] but little evidence exists on whether new vaccines, treatments, or more intensive neonatal care facilities are associated with improved outcomes.[10] In this case series, we report the survival of two neonates in the Democratic Republic of the Congo (DRC) born to mothers with active severe Ebola virus disease at the time of delivery.

Methods

Study design and participants

In this case series, cases were managed at the Médecins Sans Frontières (MSF)-supported Ebola Treatment Centre, in Beni, North Kivu, DRC, between October and December, 2019.

Mother–infant dyads were enrolled in the extension phase of the PALM randomised controlled trial (RCT; NCT03719586).[11] This RCT was managed by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, the national government of the DRC, the African Coalition for Epidemic Research, Response, and Training, and WHO. It comprised staff from the Alliance for International Medical Action, the Institut National de Recherche Biomédicale, and the DRC's Ministry of Health who were stationed onsite at the MSF-managed Ebola Treatment Center. Randomisation and administration of the investigational monoclonal antibody therapies was done by the RCT team, and all other supportive care during admission was provided by MSF and Ministry of Health clinicians.

Research in context

Evidence before this study

We searched PubMed for studies published between 1990 and 2019 in any language with the terms "Ebola", "neonate", "pregnancy", "survival", "monoclonal antibody therapy", "experimental", and "treatment". We found seven publications reporting on infants liveborn to mothers with active Ebola virus disease; a mixture of case reports and data reviews published since 2014. A near totality of these infants died. Only two neonates have been reported to survive Ebola. One was born positive and received experimental therapy, and the other was born Ebola virus-negative to a mother who survived relatively mild Ebola virus disease and recovered before delivery; the only known account of an infant born Ebola virus-negative in this context. We found one additional mention of an infant who supposedly survived in Sierra Leone in 2014, but this case cannot be confirmed.

Added value of this study

This case series documents a novel neonatal outcome never before seen in the published literature, and also shows a possible way forward for clinicians treating Ebola in pregnancy. Both mother–infant dyads received monoclonal antibody therapies. Both neonates were born uninfected to mothers with active Ebola virus disease, progressed well while in the hospital, never developed evidence of Ebola virus disease, and were discharged Ebola virus-negative and in good health.

Implications of all the available evidence

These cases warrant review because they are the first documented Ebola virus-negative infants liveborn to Ebola virus-positive mothers that were also given post-delivery prophylactic or presumptive treatment. Although no conclusions can be drawn from this small case series, we believe further research is urgently required to examine potentially positive neonatal effects of antibody therapy, and to investigate whether it should become the standard of care for all liveborn neonates of Ebola virus-positive mothers, regardless of whether neonatal PCR results are available.

Case management

Mother 1, an 18-year-old, previously healthy primigravida woman, presented to an Ebola transit centre with fatigue, headache, cough, and anuria. She reported a third-trimester pregnancy with an unclear gestational age. She had not previously received an Ebola virus disease vaccine. Testing with an RT-PCR assay for Ebola virus nucleoprotein confirmed she was positive, with a cycle threshold value of 17, suggesting a high viral load. She was transferred to the Beni General Hospital Ebola Treatment Center for further management. On arrival, she presented with signs of early labour with vaginal bleeding, ruptured membranes, anaemia (haemoglobin 5·4 g/dL), and cervical dilatation (2 cm). She presented with no signs of decompensated shock, with no tachycardia or hypotension. A bedside ultrasound confirmed a viable intrauterine pregnancy of around 32 weeks. Within 8 h of arrival, she received a blood transfusion, ceftriaxone (2 g intravenously), artesunate (2·4 mg/kg intravenously), and mAb114 (50 mg/kg intravenous single dose). mAb114 is an investigational monoclonal antibody treatment, administered as part of the RCT. Within 12 h of admission, on Oct 16, 2019, a baby girl was born by vaginal delivery. The mother suffered substantial post-partum haemorrhage and haemoptysis and subsequently went into haemorrhagic shock and likely disseminated intravascular coagulopathy. Attempts were made to resuscitate the patient with multiple blood transfusions and vasopressors. The mother died approximately 24 h post partum.

Mother 2 was a 23-year-old, multigravida woman with two children. She presented to an Ebola transit centre with fatigue, headache, abdominal pain, and vomiting. Whether she previously received an Ebola virus disease vaccine is uncertain. She tested positive for Ebola virus with a nucleoprotein cycle threshold of 20·2. She was transferred to the Beni Hospital Ebola Treatment Center with fever, dysphagia, tachycardia, tachypnoea, and evidence of bleeding at injection sites. She initially showed no signs of decompensated shock or hypotension. There were no signs of active labour on admission, and a bedside ultrasound confirmed a viable, intra-uterine pregnancy estimated at 37 weeks. She received WHO recommended Ebola virus disease supportive care including ceftriaxone (2 g intravenously), artesunate (2·4 mg/kg intravenously), intravenous fluid replacement, and mAb114 (50 mg/kg intravenous single dose) 2 h after admission as per the RCT protocol. On day 3 of admission, repeat nucleoprotein cycle threshold was 21·8.

4 days after admission, a baby girl was born by planned caesarean section. The caesarean section was performed as the patient's previous two pregnancies had required a caesarean section. Following the birth, the mother had irretractable uterine atony and severe post-partum haemorrhage. A hysterectomy was done, and multiple blood transfusions were given but the mother died from haemorrhagic shock 15 h post partum.

Diagnostics

All reported cycle thresholds were determined by Cepheid (Solna, Sweden) GeneXpert Ebola assay, which was done in a biosafety level 3 laboratory by the DRC's Institut National de Recherche Biomédicale. This

	Neonatal day of life							
	–1	1	2	3	4	7	14	21
Mother–baby dyad 1								
Mother's serum	17	..	..	..	..	..	..	..
Placenta	..	17·6	..	..	..	..	..	..
Amniotic fluid	..	23·9	..	..	..	..	..	..
Umbilical cord	..	34·5	..	..	..	..	..	..
Neonatal buccal swab	..	21·9	..	34·4	39·6	Negative	..	..
Neonatal venous whole blood	..	Negative	Negative	..	..	Negative	Negative	Negative
Mother–baby dyad 2								
Mother's serum	21·8*	23·2†	..	..	..	..	..	..
Placenta	..	23·2	..	..	..	..	..	..
Amniotic fluid	..	29·1	..	..	..	..	..	..
Umbilical cord	..	35·9	..	..	..	..	..	..
Neonatal buccal swab	..	28·8	..	..	..	Negative	..	..
Neonatal venous whole blood	..	Negative	Negative	..	..	Negative	..	..

The values reported in our table are for the clinically relevant cycle threshold values. Lower values represent a higher viral load (<20 is considered a high viral load case, ≥40 is negative). Mother 1 died on day 2 of baby 1's life. *Day 3 of admission for mother. †Day 4 of admission for mother; caesarean section occurred on this day.

Table: **Nucleoprotein cycle thresholds from Cepheid GeneXpert Ebola RT-PCR assays**

platform detects Ebola virus RNA encoding surface glycoprotein and nucleoprotein.

Role of the funding source

There was no funding source for this study.

Results

Baby 1 was born at an estimated gestational age of 32 weeks, weighing 1·44 kg and initially required suctioning and oxygen with Apgar scores of 4, 8, and 9 at 1 min, 5 min, and 10 min after birth. Tests for Ebola virus disease by GeneXpert Cepheid RT-PCR were done immediately after birth at the Institut National de Recherche Biomédicale in Beni, DRC. Serum (venous whole blood) tested negative, while a buccal swab tested positive (table). After resting in a warmer near her mother for 3 h, baby 1 was transferred to an incubator in a separate area. Due to her premature status and low birthweight, the infant was started on prophylactic antibiotics (ampicillin 50 mg/kg twice daily intravenously and gentamicin 3 mg/kg once daily intravenously), caffeine (20 mg/kg intravenous loading dose then 5 mg/kg once daily orally), and an isotonic dextrose solution (glucose 10% solution). She remained nil by mouth for 48 h. The neonate received REGN-EB3 (Regeneron Pharmaceuticals; Tarrytown, NY, USA; 150 mg/kg intravenous single dose), an investigational monoclonal antibody combination therapy for Ebola, 10 h after delivery.

Despite her premature status, the neonate progressed well, starting trophic oral feeds on day 3, and had minimal signs of sepsis. Antibiotic therapy was ceased on day 11. Throughout her hospital stay, the infant fed adequately and attained a weight of 1·59 kg on day 21. She was discharged when she reached 2·0 kg of weight after 34 days of life.

All venous whole blood tests from birth to day 21 were negative for Ebola virus. The buccal swab that was initially positive at birth was negative by day 7.

Baby 2 was born at a gestational age of 37 weeks, weighing 3·00 kg, and initially required suctioning and oxygen, with Apgar scores of 3, 7, and 9 at 1 min, 5 min, and 10 min. She was transferred to an incubator in an area separate from her mother and received prophylactic antibiotics (cefotaxime 50mg/kg intravenously three times a day and gentamicin 5 mg/kg intravenously once daily) and an isotonic dextrose solution (glucose 10% solution). Her Ebola virus disease results at birth were whole venous blood negative, buccal swab positive. She started oral feeds with infant formula and received mAB114 (50 mg/kg intravenous single dose), an investigational monoclonal antibody therapy, 3 h after delivery.

The infant progressed well, fed adequately, and attained a weight of 3·8 kg on day 21. She showed no signs of sepsis during her first 21 days of life.

All venous whole blood tests from birth to day 21 were negative for Ebola virus disease. The buccal swab that was initially positive at birth was negative at day 7.

Discussion

Very few mothers who contract Ebola virus disease at any point during pregnancy deliver a liveborn infant that survives.[6,7] However, as access to vaccination and experimental treatments improve and case management becomes more refined, perhaps more can survive. These two cases highlight questions regarding reducing the risks of vertical transmission of the Ebola virus, postnatal antibody therapy for neonates, and multimodal neonatal care during the peripartum period.

In these neonates, one of whom was delivered vaginally and the other by caesarean section, positive oral swabs and negative serum test results were initially discordant; the reasons why are unclear. The GeneXpert Ebola assay typically has a very high sensitivity and specificity on blood for Ebola virus disease diagnosis (sensitivity >99%, specificity >95·8–99·5%;[12,13] sensitivity might be lower for samples within 72 h of symptoms onset) and similarly high results for buccal swabs (>99% for sensitivity and specificity).[13] Both mothers were symptomatic for more than 72 h by time of admission, placental PCR was positive, and it is unlikely that both infants' negative blood PCR samples at birth were false negatives. Future research could consider the potential effects of positive maternal amniotic fluid in infants' mouths at birth on buccal swab results, the factors involved in transplacental transmission, and the effects of maternal and neonatal

antibody treatments and preventive maternal vaccination on neonatal outcomes.

Ebola epidemics documented before the North Kivu epidemic indicated a perinatal mortality rate of nearly 100% for neonates born to Ebola virus-positive mothers.[14–16] The pregnancy outcomes of the 2018–20 North Kivu epidemic are not yet published; however, we are not aware of any cases of infant survival similar to those presented in this Article.

It is difficult to comment on the wider implications of the survival of these two neonates, except that their survival is remarkable. They are among only three neonates clearly reported to have survived into infancy after being born to women with active Ebola virus infection.

Although no conclusions can be drawn from this small case series, and further research is required to investigate the neonatal effects of antibody therapies, these cases warrant review regarding whether post-delivery antibody therapy should be considered for all liveborn neonates of Ebola virus-positive mothers.

Strict infection prevention and control measures appear crucial in the immediate post-partum period for all infants of Ebola virus-positive mothers, but the exact mechanisms and risks of transmission need further research. In our study, baby 1 was assumed to be Ebola virus-positive at birth (despite results later proving she was Ebola virus-negative) and treated in an incubator in the same isolation cubicle as Mother 1, potentially exposing the infant to more than 3 h in a high-risk infection zone. Given this risk, we adjusted our practice in the Ebola Treatment Center, so that neonates were considered Ebola virus disease-suspect at birth and followed normal segregation circuits between suspected and confirmed Ebola patients. Future research should determine the risk of transmission and the prudence of separating Ebola virus-positive mothers from their Ebola virus disease-suspect neonates.

As the likelihood of survival of neonates born to Ebola virus-positive mothers improves, specific protocols will be needed to address neonatal care. General neonatal guidelines with context-adapted infection prevention recommendations and routine immunisation guidelines should be implemented. This guidance should also acknowledge the possibility that the child's mother might not have survived delivery. Feeding instructions should extend beyond new breastfeeding guidelines for Ebola virus disease contexts, to account for mothers' survival and breastmilk viral status.[17] Because little is known regarding paediatric survivors of Ebola, post-discharge follow-up should be a standard for all neonates to determine their long-term developmental outcomes. Psychological support is also essential for families to address stigmatisation and the loss of other family from Ebola virus disease.

By overcoming the high neonatal mortality rate for fetuses of Ebola virus-positive mothers, these neonates defied near impossible odds. We maintain guarded optimism for both of these infants from the DRC, although we recognise their grief at the loss of their mothers and the potential risk of unknown future health complications. As more is learned about Ebola, and more preventive and therapeutic options are developed, Ebola virus disease might not continue to be uniformly fatal for fetuses and neonates. More resources should be dedicated to ensuring this.

Contributors

MPO, JDR, AN, SS, AMK, and LMP were involved in clinical care of patients in the treatment centre. MPO, JDR, AN, SS, AMK, and RP did the literature search. All authors were responsible for writing and editing the manuscript.

Declaration of interests

We declare no competing interests.

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