INT J TUBERC LUNG DIS 24(9):880–891

http://dx.doi.org/10.5588/ijtld.20.0122

STATE OF THE ART

Breastfeeding in women living with tuberculosis

M. Loveday,[1,2] S. Hlangu,[1] J. Furin[3]

[1]Health Systems Research Unit, South African Medical Research Council, KwaZulu-Natal, [2]CAPRISA-MRC HIV-TB Pathogenesis and Treatment Research Unit, KwaZulu-Natal, South Africa; [3]Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA

SUMMARY

Breast milk provides optimal nutrition, and is recommended for neonates and infants. In women with TB, there has been uncertainty about optimal feeding practices due to the risk of transmission to the neonate and the possibility of drug exposure via breast milk. For women who have drug-susceptible TB (DS-TB) who are no longer infectious, it is safe to breastfeed as breast milk does not contain *Mycobacterium tuberculosis* bacilli and only minor, non-toxic quantities of the drugs pass into breast milk. Most guidelines therefore encourage breastfeeding in women with DS-TB. However, there is uncertainty and guidelines vary regarding women with DS-TB who are still infectious and in women with rifampicin-resistant TB (RR-TB). Although the transmission dynamics of DS- and RR-TB are similar, additional infection control precautions for RR-TB may be necessary until the mother is responding to treatment, as second-line therapy may be less efficacious and preventive therapy is not widely offered to infants. In addition, there are no published data describing the extent to which second-line drugs are secreted into breast milk or subsequent exposure in breastfed infants. The implications of limited information on policy and consequent dilemmas regarding patient care are illustrated in a patient scenario. Areas for future research are suggested.
KEY WORDS: TB; RR-TB; transmission

MORE THAN 10 MILLION PEOPLE worldwide were estimated to have developed TB in 2018, with the highest burden occurring among women of reproductive age (15–45 years), in whom TB is the leading infectious cause of death and a common non-obstetric cause of maternal mortality.[1–4] In 2011, it was estimated that 216 500 pregnant women worldwide developed TB, with the greatest burden in Africa.[5] The annual burden of rifampicin-resistant TB (RR-TB) is estimated to be 500 000,[1] and as the burden of RR-TB increases, the number of pregnant women with RR-TB will also likely increase. Not only do biological changes in pregnancy increase the risk of developing TB, but pregnancy complicates the treatment of TB, increases the risk of maternal mortality and neonatal morbidity and mortality.[2,6]

Breast milk has provided optimal nutrition for human babies for thousands of years and probably hundreds of thousands of years if our hominid ancestors are included. It is the nutrition source of choice for infants, as it promotes growth and enhances brain development, provides immune protection and contains enzymes that enhance digestion.[7] Given these factors, women are routinely encouraged to breastfeed, particularly in low-income settings where resources are limited.[7] However, due both to the risk of transmission to the neonate and the possibility of drug exposure via breast milk, there has been uncertainty as to whether women with TB should breastfeed their children. This uncertainty is heightened in pregnant and lactating women with RR-TB, who have been excluded from clinical trials for fear of harming the foetus and the possible legal implications.[8] This vulnerable group has therefore not benefitted from the scientific advances that have transformed the field in the past decade. In 2018, for example, access to the life-saving medication, bedaquiline (BDQ), was compromised for breastfeeding women—unless they opted to use infant formula—given that high levels of this medication were found in breast milk in animal models.[9]

In this paper, we present a patient scenario to illustrate some of the dilemmas faced by both breastfeeding women with RR-TB and their health care providers. We then review the literature on breastfeeding and TB, presenting possible solutions and directions for future research that could provide additional clarity on this issue for women of reproductive age living with RR-TB.

Patient scenario

Ms Shandu (name changed to protect privacy) is a slight woman of 23 years who lives in a rural area of KwaZulu-Natal, South Africa. She has 5 years formal

Correspondence to: Marian Loveday, South African Medical Research Council, Francie van Zijl Drive, Parow Valley, Cape Town, PO Box 19070, Tygerberg, 7505, South Africa. e-mail: marian.loveday@mrc.ac.za
Article submitted 4 March 2020. Final version accepted 27 April 2020.

education and in 2014 was found to be infected with HIV and started on antiretroviral therapy. She was diagnosed with RR-TB in January 2019, and as she was pregnant and co-infected with HIV, hospitalised for treatment initiation. According to the country protocol, she was started on a short (9-month) treatment regimen which included BDQ in the intensive phase.[10] After discharge, her first child, a baby girl, born at 32 weeks' gestational age weighed 2000 g. In line with the country protocol at the time and the theoretical risks regarding breastfeeding for mothers living with RR-TB, the clinician responsible for her management informed Ms Shandu of the uncertainty concerning levels of BDQ in breast milk, the possible airborne transmission of RR-TB to her baby during breastfeeding and suggested that formula feeding might be the best option.

Given her level of education, the shock of her diagnosis and the thought of infecting her unborn baby, Ms Shandu was in no position to discuss the risk of transmission during breastfeeding compared to bottle feeding, or the implications of higher levels of BDQ in breastmilk. After much thought she decided to breastfeed, as not only is breastfeeding strongly encouraged in all primary health care clinics in the country, but with no fixed income, she had limited resources with which to buy formula milk and sterilise bottles. However, this decision was fraught with anxiety and a constant concern about BDQ in her breast milk, and the risk of airborne transmission of RR-TB to her baby while breastfeeding.

A month after the birth of the baby, Ms Shandu returned to the hospital for her monthly review meeting. On presentation, Ms Shandu who was slight to begin with, had lost weight as the RR-TB treatment, taken in the morning, gave her day-long nausea and no appetite. Eating was difficult, and she often vomited. Joint pain, a known side effect of one of the medications in her treatment regimen (pyrazinamide), in her ankles made walking difficult. She expressed her constant anxiety (and possible depression) about her baby, who was still small. She feared that the baby's low weight was either because she had infected her baby with RR-TB or because she had decided to breastfeed despite the doctor's concern that breastfeeding was not necessarily the optimal choice while on BDQ.

Despite these complexities, Ms Shandu completed her treatment and was cured. Six months later she was healthy, picking up weight and had resumed all her household responsibilities. Her child was thriving, with her weight increasing and following the normal trajectory of the growth chart; she was also reaching her developmental milestones in a timely fashion.

Search strategy

For this review, we searched the scholarly literature from 1946 to 28 February 2020 in PubMed, Ovid, Cochrane, Epistemonikos, PDQ, Health Evidence, TRIP, Prospero and Center for Reviews & Dissemination databases using the search terms 'tuberculosis', 'breastfeeding', 'breast milk', 'neonates', 'newborn', 'perinatal', 'first-line TB treatment', 'second-line TB treatment' 'rifampicin-resistance' and 'drug resistance'. We also searched national and international TB guidelines to assess their recommendations on breastfeeding. Our review focused on two areas: 1) the risk of TB transmission to the infant during breastfeeding; and 2) the risk of drug exposure for the infant via breast milk.

Ethical approval

This work was nested within a study approved by the South African Medical Research Council (Cape Town, South Africa) Ethics Review Committee (EC017-6/2016) and the KwaZulu-Natal Health Research Committee. The patient scenario is extracted from an interview with a participant who agreed to participate, provided written informed consent and was reimbursed for her travel and time.

FINDINGS

Summary of guideline recommendations

Table 1 gives a summary of recommendations regarding breastfeeding during pregnancy for both drug-susceptible TB (DS-TB) and RR-TB.

Risk of TB transmission to the neonate/infant

As breast milk does not contain *M. tuberculosis* bacilli, the transmission of TB through breast milk does not occur;[11,12] feeding is, however, contraindicated in the case of active TB mastitis or any other active TB breast or nipple lesion, until these have healed.[7,13,14] However, in women who have active TB and are still infectious, guidelines vary from the wearing of masks by the mother,[13] to separation from the newborn for 2–3 weeks until the mother has been effectively treated, is smear-negative and no longer considered infectious, and the newborn has been given chemoprophylaxis.[14] However, with the current tools available, it is not possible to conclusively determine the 'infectiousness' of a mother with RR-TB, which might be slightly delayed due to the less efficacious second-line treatment. Sputum microscopy has limited specificity and sensitivity, particularly in people co-infected with HIV, and is unable to distinguish between viable and dead organisms. The turnaround time for mycobacterial culture can be as long as 6-8 weeks, whereas the Xpert® MTB/RIF test (Cepheid, Sunnyvale, CA, USA) is unable to distinguish between viable and dead organisms.[15–17] Consequently, some guidelines focus on smear positivity and others on culture positivity. Although the transmission dynamics of DS-TB and RR-TB appear to be similar, once effective therapy has been

Table 1 Guidelines for breastfeeding in lactating women on TB treatment

Guideline	DS-TB	RR-TB
WHO 2010,[31] 2014[32] and 2019[33]	Maternal infectiousness and drug susceptibility should be determined. It is not necessary to separate the neonate from the mother if the mother does not have (or is not suspected of having) MDR-TB. It is not necessary to stop breastfeeding. Breastfeeding is recommended, irrespective of the TB status of the mother; the risk of TB transmission through breast milk is negligible and, although the most commonly used anti-TB drugs are excreted into breast milk in small amounts, there is no evidence that this induces drug resistance. Separation from the mother is not advised, especially in resource-limited settings where establishing breastfeeding can be critical for child survival.	No formal guidelines issued in the past decade on breastfeeding and RR-TB Knowledge about the safety of bedaquiline and delamanid in pregnancy and while breastfeeding is sparse. It is recommended that in such cases, a longer regimen be individualized to include components with a safety profile that is better established.
WHO Companion Handbooks for RR-TB, 2014[34]		The mother and her baby should not be completely separated. However, if the mother is sputum smear-positive, the care of the infant should be left to family members until she becomes sputum smear-negative, if this is feasible. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. The mother should use a surgical mask until she becomes sputum smear-negative. Any effects on infants of such exposure during the full course of drug-resistant TB treatment have not been established. Therefore, it is preferable to provide infant formula options as an alternative to breastfeeding.
United States Centers for Disease Control and Prevention, 2020[35]	Breastfeeding is encouraged for women who are deemed non-infectious and are being treated with first-line agents.	
South African National Department of Health, 2014,[36] 2019[10]	Mothers must be encouraged to breastfeed their babies whilst on TB treatment. All the TB drugs are safe for use during breastfeeding. If the mother is infectious (both smear-positive and smear-negative/ culture positive PTB) surgical masks must be used to protect the child from infection.	Pregnant and breastfeeding women with pulmonary RR-TB and/or uncomplicated EPTB, regardless of HIV status, may receive the short regimen [for RR-TB]. The patient should be reviewed by the National Clinical Advisory Committee (NCAC) – this is for surveillance purposes due to lack of data on use of these regimens.
Curry International Tuberculosis Center, 2018[37]		If the mother is still potentially infectious with drug-resistant TB, mother and baby should be separated until the mother is not infectious. However, mother-infant bonding is important and there are trade-offs to be considered in making a decision about separating a newborn and its mother. Options such as outdoor visitation with the mother wearing a mask may be appropriate. Because of the risk of arthropathy in immature animal models, ATS (the American Thoracic Society) does not recommend use of fluoroquinolones during breastfeeding. However, in the setting of MDR-TB, where fluoroquinolones play such an essential role, the potential benefit may outweigh the potential risk. In these situations, the family should be informed of the theoretical risk.

TB = tuberculosis; DS-TB = drug-susceptible TB; RR-TB = rifampicin-resistant TB; WHO = World Health Organization; MDR-TB = multidrug-resistant TB; PTB = pulmonary TB; EPTB = extrapulmonary TB; HIV = human immunodeficiency virus.

initiated to which the mother is responding, there should be no need for additional infection control precautions for RR-TB.[18] However, where practical and resources allow, the importance of good ventilation when breastfeeding and the wearing of masks by the mother, if provided by the health services, should be encouraged until the mother's sputum is smear-negative and she is responding to treatment.

In our review, we found no formal studies showing a direct link of airborne TB transmission from a breastfeeding mother to neonate/infant. One study undertaken in South Africa reported an increased risk of TB transmission from mothers with TB to neonates and infants in the first year of life: 9/74 (12%) of the infants born to mothers with TB developed TB in the first year of life.[19] This was significantly higher than

the control group of infants born to mothers without TB. Several other studies have documented the increased risk of transmission with the degree of sputum smear positivity of the TB index case, the geographical proximity, intensity and frequency of exposure of the child to the individual with TB and the child's HIV status and age.[20–22] Although these studies did not establish a link between breastfeeding and TB transmission, there could be an increased risk of transmission during breastfeeding due to the proximity and duration of shared airspace during feeding of any kind.

Risk of neonatal drug exposure

For women being treated with first-line TB drugs, it is safe to breastfeed, as only minor quantities of the drugs, which are not toxic, have no adverse effects and do not seem to predispose to the development of drug resistance, pass into breast milk.[23–25] Most guidelines therefore encourage breastfeeding in a woman on first-line TB treatment who is no longer infectious.[24] In addition, it is recommended that breastfeeding infants receiving isoniazid prophylaxis, should also receive pyridoxine supplementation at a dose of 1 mg kg^{-1} day^{-1}.[25]

However, there is a paucity of evidence regarding the safety of exposing a developing foetus to second-line TB treatment. In addition, there are no published data describing the effect during the pre- and post-partum period on the pharmacokinetics (PK) of second-line TB drugs and the extent to which these drugs are secreted into the breast milk of lactating mothers.[14] The subsequent exposure to breastfeeding infants is also unknown. The uncertainty regarding breastfeeding and second-line TB treatment has been exacerbated by the inclusion of new and repurposed drugs in RR-TB treatment regimens. Recent studies in animal models showed a high exposure of BDQ in breast milk,[9] and data on the exposure of drugs such as linezolid and clofazimine in breast milk with subsequent infant exposure is limited to case reports and small case series.[26–28]

In Table 2, all the drugs used to treat both DS-TB and RR-TB are listed, together with what is known about the extent of their concentration in breast milk. Much of the information is based on case reports and small case studies.

Patient care dilemmas, policy considerations and areas for future research

While it is clear that breastfeeding is recommended for all women with DS-TB once they are no longer considered 'infectious', there is uncertainty about what to recommend for women who are being treated for RR-TB. A paucity of evidence, fear-based infection control practices and unclear guideline recommendations mean that providers caring for women with RR-TB who have to advise women on how best to nourish their newborn, are unsure about what to tell them. While more reseach is clearly needed to remedy this situation, the current situation is in need of urgent improvement.

What is patient- and family-centred care for breastfeeding women with RR-TB?

One area that could be a targetted for immediate improvement could be how providers communicate uncertainty and unknowns about RR-TB treament, and what patient- and family-centred care for breastfeeding women is. Patients with RR-TB do need to be informed about their treatment so that they can actively participate in shared decision making with their providers. However, this should not involve providing a list of risks and 'unknowns' and expecting the patient to choose what they prefer. This was illustrated in the patient scenario, in which, in accordance with the breastfeeding policy at the time, the clinician responsible for Ms Shandu's care described to her the uncertainties and concerns around BDQ and breastfeeding. These uncertainties only served to increase Ms Shandu's anxieties about her health and the health of her child, and she consequently disengaged from her providers.

However, very little is known about the other second-line drugs, their concentration in breast milk and the consequences of exposure to these drugs via breast milk. One wonders therefore whether questioning the use of one of the most effective drugs in RR-TB treatment and the practice of breastfeeding to a young ill woman who has just delivered her first baby is wise or beneficial in any way. Similarly, one could also question the wisdom of proposing bottle feeding without knowing the patient's social circumstances, given the consequent financial implications, especially in the case of patients like Ms Shandu who have no fixed income and live in rural areas. Instead, sharing uncertainties only increased this young vulnerable mother's anxiety, fears and guilt.

Patient- or family-centred care means listening to the patient's hopes and concerns, understanding their social situation, whereby a collaborative decision is taken jointly by the health care provider and the patient after taking into account all relevant factors.

Risk of RR-TB transmission during breastfeeding

Common sense is essential in the formulation of policy; however, recommendations of formula feeding for women with RR-TB appear to contradict this. With regard to the risk of airborne transmission, the mother generally holds her baby at the same distance from her face when she is breastfeeding, bottle feeding or just holding her baby. Although the recommendation for formula feeding may seem intuitive to avoid the risk of second-line drug exposure, there are multiple benefits to breastfeeding, which may be negated when formula is given. Even

Table 2 Breast milk excretion and breastfeeding recommendations for first and second-line TB drugs

TB drug	Breast milk excretion/breastfeeding
First-line drugs	
INH	Although there have been no reports of INH-induced effects in the nursing infant, there may be potential for interference with nucleic acid function and for hepatotoxicity,[38,39] as INH and its metabolite, acetylisoniazid, are excreted in breast milk.[39,40] A woman was given a single oral dose of 300 mg. Both INH and the metabolite were present in her milk within 1 h, with peak levels of INH (16.6 μg/mL) occurring at 3 h and those of the metabolite (3.76 μg/mL) at 5 h. At 5 and 12 h after the dose, INH levels in the milk were twice the levels in simultaneously obtained plasma. Levels of acetylisoniazid were similar in plasma and milk at 5 and 12 h. The elimination half-life for milk INH was calculated to be 5.9 h, whereas that of the metabolite was 13.5 h. Both were detectable in milk 24 h after the dose. The 24-h excretion of INH was estimated to be 7 mg.[39] Two other studies also reported substantial excretion of INH into human milk.[40,41] A milk:plasma ratio of 1.0 was reported in one of these studies,[40] and in the other, milk levels 3 h after a maternal dose of 5 mg/kg were 6 μg/mL.[41] Doubling the maternal dose of INH doubled the milk concentration. Women can safely breastfeed their infants while taking INH if the infant is periodically examined for signs and symptoms of peripheral neuritis or hepatitis.[14,38] The American Academy of Pediatrics classifies INH as compatible with breastfeeding.[42] The amount of INH in breast milk is insufficient to treat TB in the breastfed infant.
PZA	PZA is excreted into human milk. A non-breastfeeding woman was given an oral 1 g dose of PZA, the peak milk concentration, 1.5 μg/mL, occurred at 3 h.[43] The peak maternal plasma concentration, 42.0 μg/mL, occurred at 2 h and the milk:plasma ratio was approximately 0.04.[44] These data suggest that breastfeeding should not be discouraged in women taking PZA but breastfeeding infants should be monitored for the rare toxicities observed in patients taking the drug: jaundice, fever, loss of appetite, nausea and vomiting, thrombocytopenia, rash and arthralgia.[45] The amount of PZA in breast milk is insufficient to treat TB in the breastfed infant.
EMB	EMB is excreted into human milk. Milk concentrations in two women (unpublished data) were 1.4 μg/mL (after an oral dose of 15 mg/kg) and 4.60 μg/mL (dosage not given).[38] Corresponding maternal serum levels were 1.5 and 4.62 μg/mL, respectively, indicating milk:serum ratios of approximately 1:1. A physiologically based pharmacokinetic model of EMB predicted an exclusively breastfed infant would receive a daily dose of 0.08 mg/kg with a maternal dosage of 24.5 mg/kg, 0.3% of the weight-adjusted maternal dosage.[46] The American Academy of Pediatrics classifies EMB as compatible with breastfeeding.[42] The amount of EMB in breastmilk would be insufficient to treat TB in a breastfed infant.
Rifamycins	Rifamycin antibiotics are effective against mycobacteria and key first-line TB drugs. Rifamycin derivatives include RBT, RIF and RPT. Rifamycin derivates are bactericidal and act against the persistent metabolically quiescent bacterial population. They work by inhibiting RNA polymerase by binding to the DNA-dependent RNA.[47] The most common adverse events associated with rifamycin antibiotics are renal toxicity, immunological reactions and hepatotoxicity. RBT There are no reports describing the use of RBT during breastfeeding.[48] However, the molecular weight (about 847), moderate plasma protein binding, and a long half-life (45 h) suggest that excretion into milk should be expected and the infant should be monitored for adverse events such as leukopenia, neutropenia and rash. The Centres for Disease Control and other professional organisations state that breastfeeding should not be discouraged in women taking RBT.[49] Breastfeeding women must be informed that their milk may be stained a brown-orange colour.[48] The amount of RBT in milk is insufficient to treat TB in the breastfed infant. RIF RIF (molecular weight 823) is excreted in low amounts into breast milk. Concentrations of 1–3 μg/mL were reported in one study, with about 0.05% of the daily dose appearing in the milk.[40,45] A second study reported concentrations of 3.4–4.9 μg/mL 12 h after a single 450 mg oral dose, with an average 21.3 μg/mL in the maternal serum levels, indicating a milk:plasma ratio of about 0.20.[50] Measured infant serum levels have not been reported. A physiologically based pharmacokinetic model of RIF predicted that a fully breastfed infant would achieve a maximum serum concentration of about 0.2 mg/L with a maternal dose of 10.9 mg/kg daily.[46] In one case report, in a woman taking RIF 450 mg and INH 300 mg for the first 7 months of lactation, the infant had no adverse reactions.[51] No reports describing adverse effects in breastfeeding infants have been located.[38,45] This limited information suggests that the low levels of RIF in breast milk would not cause adverse effects in breastfed infants. The American Academy of Pediatrics has classified RIF as compatible with breastfeeding, but suggests monitoring for jaundice.[14,42] The amount of RIF in breast milk would be insufficient to treat TB in a breastfed infant.[38,45] RPT RPT (molecular weight 877) is closely related to RIF. The molecular weight of RPT and the 13-h half-life of RPT and the active metabolite suggest that these agents will be excreted into milk. Although little is known about the effects of exposure of RPT on a breastfed infant, the Centres for Disease Control and other professional organisations state that breastfeeding should not be discouraged in women on RPT.[49] However, breastfeeding women should be informed that their breast milk may be stained red-orange. The amount of RPT in breast milk is insufficient to treat TB in the breastfed infant.

Table 2 (*continued*)

TB drug	Breast milk excretion/breastfeeding
Second-line drugs in drug groups from the WHO RR-TB treatment recommendations[52]	
Group A	
Quinolones[53]	When the quinolones first became available their use in breastfeeding women was not recommended due to possible arthropathy and other serious adverse events such as phototoxicity. However, recent studies indicate little risk.[54,55] Two quinolones (LVX and MFX) are currently recommended by the WHO in the treatment of RR-TB. OFX, an earlier generation quinolone is not currently recommended, but included at the bottom of the table under drugs used previously. The use of LVX and MFX is acceptable in breastfeeding mothers, but infants must be monitored for possible effects on the gastrointestinal flora, such as diarrhoea, thrush or diaper rash.[45] Given the lack of information available on the effect of infant exposure to both drugs, it would be preferable to use an alternate drug for which safety information is available. LVX LVX is excreted into breast milk.[56] One breastfeeding woman was given 500 mg LVX/day during the first 23 days postpartum.[56] Milk samples were collected at various times. The peak concentration in milk was 8.2 μg/mL 5 h after a dose and the pharmacokinetics were similar to those in the plasma. Minimal levels of the drug were detectable 65 h after the last dose. From these data, it was calculated that an exclusively breastfed infant whose mother was taking 500 mg daily would receive 1.25 mg daily in breast milk, which is far below the dose of LVX for children.[56] Infant exposure can be reduced by avoiding breastfeeding for 4 to 6 h after a dose. MFX There are no known reports describing the use of MFX during breastfeeding, so the effect of this exposure on a breastfed infant is unknown. The molecular weight (about 401), moderate metabolism (52%), plasma protein binding (30–50%), and half-life of 8–15 h suggest MFX will be excreted into breast milk.
BDQ	There are no known reports describing the use of BDQ during breastfeeding. The molecular weight (about 556) and long half-life (almost 6 months) suggest that both may be excreted into breast milk, but the high plasma protein binding might reduce the amount excreted. In animal models, the breast milk concentration of BDQ was 6–12 times the maximum maternal plasma level.[9] However, there are no human data available. Breastfed infants should be monitored for nausea, arthralgia, headache, haemoptysis, and chest pain, the most common (≥10%) adverse reactions observed in patients.[57]
LZD	The molecular weight of LZD (about 337) is low enough that excretion into breast milk is likely. Three case reports of a single woman each documented LZD levels in breastfed infants. From their data, all three studies concluded that breastfed infants would receive far less than the 30 mg/kg daily maximum dosage of LZD for infants.[58] • A lactating woman was given a single dose of 600 mg of LZD orally. Milk samples were taken at 10 time points over the next 24 h. The peak concentration of LZD in breast milk occurred 2 h after the dose with a value of 12.4 mg/L. Milk concentrations fell with a half-life of 6.5 h and were detectable up to 24 h after the dose.[59] Using these data, an exclusively breastfed infant would receive 2 mg/kg daily. • A woman was given oral LZD 600 mg every 12 h. She pumped milk from both breasts 8 times daily on Days 1 and 14 of therapy. Peak breast milk LZD levels were 9.75 mg/L on Day 1 and 18.73 mg/L on Day 14. Using these data, an exclusively breastfed infant would receive 7.85% of the weight-adjusted maternal dosage on Day 1 and 15.61% on Day 14. Using the average milk level on Day 14, a fully breastfed infant would receive a dosage of 1.84 mg/kg daily. • A woman given LZD 600 mg orally every 12 h donated breast milk samples at various times over a 24-h period, 45 h after the first dose. Breast milk LZD levels ranged from 3.5 to 12.2 mg/L, with the highest level shortly after a dose and the lowest shortly before the following dose.[60] One case report documents the levels of LZD in an infant. A random blood sample was taken from a breastfed infant 3–4 h after a maternal dose and found to contain <0.2 mg/L of LZD, although the time of previous breastfeeding was unknown. A breast milk sample obtained 1 h after the infant's serum sample and 4 h after LZD administration was 8.9 mg/L.[60] Given the limited information available and possible complications of myelosuppression and reversible thrombocytopenia, women taking LZD should probably not breastfeed.[45]
Group B	
CFZ	CFZ is excreted into breast milk. Milk can be coloured pink to bright red and pigmentation of the breastfed infant may result. There are four case reports of infants exposed to CFZ via breast milk: • Eight lactating mothers who had leprosy received CFZ either 50 mg daily ($n = 5$), 100 mg every other day ($n = 2$) or 100 mg daily ($n = 1$) for an average of 5 months. Milk levels collected 4–6 h after the dose averaged 1.33 mg/L (range 0.8–1.7). Infants received an average of 0.199 mg/kg daily (range 0.17–0.26), which averaged 22.1% (range 13.5–30) of the maternal weight-adjusted dosage.[61] • A lactating mother received CFZ (between 100 and 300 mg/day), 6 days/week, for a 6-month period. Her breastfed infant became 'ruddy and then slightly hypermelanotic.' [62] The baby's skin colour returned to a normal 5 months after the mother's medication was stopped. • In a further two case reports of single infants, both developed skin discolouration, which reversed a couple of months after breastfeeding was stopped.[63,64] The American Academy of Pediatrics classifies CFZ as a drug whose effect on the breastfeeding infant is unknown, except for skin pigmentation.[42]
CS	CS is excreted into breast milk. Milk concentrations in four lactating women taking 250 mg of the drug four times daily ranged from 6 to 19 μg/mL, an average of 72% of serum levels.[65] It is estimated that an exclusively breastfed infant would receive 1.7 mg/kg daily, 11–28% of a usual infant dosage.[38] No adverse effects were observed in the nursing infants.[65] The American Academy of Pediatrics classifies CS as compatible with breastfeeding.[42]
TRD	We were unable to find any data regarding the use of TRD during breastfeeding.

Table 2 (*continued*)

TB drug	Breast milk excretion/breastfeeding
Group C (EMB and PZA are included above in the first-line drugs)	
DLM	We were unable to find any data regarding the use of DLM during breastfeeding.
Carbapenums	Three carbapenems, members of the β-lactam class of antibiotics, are recommended by the WHO for the treatment of RR-TB. These include imipenem-cilastatin (Imp/Cln), meropenem and ertapenem. There have been reports of disruption of the infant's gastrointestinal flora with β-lactam antibiotics, resulting in diarrhoea or thrush. However, these effects have not been adequately evaluated.[45] Imp/Cln Small amounts of Imp/Cln are excreted into breast milk, amounts which are comparable to other β-lactam antibiotics.[66] There are no known reports describing the use of Imp/Cln during breastfeeding, so the effects of this exposure on a breastfed infant are unknown. However, Imp/Cln can be used to treat breastfeeding mothers.[45] MPM As the molecular weight of MPM is low (about 384), MPM is excreted into breast milk. There are two case reports documenting levels of MPM in breast milk and the effects of exposure on infants: • One mother who exclusively breastfed her infant took MPM (3 g/day) for 7 days.[67] The average and maximum MPM concentrations of respectively 0.48 and 0.644 μg/mL were reported; this gave an estimated infant dose of 97 μg/kg/day. No adverse effects in the infant were noted. • A second mother breastfed her infant for four months.[68] At 2 months, the mother was treated with a 2-week course of MPM and tobramycin (doses not specified) for a cystic fibrosis exacerbation with no change in the infant's stool pattern. At 6 months, the infant's renal function was normal. Given the absence of toxic effects in the nursing infants, it appears that MPM is compatible with breastfeeding. However, as data are so limited, breastfed infants should be monitored for the most common adverse effects observed in adult patients: headache, nausea, constipation, diarrhoea, anaemia, vomiting and rash. [69] ETP There is one study documenting drug levels of ETP in five lactating mothers and their infants.[70] The women received 1 g ETP daily for 5–14 days postpartum, for acute pelvic infections. Breast milk samples were obtained before the first dose, twice during the 24 h after the last dose and daily in the morning 2–5 days after the last dose. Milk concentrations during the first 24 h of the last dose ranged from <0.125 mg/L to 0.3 mg/L. Milk concentration was <0.125 mg/L by Day 3 in four of the women and after 5 days in the fifth. This limited information suggests that as the concentration of ETP in breast milk is low, it is unlikely to cause adverse effects in breastfed infants and can be used in lactating mothers.
Aminoglycosides	Two of the four aminoglycosides (AMK and SM) are presently included in the WHO treatment guidelines. KM and CPM are no longer recommended in the treatment of RR-TB and are included at the bottom of the table under drugs used previously. The use of aminoglycosides in pregnancy is avoided because of the potential for otoxicity and deafness.[71,72] However, as oral absorption of the aminoglycosides is poor, the risk of ototoxicity from breastfeeding is not expected. In three of the four aminoglycosides (AMK, KM and SM), the potential problems for a breastfed infant include modification of bowel flora, direct effects on the infant and interference with interpretation of culture results if a fever workup is required.[48] AMK AMK is excreted into breast milk in low concentrations. In three separate case reports, AMK drugs levels in the breast milk of lactating women were documented. In all three instances, after a single dose of 100 mg AMK intramuscularly, only traces of the drug were found 2 and 6 h after the dose.[73–75] As oral absorption is poor, ototoxicity in infants exposed to AMK is not expected and is considered compatible with breastfeeding.[45] SM SM is poorly excreted into breast milk and milk:plasma ratios of 0.5–1.0 have been reported.[76] In a Russian study, 46 women received a 1 g intramuscular dose of SM resulting in a peak SM milk level of 2.6 mg/L.[77] The American Academy of Pediatrics classifies SM as compatible with breastfeeding.[42]
ETH	The relatively low molecular weight (about 166) suggests that the drug will be secreted into breast milk, but there are no reports describing the amount in milk. There is one report of infants exposed to ETH in breast milk who had developmental problems, but their mothers were exposed to several drugs during pregnancy and breastfeeding, so the problems cannot be attributed to ETH.[78] Although the effect of ETH exposure on an infant is unknown, breastfeeding should not be discouraged in a woman who is breastfeeding.[45] If possible however, an alternate drug maybe preferred.
PTH	We were unable to find any data regarding its use during breastfeeding.
PAS	PAS is excreted into breast milk. One lactating woman took a single 4 g oral dose of PAS. A peak milk level of 1.1 mg/L occurred at 3 h after the dose. The drug's half-life in milk was estimated to be 2.5 h.[43] Using these data, a fully breastfed infant would receive a maximum of about 0.25% of the maternal weight-adjusted dosage. No published information on levels of PAS in infants was found. This limited information indicates that maternal PAS produces low levels in milk and would not cause any adverse effects in breastfed infants, especially if the infant is older than 2 months. Exclusively breastfed infants should be monitored for rare instances of jaundice, gastrointestinal disturbances, hypokalemia, thrombocytopenia and haemolysis if this drug is used during lactation. [79]
Pretomanid	We were unable to find any data regarding its use during breastfeeding.

Table 2 (*continued*)

TB drug	Breast milk excretion/breastfeeding
Drugs used previously, but not included in the current WHO treatment guidelines	
Quinolone	OFX OFX, an early generation quinolone, is no longer recommended by the WHO in 2018 for the treatment of RR-TB.[52] OFX is excreted into breast milk in concentrations similar to those in maternal serum.[53, 80] Ten breastfeeding women were each given three oral doses of 400 mg OFX.[80] Six simultaneous serum and milk samples were drawn between 2 and 24 h after the third dose of the antibiotic. Milk concentrations were similar to maternal serum concentrations peaking at 2 h (2.41 μg/mL) and falling to 0.05 μg/mL at 24 h. The mean milk:serum ratio varied from 0.98 to 1.66, with the highest ratio occurring 24 h after the last dose. The American Academy of Pediatrics classifies OFX as compatible with breastfeeding.[42]
Aminoglycosides	The following two aminoglycosides were not recommended by the WHO in 2018 for the treatment of RR-TB.[52] KM KM is excreted into breast milk and milk:plasma ratios of 0.05–0.40 have been reported.[76] A lactating mother was given a 1 g intramuscular dose of KM and a peak milk level of 18.4 μg/mL was reported.[81] No effects in breastfed infants have been reported. The American Academy of Pediatrics classifies KM as compatible with breastfeeding.[42] CPM The molecular weight (about 653–669) suggests that the drug will be excreted into breast milk. However, no studies reporting the excretion of CPM into breast milk or infants were located. Given that <1% of an oral dose is absorbed by adults, the risk, if any, to a nursing infant will be minimal.[48] There is one case report of two breastfed infants whose mothers had RR-TB, for which they received intravenous CPM and other anti-tuberculosis drugs.[82] No other details were available, but the long-term follow-up revealed no evidence of CPM-induced toxicity. Given the dearth of information available, the effect of CPM exposure on a breastfed infant is unknown. However, as CPM is not orally absorbed, it is unlikely to adversely affect the breastfed infant.[45]
CLM	CLM is excreted into breast milk. There are three studies reporting drug levels in breast milk and the exposed infant, two of which also report the risk of infantile hypertrophic pyloric stenosis in infants exposed to CLM: • Twelve breastfeeding mothers were given 250 mg CLM twice daily. Both the parent drug and metabolite were excreted into milk.[83] Peak levels were measured at respectively 2.2 and 2.8 h and the half-lives of the drug and metabolite were respectively 4.3 and 9 h. The combined exposure for an exclusively breastfed infant was ~2% of the mother's weight-adjusted dose.[85] • In 2003, a cohort study with 1 166 women investigated the association between maternal use of macrolides (including CLM) and infantile hypertrophic pyloric stenosis.[84] The 1 166 breastfeeding women who were prescribed a macrolide from birth to 90 days post-natally were compared to 41 778 controls. The OR for stenosis was 2.3–3.0, depending on the postnatal period of exposure (42, 56, 70, or 90 days), but no ORs were significant. When stratified by sex, the ORs for male infants was 1.8–3.1, but this was not significant. The ORs for females at 70 and 90 days post-birth were 10.3 and 7.5, but only the 70 day OR was significant (95%CI 1.2–92.3). • In an Israeli study, 55 breastfed infants exposed to a macrolide (including CLM) were compared to 36 infants exposed to AMX to investigate the possible association between macrolide exposure in milk and infantile hypertrophic pyloric stenosis.[85] The rates of adverse reactions were comparable with 7 (12.7%) in the macrolide group experiencing an adverse reaction (rash, diarrhoea, loss of appetite, somnolence), compared to 3 infants (8.3%) in the AMX group. No cases of infantile hypertrophic pyloric stenosis were observed. Given the limited information available, the effect of CLM exposure on a breastfed infant is unknown.[45] However, given the low levels of CLM in breast milk and safe administration directly to infants, adverse events are unlikely and breastfeeding should not be discouraged in women who need to be treated with CLM.[45] However, the infant should be monitored for possible effects on the gastrointestinal flora, such as diarrhoea, thrush and diaper rash.
AMX-CLV/augmentin	Limited information on AMX-CLV is available. Based on AMX data, it has been determined that an exclusively breastfed infant will receive a maximum of 0.1 mg/kg daily of AMX with a maternal AMX-CLV dose of 500 mg 3 times daily.[86] This amounts to 0.25% to 0.5% of the recommended infant dose of AMX-CLV. There are two case reports documenting the effect of AMX-CLV exposure in breastfed infants: • In a prospective study with 67 breastfeeding women, 15 infants (22%) had adverse events which increased with an increase in dosing. All adverse effects were minor and self-limiting, and did not require interruption of breastfeeding, suggesting that AMX-CLV may be safe during lactation.[87] However, larger studies are needed to confirm this finding. • In a case-report of a single month-old infant breastfed since birth, the mother developed mastitis and was treated with 1 g AMX-CLV orally every 12 h and 160 g gentamicin intramuscularly once daily. The infant was breastfed for 10 min, starting 15 min after the first dose of both drugs and 20 min later developed a generalised urticaria which disappeared after 30 min. A few hours later, the infant breastfed again and the urticaria reappeared. After switching to formula feeding, the reaction did not reappear, suggesting that the adverse reaction was related to antibiotic exposure. Although it is not possible to conclusively determine which drug that caused the reaction, AMX-CLV was the most likely candidate. [88] The limited information available suggests that adverse reactions in infants exposed to AMX-CLV are uncommon and it can be used in breastfeeding mothers.[45]

TB = tuberculosis; INH = isoniazid; PZA = pyrazinamide; EMB = ethambutol; RBT = rifabutin; RIF = rifampicin; RPT = rifapentine; WHO = world health organization; RR-TB = rif-resistant tb; LVX = levofloxacin; MFX = moxifloxacin; OFX = ofloxacin; CS = cycloserine; TRD = terizidone; DLM = delamanid; IMP/CLN = imipenem/cilastatin; MPM = meropenem; ETP = ertapenem; AMK = amikacin; SM = streptomycin; KM = kanamycin; CPM = capreomycin; ETH = ethionamide; PTH = prothionamide; PAS = para-aminosalicylic acid; CLM = clarithromycin; OR = odds ratio; CI = confidence interval; AMX-CLV = amoxicillin-clavulanic acid.

though there was clear evidence of HIV transmission in breast milk, women were encouraged to breastfeed because of multiple benefits before widespread access to antiretroviral therapy. One wonders why despite such well-documented benefits and the possibly small risk of exposure to second-line TB drugs in the child, breastfeeding is still discouraged.

Although breastfeeding is recommended for women with DS-TB once they are no longer considered 'infectious', persons with RR-TB may be infectious for a longer period of time, as second-line therapy is less efficacious. This 'uncertainty' is illustrated in the patient scenario, with a resultant increase in the patient's anxieties and fears for her own health and the health of her child. Determining 'infectiousness' in patients with RR-TB is a research priority, not only for lactating women, but also for those infected with RR-TB.

To reduce the chance of transmission in the household and to her infant, Ms Shandu and many other patients with RR-TB were encouraged to wear masks. However, it is uncertain as to which type of mask reduces the risk of TB transmission to the infant in a woman with RR-TB who is still infectious and breastfeeding: 1) an N95 mask worn by the mother; 2) a scarf or piece of cloth wound round the mouth of the mother; or 3) a surgical mask worn by the infant.

Moreover, policy must also be feasible and implementable. To reduce the risk of transmission in the household, Ms Shandu and many other patients with RR-TB are encouraged to wear masks, which are not provided. If the provision of masks to RR-TB patients is not funded, governments either need to find the money to do so or such recommendations amount to 'lip service' that cannot be followed. It cannot be expected that Ms Shandu would find and buy her own masks in the rural area where she lives, and it is possible that the recommendation only increased her anxiety and fears about transmitting RR-TB to her baby. Given that she was on effective therapy, it is uncertain as to whether the recommendation was even necessary.

Risks and benefits of all second-line TB drugs

A robust analysis of the overall risks and benefits of the second-line TB drugs is therefore vital. Enhanced knowledge regarding the safety and efficacy of second-line TB drugs will improve treatment and pregnancy outcomes and minimise the risk of neonatal RR-TB infection.

A safety profile of all second-line TB drugs

BDQ is a highly effective medication that has been shown to reduce mortality and is strongly recommended for the treatment of RR-TB.[29,30] Even if it is found in breast milk, it is debatable whether women should be denied access to this lifesaving drug. The WHO recommends that drugs with a safety profile that is 'better established' should be used. However, it is unclear which drugs have a better-established safety profile, as most second-line TB drugs have not been formally studied in breastfeeding women. Healthy, non-infectious women are essential for the lives and health of their children and therefore should be given the most robust therapy possible in order to ensure treatment success. A safety profile of all second-line TB drugs is needed.

The safety of exposing infants to second-line TB treatment through breastfeeding

The effect of second-line TB drug exposure through breast milk on infants and the long-term consequences of this exposure on the quality of life and the physical, emotional, behavioural and cognitive development in children is unknown. Pregnant and lactating women should be included in expanded access programmes to new regimens for RR-TB. Rigorous monitoring of women and infants included in these programmes will provide data on the safety of exposing infants to second-line TB treatment through breastfeeding. In addition, longitudinal cohort studies of children exposed to second-line TB treatment during breastfeeding will provide information on the long-term consequences of this exposure on the quality of life and the physical, emotional, behavioural and cognitive development of these children.

Optimal dosing of second-line TB drugs in pregnant, postpartum and breastfeeding women is unknown

Very little is known about the concentrations of second-line TB drugs in pregnant woman and how these vary pre- and post-term. Similarly, little is known about the pharmacokinetics of these drugs in breast milk or in breastfed infants. There are some data from case reports and small case series describing drug concentrations of second-line drugs secreted into breast milk, with subsequent infant exposure (Table 2), but these data are limited for old, novel and repurposed second-line TB drugs alike. A better understanding of the effects of pregnancy on the pharmacokinetics of second-line TB drugs will enhance dose optimisation. Determining the concentrations of second-line TB drugs in breastfed infants is important, as therapeutic concentrations could protect the infant, obviating the need for preventive therapy; it should be noted that toxic concentrations could cause harm, and sub-therapeutic concentrations could select for resistance in those infants who develop RR-TB. This information will inform the practice of clinicians managing pregnant women who require second-line TB treatment.

CONCLUSIONS

TB in all its forms is commonly found in women of childbearing age, and there are thousands of TB-

affected women each year who must make choices about optimal feeding practices for their children. While the risk of TB transmission through breast milk has not been documented, concerns about airborn transmission of TB during feeding and possible drug exposure for infants receiving breast milk have led to complicated recommendations for nursing mothers, especially regarding women with RR-TB. Current policy recommendations are clear for DS-TB, but confusing and lacking evidence for RR-TB. Further research is clearly needed, but in the meantime, women who are breastfeeding while on TB treatment must be offered compassionate counselling that is mindful of their psychosocial and socio-economic situations. While it can be a challenge to convey the true uncertainty that exists around RR-TB and breastfeeding, offering guidance in a supportive way can help improve the quality of life for both mothers and their infants. Physicians, nurses counsellors and mothers are all partners with a shared goal of providing the best possible nutrition for growing babies. Regardless of what feeding decision is made, the children will need to be followed over time to ensure they are doing well. Participatory conversations in which the concerns and values of all parties can be expressed in a respectful manner will foster the best environment for children and their mothers when their families are facing TB.

Acknowledgements

The authors thank W Odendaal for his support with the literature review.

This work was supported by the South African Medical Research Council, Cape Town, South Africa.

The funder had no role in study design; the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. All researchers were independent of funders and sponsors.

Conflicts of interest: none declared.

References

1 World Health Organization. Global tuberculosis report, 2019. WHO/CDS/TB/2019.15. Geneva, Switzerland: WHO, 2019.
2 Mathad J S, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. Clin Infect Dis 2012; 55: 1532–1549.
3 Mnyani C, McIntyre J. Tuberculosis in pregnancy. BJOG 2011; 118: 226–231.
4 Grange J, Adhikari M, Ahmed Y, et al. Tuberculosis in association with HIV/AIDS emerges as a major nonobstetric cause of maternal mortality in Sub-Saharan Africa. Int J Gynaecol Obstet 2010; 108: 181–183.
5 Sugarman J, Colvin C, Moran A, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. Lancet Global Health 2014; 2: e710–e716.
6 Ribeiro P, Jacobsen K, Mathers C, Garcia-Moreno C. Priorities for women's health from the Global Burden of Disease study. Int J Gynaecol Obstet 2008; 102: 82–90.
7 Aquilina S, Winkelman T. Tuberculosis: a breast-feeding challenge. J Perinat Neonat Nurs 2008; 22: 205–213.
8 Gupta A, Hughes M, Garcia-Prats A, McIntire K, Hesseling A. Inclusion of key populations in clinical trials of new antituberculosis treatments: Current barriers and recommendations for pregnant and lactating women, children, and HIV infected persons. PLoS Med 2019; 16: e1002882.
9 Federal Drug Agency. Full prescribing information: SIRTURO. Washington DC, USA: FDA, 2012. https: //www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf. Accessed June 2019.
10 South African National Department of Health. Interim clinical guidance for the implementation of injectable-free regimens for rifampicin resistant tuberculosis in adults, adolescents and children. Pretoria, South Africa; NDoH, 2018. https: // tbsouthafrica.org.za/resources/interim-clinical-guidance-implementation-injectable-free-regimens-rifampicin-resistant.
11 Lawrence R, Lawrence R. Given the benefits of breastfeeding, what contraindications exist? Pediatr Clin N Am 2001; 48: 235–251.
12 Mittal H, Das S, Faridi M. Management of newborn infant born to mother suffering from tuberculosis: current recommendations & gaps in knowledge. Indian J Med Res 2014; 140: 32–39.
13 Adamczick C, Feiterna-Sperling C, Brinkmann F, et al. S2k-Leitlinie zur Diagnostik, Prävention und Therapie der Tuberkulose im Kindes- und Jugendalter. Pneumologie 2017; 71: 629–680. [German]
14 Di Comite A, Esposito S, Villani A, et al. How to manage neonatal tuberculosis. J Perinatol 2016; 36: 80–85.
15 Cattamanchi A, Davis J L, Worodria W, et al. Sensitivity and specificity of fluorescence microscopy for diagnosing pulmonary tuberculosis in a high HIV prevalence setting. Int J Tuberc Lung Dis 2009; 13: 1130–1136.
16 Pfyffer G E, Wittwer F. Incubation time of mycobacterial cultures: how long is long enough to issue a final negative report to the clinician? J Clin Microbiol 2012; 50: 4188–4189.
17 Mishra H, Reeve B, Palmer Z, et al. Xpert MTB/RIF Ultra and Xpert MTB/RIF for diagnosis of tuberculosis in an HIV-endemic setting with a high burden of previous tuberculosis: a two-cohort diagnostic accuracy study. Lancet Respir Med 2020; doi.org/10.1016/S2213-600(19)30370-4.
18 Dharmadhikari A, Mphahlele M, Venter K, et al. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2014; 18: 1019–1025.
19 Salazar-Austin N, Hoffmann J, Cohn S, et al. Poor obstetric and infant outcomes in human immunodeficiency virus-infected pregnant women with tuberculosis in South Africa: The Tshepiso Study. Clin Infect Dis 2018; 66: 921–929.
20 Lienhardt C, Sillah J, Fielding K, et al. Risk factors for tuberculosis infection in children in contact with infectious tuberculosis cases in the Gambia, West Africa Pediatrics 2003; 111: 608–614.
21 Kenyon T, Creek T, Laserson K, et al. Risk factors for transmission of *Mycobacterium tuberculosi*s from HIV-infected tuberculosis patients, Botswana. Int J Tuberc Lung Dis 2002; 6: 843–850.
22 Seddon J A, Hesseling A C, Godfrey-Faussett P, Fielding K, Schaaf H S. Risk factors for infection and disease in child contacts of multidrug-resistant tuberculosis: a cross-sectional study. BMC Infect Dis 2013; 13: 392.
23 Schaberg T, Bauer T, Brinkmann F, et al. S2k-Leitlinie: Tuberkulose im Erwachsenenalter. Pneumologie 2017; 71: 325–397. [German]
24 Nahid P, Dorman S, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/ Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis 2016; 63: 853–867.
25 Nahid P, Dorman SE, Alipanah N, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of

America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis 2016; 63: 853–867.
26 Lim F, Lovering A, Currie A. Linezolid and lactation: measurement of drug levels in breast milk and the nursing infant. J Antimicrob Chemother 2017; 72: 2677–2678.
27 Tran J, Montakantikul P. The safety of antituberculosis medications during breastfeeding. J Hum Lact 1998; 14: 337–340.
28 Venkatesan K, Mathur A, Girdhar A, Girdhar B. Excretion of clofazimine in human milk in leprosy patients. Lepr Rev 1997; 68: 242–246.
29 Mbuagbaw L, Guglielmetti L, Hewison C, et al. Outcomes of bedaquiline treatment in patients with multidrug-resistant tuberculosis. Emerg Infect Dis 2019; 25: 936–943.
30 Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med 2018; 6: 699–706.
31 World Health Organization. Treatment of tuberculosis guidelines. 4th ed. Geneva, Switzerland: WHO, 2010. https://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833_eng.pdf;jsessionid=B96BED214F727B8351FF31758A2432A9?sequence=1.
32 World Health Organization. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. 2nd ed. Geneva, Switzerland: WHO, 2014. https://apps.who.int/iris/bitstream/handle/10665/112360/9789241548748_eng.pdf?sequence=1.
33 World Health Organization. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update. WHO/CDS/TB/2018.15. Geneva, Switzerland: WHO, 2018.
34 World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2014.11. Geneva, Switzerland: WHO, 2014.
35 Center for Disease Control and Prevention. Tuberculosis in special populations. Atlanta, GA, USA. https://www.cdc.gov/tb/topic/populations/pregnancy/default.htm Accessed October 2018.
36 South African National Department of Health. National tuberculosis management guidelines, 2014. Pretoria, South Africa: NDoH, 2014. http://www.tbonline.info/media/uploads/documents/ntcp_adult_tb-guidelines-27.5.2014.pdf.
37 Curry International Tuberculosis Center. Curry International Tuberculosis Center. Drug-resistant tuberculosis: a survival guide for clinicians. 3rd ed. San Francisco, CA, USA: Curry International, 2018. https://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition.
38 Snider D J, Powell K. Should women taking antituberculosis drugs breast-feed? Arch Intern Med 1984; 144: 589–590.
39 Berlin C J, Lee C. Isoniazid and acetylisoniazid disposition in human milk, saliva and plasma. Fed Proc 1979; 38: 426.
40 Vorherr H. Drugs excretion in breast milk. Postgrad Med 1974; 56: 97–104.
41 Ricci G, Copaitich T. Modalta di eliminazione dili'isoniazide somministrata per via orale attraverso il latte di donna. Rass Clin Ter 1954-5; 209: 53–54. [Italian]
42 American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics 2001; 108: 776–789.
43 Holdiness M. Antituberculosis drugs and breast-feeding. Arch Intern Med 1984; 144: 1888.
44 Keskin N, Yilmaz S. Pregnancy and tuberculosis: to assess tuberculosis cases in pregnancy in a developing region retrospectively and two case reports. Arch Gynecol Obstet 2008; 278: 451–455.
45 US National Library of Medicine. Drugs and Lactation Database (LactMed) [Internet]. Bethesda, MD, USA: US National Library of Medicine: 2006-. https://www.ncbi.nlm.nih.gov/books/NBK547442/ Accessed March 2020.
46 Partosch F, Mielke H, Stahlmann R, Gundert-Remy U. Exposure of nursed infants to maternal treatment with ethambutol and rifampicin. Basic Clin Pharmacol Toxicol 2018; 123: 213–220
47 Rothstein D M. Rifamycins, alone and in combination. Cold Spring Harb Perspect Med 2016; 6: a027011.
48 Briggs G, Freeman R, Yaffe S. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th ed. Philadelphia, PA, USA: Wolters Kluwer Health, 2015.
49 Blumberg H, Burman W, Chaisson R, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003; 167: 603–662.
50 Lenzi E, Santuari S. Preliminary observations on the use of a new semi-synthetic rifamycin derivative in gynecology and obstetrics. Atti Accad Lancisiana Roma 1969; 13: 87–94.
51 Peters C, Nienhaus A. Case report—tuberculosis in a health care worker during pregnancy Pneumologie 2008; 62: 695–698.
52 World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva, Switzerland: WHO, 2019.
53 Ortho-McNeil Pharmaceutical. Product information. Floxin. Raritan, NJ, USA: Ortho-McNeil Pharmaceutical, 2000.
54 Gurpinar A, Balkan E, Kilic N, Kiristioglu I, Dogruyol H. The effects of a fluoroquinolone on the growth and development of infants. J Int Med Res 1997; 25: 302–306.
55 van den Oever H, Versteegh F, Thewessen E, Vand den Anker J, Mouton J, Neijens H. Ciprofloxacin in preterm neonates: case report and review of the literature. Eur J Pediatr 1998; 157: 843–845.
56 Cahill J J, Bailey E, Chien S, Johnson G. Levofloxacin secretion in breast milk: a case report. Pharmacotherapy 2005; 25: 116–118.
57 Janssen Therapeutics. Product information. Sirturo. Beerse, Belgium; Janssen Therapeutics, 2012.
58 Rowe H, Felkins K, Cooper S, Hale T. Transfer of linezolid into breast milk. J Hum Lact 2014; 30: 410–412.
59 Sagirli O, Onal A, Toker S, Oztunc A. Determination of linezolid in human breast milk by high-performance liquid chromatography with ultraviolet detection. J AOAC Int 2009; 92: 658–662.
60 Lim F, Lovering A, Currie A. Linezolid and lactation: Measurement of drug levels in breast milk and the nursing infant. J Antimicrob Chemother 2017; 72: 2677–2678.
61 Venkatesan K, Mathur A, Girdhar A, Girdhar B. Excretion of clofazimine in human milk in leprosy patients. Lepr Rev 1997; 68: 242–246.
62 Browne S, Hogerzeil L. 'B 663' in the treatment of leprosy. Preliminary report of a pilot trial. Lepr Rev 1962; 33: 6–10.
63 Waters M. G 30 320 or B 663—Lampren (Geigy). A working party held at the Royal Garden Hotel London, September 1968. Lepr Rev 1969; 1: 21–47.
64 Ozturk Z, Tatliparmak A. Leprosy treatment during pregnancy and breastfeeding: a case report and brief review of literature. Dermatol Ther 2017; 30: e12414.
65 Morton R, McKenna M, Charles E. Studies on the absorption, diffusion, and excretion of cycloserine. Antibiot Annu 1955–1956; 3: 169–172.
66 Matsuda S, Suzuki M, Oh K, et al. Pharmacokinetic and clinical studies on imipenem/cilastatin sodium in the perinatal period. Jpn J Antibiot 1988; 11: 1731–1741.
67 Sauberan J, Bradley J, Blumer J, Stellwagen L. Transmission of meropenem in breast milk. Pediatr Infect Dis J 2012; 31: 832–834.
68 Festini F, Ciuti R, Repetto T ea. Safety of breast-feeding during an IV tobramycin course for infants of CF women (abstract). Pediatr Pulmonol Suppl 2004; 27: 288–289.

69 APP Pharmaceuticals. Product information. Meropenem. Los Angeles, CA, USA: APP Pharmaceuticals, 2013.
70 Food & Drug Administration. Center for Drug Evaluation and Research. Clinical pharmacology and biopharmaceutics reviews. NDA 21-337. Silver Spring, MD, USA: FDA, 2008: pp 37–40.
71 Davidson P. Managing tuberculosis during pregnancy. Lancet 1995; 346: 199–200.
72 Robinson C, Rose N C. Tuberculosis: current implications and management in obstetrics. Obstet Gynecol Surv 1996; 51: 115–124.
73 Matsuda C, Mori C, Maruno M, Shiwakura T. A study of amikacin in the obstetrics field. Jpn J Antibiot 1974; 27: 633–636.
74 Yuasa M. A study of amikacin in obstetrics and gynecology. Jpn J Antibiot 1974; 27: 377–381.
75 Matsuda S. Transfer of antibiotics into maternal milk. Biol Res Pregnancy Perinatol 1984; 5: 57–60.
76 Wilson J. Milk/plasma ratios and contraindicated drugs. In: Wilson JT, ed. Drugs in breast milk. Balgowlah, NSW, Australia: ADIS Press, 1981.
77 Rudneva N. Effect of penicillin and streptomycin on lactation in parturients. Akush Ginekol (Mosk) 1967; 43: 48–52.
78 Drobac P C, del Castillo H, Sweetland A, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: long-term follow-up of 6 children with intrauterine exposure to second-line agents. Clin Infect Dis 2005; 40: 1689–1692.
79 Holdiness M. Antituberculosis drugs and breast-feeding. Letter. Arch Intern Med 1984; 144: 1888.
80 Giamarellou H, Kolokythas E, Petrikkos G, Gazis J, Aravantinos D, Sfikakis P. Pharmacokinetics of three newer quinolones in pregnant and lactating women. Am J Med Qual 1989; 87: 49S–51S.
81 O'Brien T. Excretion of drugs in human milk. Am J Hosp Pharm 1974; 31: 844–854.
82 Shin S, Pasechnikov A, Gelmanova I, et al. Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia. Int J Tuberc Lung Dis 2006; 10: 402–408.
83 Sedimayr T, Peters F, Raasch W, Kees F. Clarithromycin, a new macrolide antibiotic: effectiveness in puerperal infections and pharmacokinetics in breast milk. Geburtshilfe Frauenheilkd 1993; 53: 488–491.
84 Sorensen H, Skriver M, Pedersen L, Larsen H, Ebbesen F, Schonheyder H. Risk of infantile hypertrophic pyloric stenosis after maternal postnatal use of macrolides. Scand J Infect Dis 2003; 35: 104–106.
85 Goldstein L, Berlin M, Tsur L, Bortnik O, Binyamini L, Berkovitch M. The safety of macrolides during lactation. Breastfeed Med 2009; 4: 157–200.
86 Kafetzis D, Siafas C, Georgakopoulos P, Papadatos C. Passage of cephalosporins and amoxicillin into the breast milk. Acta Paediatr Scand 1981; 70: 285–288.
87 Benyamini L, Merlob P, Stahl B, et al. The safety of amoxicillin/clavulanic acid and cefuroxime during lactation. Ther Drug Monit 2005; 27: 499–502.
88 Cherif F, El Aidli S, Kastalli S. Drug induced urticaria via breastfeeding. Abstract 203. Fundam Clin Pharmaco 2009; 23: 37.

RÉSUMÉ

Le lait maternel est le meilleur aliment pour les nouveaux-nés et les nourrissons. Chez les femmes atteintes de TB, le risque de transmission au nouveau-né et la possibilité d'exposition aux médicaments via le lait maternel a créé une incertitude en ce qui concerne les meilleures pratiques d'alimentation. Pour les femmes atteintes de TB pharmacosensible (DS-TB) qui ne sont plus contagieuses, l'allaitement maternel est sûr car le lait maternel ne contient pas de bacilles de *Mycobacterium tuberculosis* et seulement très peu ou pas de médicaments passent dans le lait maternel. En conséquence, la majorité des directives encourage l'allaitement maternel en cas de DS-TB. Il reste cependant une incertitude et les directives varient en ce qui concerne les femmes atteintes de DS-TB qui sont encore contagieuses et celles qui sont résistantes à la rifampicine (RR-TB). Bien que les dynamiques de transmission de la DS- et de la RR-TB soient similaires, comme les médicaments de deuxième ligne peuvent être moins efficaces et que le traitement préventif n'est pas largement offert aux nourrissons, des précautions supplémentaires de lutte contre l'infection peuvent être nécessaires pour la RR-TB jusqu'à ce que la mère réponde au traitement. Il n'y a de plus pas de données publiées décrivant à quel degré les médicaments de deuxième ligne passent dans le lait maternel ni l'exposition ultérieure des nourrissons qui le reçoivent. Les implications de cette limitation des informations disponibles en termes de politique et les dilemmes relatifs à la prise en charge des patients sont illustrés dans un scénario. Nous suggérons des domaines de recherche future.

RESUMEN

La leche materna aporta una nutrición óptima y se recomienda a los recién nacidos y los lactantes. En las mujeres con TB, debido al riesgo de transmisión de la enfermedad al recién nacido y la posibilidad de una exposición a los fármacos por la leche materna, ha existido incertidumbre con respecto a las mejores prácticas de alimentación. Las mujeres con TB farmacosensible (DS-TB) que ya no son contagiosas pueden practicar sin riesgo la lactancia materna, dado que la leche no contiene bacilos de *Mycobacterium tuberculosis* y solo pasan a la leche materna cantidades mínimas de fármacos, que no son tóxicas. Por consiguiente, la mayoría de las directrices recomienda la lactancia materna en las mujeres con DS-TB. Sin embargo, persisten dudas y divergencia en las directrices con respecto a las mujeres con DS-TB que aún son contagiosas y las mujeres con TB resistente a rifampicina (RR-TB). Si bien las dinámicas de transmisión de la DS-TB y la RR-TB son semejantes, dado que el tratamiento de segunda línea puede ser menos eficaz y que no se ofrece el tratamiento preventivo a los lactantes ampliamente, en los casos de RR-TB puede ser necesario adoptar precauciones complementarias de control de la infección hasta que la madre responda al tratamiento. Además, no existen datos publicados sobre la magnitud de la excreción de los fármacos de segunda línea en la leche materna ni la subsiguiente exposición de los lactantes que la reciben. Mediante la presentación de un caso, se abordan las consecuencias de la información limitada sobre las políticas y los consiguientes dilemas alrededor de la atención de las pacientes. El artículo propone esferas de investigación para el futuro.