

## Progress Towards the Elimination of Mother to Child Transmission of Syphilis in Ukraine

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Syphilis is one of the most common sexually transmitted infections (STIs) worldwide, with approximately 6 million new cases each year. If a pregnant woman who is infected with syphilis does not receive early and effective treatment, she can transmit the infection to her unborn infant. New estimates published by the World Health Organization (WHO) show that there were approximately 661,000 cases of congenital syphilis worldwide in 2016, resulting in more than 200,000 stillbirths and neonatal deaths (1).

In 2007 the WHO launched an initiative for the global elimination of congenital syphilis, setting country targets, as described in “The global elimination of congenital syphilis: rationale and strategy for action” (2).

The term “congenital syphilis” has traditionally been used to describe the adverse outcomes of syphilis infection in pregnancy. However, expert consensus from a global consultation in 2012 suggested that, whenever possible, the term “mother-to-child transmission of syphilis” should be used in place of “congenital syphilis” in order to increase awareness of the full spectrum of adverse outcomes, including stillbirths, neonatal deaths, premature and low-birth-weight infants, as well as deformities at birth (3).

The global community has committed itself to eliminating mother-to-child transmission (MTCT) of HIV and syphilis as a public health priority, as exemplified in the 2014 “WHO global guidance on criteria and processes for validation” (4).

Elimination is defined as a reduction to zero of the incidence of a disease or infection in a defined geographical area. However, because both HIV and syphilis remain public health issues, and prevention of MTCT measures are highly, but not 100%, effective, it is currently not possible to reduce the incidence of either infection to zero. Therefore, the goal for elimination of MTCT initiatives is to reduce MTCT of HIV and syphilis to a very low level.

The WHO has announced elimination of MTCT of HIV and syphilis in Cuba, Thailand, Belarus, Republic of Moldova (syphilis only), Armenia (HIV only), Anguilla, Montserrat, Malaysia, Cayman Islands, Bermuda, Antigua and Barbuda, St

Christopher Nevis, and Maldives (5). While other countries are on the way to achieving those targets, a recent report from the European Center for Disease Control and Prevention (CDC) highlighted an alarming rate of MTCT of syphilis among infants in the USA (6). The CDC found that rates of CS and syphilis among women in Eastern Europe have decreased since 2005. However, it expressed concerns over the probably under-reporting of congenital syphilis in several member states and increasing syphilis rates among women in some western EU/EEA countries (7).

The objective of this study was to analyse cases of MTCT of syphilis in Ukraine in order to describe potential risk factors; knowledge that will help in working to eliminate this infection according to the WHO target and indicators.

### METHODS

#### *Study design and study population*

This retrospective study is based on a survey of the number of MTCT cases of syphilis from 14 regions of Ukraine and Kyiv, the city capital of Ukraine, during the period 2002 to 2007. The survey included epidemiological, sociodemographic, clinical and serological data for infants with MTCT of syphilis and their mothers. The survey was completed by dermatovenereologists, who diagnosed the cases of MTCT of syphilis and submitted the notification forms. The survey was approved by order of the Ministry of Health in 2002 (order number 14, from 17 Jan 2002) when the incidence of cases of MTCT, as well as syphilis in general, in Ukraine was high. The Wassermann test and the cardiolipin-based microprecipitation assay (MPR) were used as screening tests for pregnant women with syphilis, while rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL), the WHO-recommended tests, are not in routine use. To confirm the diagnosis, samples found to be reactive on non-treponemal tests were subsequently tested with assays that detect treponemal antibodies, such as fluorescent treponemal antibody (FTA) or enzyme-linked immunosorbent assay (ELISA).

The assessment of laboratory services, human rights and community participation were not part of this work.

### Statistical analysis

The survey was statistically processed using STATISTICA 7.0 and MS Excel XP. The statistics presented in this study are descriptive only.

In order to facilitate international contextualization of the findings, we used the case definition of MTCT of syphilis from European STI guidelines which distinguishes between confirmed and presumed congenital infection (8), as follows:

- An infant was classified as a *presumed case* when: (i) it was born to an inadequately treated or untreated mother (regardless of signs in the infant); (ii) an infant had a positive serological test for syphilis and any of the following: evidence of MTCT of syphilis on physical examination, placental changes, confirmed necropsy;
- An infant was classified as a *confirmed case* when *Treponema pallidum* was identified by darkfield microscopy of lesions, placenta, umbilical cord, or necropsy (no such case was reported).

Adequate treatment was defined according to the WHO as the administration of parenteral penicillin (9). Whereas the WHO and CDC treatment guidelines recommend treatment with long-acting benzathine penicillin G (BPG) for primary, secondary, and all forms of latent syphilis during pregnancy, standard treatments in Ukraine include either long-acting or daily doses of short-acting (aqueous or procaine) penicillin G preparations. Therefore, we defined adequate treatment as the administration of long-acting or short-acting penicillin G regimens, completed at least 30 days before delivery.

## RESULTS

### Characteristics of infants with mother-to-child transmission of syphilis

A total of 107 registered cases of MTCT of syphilis were identified from the 14 regions of Ukraine and Kyiv. Five infants were excluded from the study because their diagnosis was not consistent with the case definition of MTCT of syphilis. Syphilis serology data were available for all the infants. All 102 cases of registered MTCT of syphilis in the newborns were defined as presumed, since *Treponema pallidum* was not identified by darkfield microscopy in any skin lesions or discharge.

Table I shows the characteristics of infants with MTCT of syphilis. The vast majority of these infants (85; 83.3%) had symptoms, compared with 13 (12.7%) without symptoms. Furthermore, 4 cases of stillbirth were registered with a range of gestation ages of 26.5–37.5 weeks.

The following clinical abnormalities were found in symptomatic cases of MTCT of syphilis: neurological symptoms, hepatosple-

Table I. Characteristics of newborns in general cohort (n = 102)

Characteristics	
Gestation age, weeks, mean±SD/ range	35.6±0.37/ 26–40.5
Weight, g, mean±SD/ range	2,458.81±62.99/ 903–3,850
Sex (female), n (%)	51 ww(50.0)
Symptomatic cases of MTCT of syphilis, total, n (%)	85 (83.3)
Neurological symptoms, n (%)	74 (73.5)
Hepatosplenomegaly, n (%)	62 (60.7)
Metaphyseal osteochondritis, n (%)	36 (35.2)
Diaphyseal periostitis, n (%)	23 (23.4)
Maculopapular skin rash, n (%)	28 (27.4)
Interstitial pneumonia, n (%)	10 (9.8)
Snuffles (sticky and bloody nasal discharge), n (%)	7 (6.9)
Anaemia (haemolytic and non-haemolytic), n (%)	44 (3.1)
Generalized non-tender lymphadenopathy, n (%)	8 (7.8)

SD: standard deviation; MTCTS: mother-to-child transmission of syphilis.

nomegaly, metaphyseal osteochondritis, diaphyseal periostitis, interstitial pneumonia, generalized non-tender lymphadenopathy, characteristic mucocutaneous lesions, haemolytic and non-haemolytic anaemia. Asymptomatic cases in newborns with untreated or inadequately treated mothers had only serological changes without clinical manifestations (Table I).

Infants with MTCT of syphilis were born at a mean±SD gestational age of 35.6±0.3 weeks and with a low birthweight of 2,459±63 g. Despite extensive treatment, including penicillin, 7 children (4 of them in the postneonatal period) in the age range 0.5–42 days died due to various severe complications of MTCT of syphilis, including multisystem organ failure. Furthermore, mothers of 11 babies (10.7% of all women) abandoned their maternity rights. I.e. some women with syphilis that gave birth to a child with CS, refuses to take the child from the maternity home due to stigmatization and later on abandoned their maternity rights.

### Characteristics of the mothers of infants with mother-to-child transmission of syphilis

Table II shows the characteristics of the mothers of infants with MTCT of syphilis. The mean age of mothers was 25.8±0.6 years, 50% were city residents, and 19.6% were non-residents of the city or town in which they delivered, 28.4% of women were living in the countryside. There were more single women (56.9%) than married or cohabitants (36.3%). More than half of the women had a secondary (54.9%), and few had a higher level of education (3.9%). However, almost 20% had incomplete secondary education.

At the time of maternity leave, the vast majority of women in all groups were unemployed or housewives. Syphilis was found in only 19 (18.6%) of partners/husbands of the pregnant women (data not shown).

Table II. Maternal characteristics in overall cohorts (n = 102)

Characteristics	n (%)
Age at delivery	
≤19 years	12 (11.8)
≥20 years	90 (88.2)
Place of residence	
City	51 (50)
Countryside	29 (28.4)
Non-resident	20 (19.6)
Education	
High	4 (3.9)
Secondary	56 (54.9)
Incomplete secondary	20 (19.6)
Marital status	
Married/cohabitant	37 (36.3)
Single	58 (56.9)
Unknown	7 (6.9)
Employment status	
Unemployed	40 (39.2)
Employed	32 (31.3)
Housewife	30 (29.4)
Primigravida	49 (48.0)
Time of 1 <sup>st</sup> prenatal visit	
1 <sup>st</sup> trimester	16 (15.7)
2 <sup>nd</sup> trimester	26 (25.5)
3 <sup>rd</sup> trimester	15 (14.7)
No prenatal care	45 (44.1)
Time of the first syphilis test	
1 <sup>st</sup> half of pregnancy	21 (20.6)
2 <sup>nd</sup> half of pregnancy	53 (51.9)
At delivery	23 (22.5)
After delivery	5 (4.9)
Stage of syphilis	
Secondary	16 (15.7)
Early latent	69 (67.6)
Late latent	3 (2.9)
Unknown	14 (13.7)
Time of prenatal treatment	
2 <sup>nd</sup> trimester	2 (2.0)
3 <sup>rd</sup> trimester	4 (3.9)
No treatment	96 (94.1)
Co-infections	
HIV	3 (3.8)
Tuberculosis	1 (0.9)
Gonorrhoea	5 (4.9)
Trichomoniasis	9 (8.8)

This study shows that 21.5% of women belonged to key groups and vulnerable populations, including alcohol abuse, drug abuse, or drug abuse of the partner, migrants, or immigrants. In addition to syphilis, 13.7% of pregnant women had other STIs (gonorrhoea, trichomoniasis), 3 women were co-infected with HIV, and 1 woman with tuberculosis (Table II).

Of the pregnant women with active syphilis, 44.1% received no prenatal care and 14.7% received care in the third trimester of pregnancy. Only 20.6% were tested during the first 20 weeks of pregnancy, 51.9% were tested in the second half of pregnancy, and the rest during (22.5%) or after childbirth (5%).

Among the 102 pregnant women who gave birth to infants with presumed MTCT of syphilis, most of the women had early syphilis; 69 (67.6%) had early latent syphilis, and 16 (15.7%) had secondary syphilis. Of the remainder of the women, 3 (2.9%) had late latent syphilis, and 14 (13.7%) had syphilis of unknown duration.

In addition to the main risk factors for MTCT of syphilis, such as absence of prenatal care and treatment, a number of other possible predictors were identified: delay in prenatal diagnosis and prenatal treatment, late infection/low laboratory quality assurance, iatrogenic mistakes, women refusing hospitalization for treatment, delivery at home, and reinfection (Table III).

For 16 cases of pregnant women who were infected with syphilis late in the third trimester, we conclude that their first syphilis serology testing was negative due to incubating syphilis. However, negative results could occur due to the low sensitivity of the Wasserman test and cardiolipin-based microprecipitation assay (MPR), which were used as a screening test assays.

## DISCUSSION

This study revealed that an alarming proportion (94.1%) of women with newborns diagnosed with MTCT of syphilis had not received prenatal treatment, and that 28% of the women had not had a syphilis test during pregnancy. Socio-demographic and behavioural characteristics revealed that most of the pregnant women (78.5%) who gave birth to infants with MTCT of syphilis did not belong to a risk group or vulnerable population and had access to women's facilities. These women were young, and a significant proportion were single (56.9%), although 36.3% were married or cohabiting. This indicates the need to enhance the programme for primary prevention of STI/HIV in the population of reproductive age in Ukraine.

The results of our study showed that approximately 57% of pregnant women visited women's facilities, but had not been properly diagnosed and treated, resulting in a loss of opportunity to prevent MTCT of syphilis in their babies. The study revealed a delay in diagnosis and treatment of pregnant women

Table III. Risk factors for mother-to-child transmission of syphilis

Characteristics	n (%)
Mothers without prenatal treatment	96 (94.1)*
Mothers without prenatal care	45 (44.1)
Delay with prenatal diagnosis and treatment	14 (13.7)
Late infection/low laboratory quality assurance	18 (17.6)
Iatrogenic mistakes	6 (5.9)
Women refusing hospitalization for treatment	4 (3.9)
Reinfection	1 (1.3)

\* $p < 0.05$ .

with suspicion of syphilis, due to the diagnostic requirements of performing confirmation tests in centralized laboratories. In addition, the current requirement for hospitalization of pregnant women in dermato-venereological wards leads to a delay in treatment, especially for those who live in remote areas. In these cases, the WHO STI guideline suggests performing an on-site rapid syphilis test (RST) rather than the standard off-site laboratory-based screening and treatment strategy (10).

In Ukraine, the rate of syphilis in pregnancy, as well as registered cases of MTCT of syphilis, has been decreasing continually for the last decade. Ukraine is currently approaching the target indicator for achieving elimination of MTCT of syphilis (case rate of congenital syphilis  $\leq 50$  per 100,000 live births). In addition to validating elimination of MTCT, countries must reach 3 process indicators: population-level antenatal coverage (at least one visit)  $\geq 95\%$ ; coverage of testing of pregnant women  $\geq 95\%$ ; treatment coverage of syphilis-seropositive pregnant women  $\geq 95\%$  (5). A high level of antenatal coverage and testing for syphilis during pregnancy was achieved in 2016–2018, although testing for syphilis has not reached the target of 95%. No country-level reporting on treatment in pregnant women diagnosed with syphilis is performed; hence this indicator is missing.

The specific strategies in any particular country for dual elimination of MTCT of HIV and syphilis are greatly influenced by differences in HIV and syphilis epidemiology, service delivery models, coverage of health services, and available resources. In 2017 in Ukraine, the rate of syphilis in women was 4 times higher than the mean rate in EU/EEA countries (5.6 versus 1.4 cases per 100,000 population). It is also worth noting that, due to conflict with Russia, the figures for the 5 previous years do not include new infections in the non-government-controlled areas of Donetsk and Luhansk regions. Rates among women were also high (more than 3 cases per 100,000 population) in other EU/EEA countries, such as Bulgaria, Hungary, Iceland, Latvia, Lithuania, Romania and Slovakia. In addition, in EU/EEA countries, the slight increase in rates of syphilis among women, which started in 2016, continued in 2017 (11).

Ukraine has the second-largest HIV epidemic in Eastern Europe and Central Asia and, moreover, between 2005 and 2014 the proportion of women who became HIV-positive through sexual transmission increased from 53% to 86% (12). This emphasizes that a dual strategy of elimination of MTCT of HIV and syphilis is substantiated. In addition, it is known that recent maternal syphilis infection is an independent risk factor for MTCT transmission of HIV (13).

It is important to emphasize that measurement of the elimination of MTCT of syphilis should not be limited only to those

women who attend clinics and who are in contact with the healthcare system. The indicators and targets are specifically set to be population-level indicators. Thus, they should be measured among the entire population of pregnant women and not just those who are part of a healthcare programme. There is no routinely collected information on prevention of MTCT of syphilis for women from key populations in Ukraine. Access to antenatal screening for vulnerable groups remains an issue in Ukraine as well in some EU/EEA countries (14, 15).

The WHO and CDC treatment guidelines recommend the use of long-acting benzathine penicillin G for treatment of all form of syphilis during pregnancy, except neurosyphilis (15). In contrast, daily doses of short-acting aqueous benzylpenicillin preparations (intramuscular or intravenous) are usually prescribed for pregnant women, especially in the second half of pregnancy according to the national protocol in Ukraine.

Meanwhile, there are major shortages of benzathine penicillin G in many countries, including Ukraine, which complicates the elimination of MTCT of syphilis according to the WHO strategy (16). Benzathine penicillin G is the only treatment recommended for prevention of MTCT of syphilis; other drugs are contraindicated, do not cross the placenta to treat the foetus, or are less effective.

The global targets for elimination of MTCT of syphilis will not be met until the global shortage of benzathine penicillin G is taken into account, including the lack of knowledge concerning the efficiency of this low-cost medication, which has no documented risk of antibiotic resistance and is considered an essential medicine by the WHO (17, 18). Opportunities to improve global supply, demand, and use of benzathine penicillin G should be prioritized alongside efforts to eliminate MTCT of syphilis.

In order to increase the rate of elimination of MTCT of syphilis in Ukraine, it will be critical to strengthen collaborations between obstetricians, dermatovenereologists and paediatricians, as well as between academicians and public-health workers. As a result of recommendations generated by this evaluation, a national road-map for the elimination of MTCT of syphilis in Ukraine was created.

## CONCLUSION

- The elimination of MTCT of syphilis as a public health threat by 2030 is an achievable goal, although Ukraine and other countries face critical challenges.
- Taking into account the global goal of the dual elimination of MTCT of HIV and syphilis, as well as migration flows between Eastern and Western countries, better international collaboration is needed to improve measures for

the elimination of MTCT of syphilis, as well as for sharing knowledge about the prevention of this forgotten, but not eliminated, disease.

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