Effects on preventing mother-to-child transmission of syphilis and associated adverse pregnant outcomes: a longitudinal study from 2001 to 2015 in Shanghai, China

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Abstract

Background: Maternal syphilis is a health threat to both the pregnant women and the children. This study aimed to delineate the longitudinal trend of maternal syphilis and burden of associated adverse pregnant outcomes (APOs) in Shanghai from 2001 to 2015; and to evaluate the effects of preventing mother-to-child transmission (PMTCT) of syphilis in Shanghai with regard to service coverage and APOs averted.

Methods: PMTCT program of syphilis has been implemented since 2001. Municipal and national PMTCT surveillance data were used in analysis. By using WHO estimation model, the burden of associated APOs and APOs averted were estimated. The differences in access to antenatal care and PMTCT services between resident and non-resident pregnant women were analyzed.

Results: The prevalence of seropositivity for maternal syphilis in Shanghai ranged from 0.20% to 0.38% during 2001–2015. The treatment rate varied from 69.8% to 96.8% and remained 83.6% in 2015. Under the PMTCT program, 2163 APOs had been averted during the 15-year period, including 852(39.4%) early fetal loss/stillbirth, 356(16.4%) neonatal death, 190(8.8%) prematurity or low birth weight, and 765(35.4%) clinical evidence of congenital syphilis. Compared with the residents, the non-resident pregnant women had a higher prevalence of syphilis (1.2‰ vs. 2.5‰) and contributed to 81.7% of the syphilis associated APOs in 2015.

Conclusion: Screening of maternal syphilis has reached a full coverage both in residents and non-residents. Large numbers of APOs has been averted attributing to the PMTCT program. More attentions should be paid to those vulnerable non-resident pregnant women and tailored interventions including health education, PMTCT promotion and point of care should be given to maximize the effects of PMTCT in Shanghai.

Keywords: Syphilis, Mother-to-child transmission, Adverse pregnant outcomes, Epidemiology

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Background
Syphilis, a severe sexually transmitted disease, remains a global public health problem with an estimated 17.7 million prevalent cases at the age of 15–49 years in 2012 [1–3]. Pregnant women with syphilis can transmit the infection to their fetus, causing congenital syphilis and other adverse preganant outcomes (APOs), especially when there is no treatment or no adequate treatmen [4]. In early maternal syphilis, the mother-to-child transmission can be up to 80% [5]. According to the World Health Organization (WHO), every year, there are 2 million pregnant women infected with syphilis, and about 1.2 million mother-to-child transitions happened [6]. Globally, it was estimated that nearly 0.5 million APOs were caused by maternal syphilis, including stillbirths, neonatal deaths, preterm or low birth weight (LBW), and congenital syphilis. About 66% of these APOs occurred in women without receiving syphilis screening and treatment during pregnancy [7]. In China, according to national surveillance, the prevalence of maternal syphilis among pregnant women increased from 0.20% in 2011 to 0.24% in 2013 [8].

Congenital syphilis could be prevented through antenatal screening and adequate treatment [5]. Many studies have proved that the intervention on preventing mother to child transmission (PMTCT) of syphilis are feasible and highly cost-effective [9–11]. In 2007, WHO launched the initiative for the global elimination of congenital syphilis (ECS), with the goal that by 2015 at least 90% of pregnant women are tested for syphilis in antenatal care (ANC) and at least 90% of seropositive pregnant women receive adequate treatment [5]. At the early days of New China, the laws and regulations against commercialized sex were enacted and sexually transmitted diseases including syphilis were almost eliminated in 1960s [12]. However, syphilis has staged a comeback and become epidemic again in China since 1980s with the rapid urbanization, sexual revolution and reemerging of commercial sex services [13, 14]. At the beginning of 21 century, PMTCT program of human immunodeficiency virus (HIV) had been initiated in China, together with a pilot PMTCT of syphilis in some cities like Shanghai and Shenzhen [15–17]. After a decade practice, in 2011, the integrated program for PMTCT of HIV, syphilis and hepatitis B virus (HBV) were formally launched by the ministry of health (MOH), China [8].

Shanghai, as one of the most developed cities in China, has attracted millions of domestic rural migrants dwelling. The population in Shanghai has been expanded from 11.0 million in 1978 to 24.3 million in 2015 consisting of 58.9% resident people and 41.1% being non-residents [18]. The reported syphilis incidence in Shanghai has also been rising from 0.48 per 100,000 in 1990 [19] to 56.32 per 100,000 in 2013 [20]. In 2015, there were 13,649 syphilis reported (23.3% were non-residents) [21]. For the prevention of maternal-to-child transmission of syphilis, the municipal PMTCT program of syphilis was launched in 2001 [22]. The PMTCT program was upgraded and adjusted for local situation in 2011 following the announcement of the national PMTCT guideline [23]. Nowadays, the program has been integrated comprehensively into the municipal maternal health care system and implemented at all the health facilities for ANC and delivery service.

This study aimed to delineate the longitudinal trend of maternal syphilis and burden of associated APOs in Shanghai from 2001 to 2015; and to evaluate the effects of PMTCT of syphilis in Shanghai with regard to service coverage and APOs averted.

Methods
PMTCT of syphilis in Shanghai
PMTCT program of syphilis has been set in routine antenatal care in Shanghai since 2001 covering both resident and non-resident pregnant women. At the first ANC visit, treponemal and non-treponemal serological screening should be provided to all pregnant women free of charge. Diagnosis of maternal syphilis is confirmed by both seropositive results. All diagnosed cases should be referred to “designated hospital” for sexually transmitted diseases (STDs), where the adequate treatment with penicillin and/or other antibiotics should be given immediately. The infected women should be followed up monthly with non-treponemal testing until delivery. As for pregnant women with a single-positive result, they would receive a one course preventive treatment. Serological testing should also be performed at late gestation and before delivery in order to evaluate the antibody-titer levels of syphilis and to catch those who haven’t attended a full ANC procedure (Fig. 1).

Diagnosis of maternal syphilis
The serologic-based diagnosis of maternal syphilis uses both non-treponemal and treponemal testing. The non-treponemal test detects the non-specific antibody to reaginic antigen, including the tolulized red unheated serum test (TRUST) and rapid plasma reagin (RPR) test. The treponemal test uses the specific antigen of T. pallidum mainly through T. pallidum particle agglutination assay (TPPA) and Enzyme Linked Immunosorbent Assay (ELISA). Syphilis screening using non-treponemal test or treponemal test should be provided to pregnant women at the time of their first ANC visit. If the screening test shows a positive result, these women should be asked to have the second test for confirmatory diagnosis. Only when both serologic tests of syphilis present a positive result could the pregnant women be diagnosed as maternal syphilis.
Data collection

Data on maternal syphilis screening and treatment in this study were distracted from the municipal and national PMTCT surveillance systems. Once diagnosed with maternal syphilis, information on demographics, history of syphilis infection and the serologic testing results of the infected women should be collected and further recorded into the PMTCT surveillance system by health providers at the ANC hospitals. Additional information about syphilis treatment, pregnant outcomes and health status of newborns should also be reported to the surveillance system. The population data used for the APOs estimation, including live-births and stillbirths etc., were collected from Shanghai antenatal care system and Shanghai health statistical yearbooks.

Data analysis

WHO has developed an estimation model to evaluate the disease burden of syphilis in pregnancy and associated APOs, which could be applied online [24]. The methodology has been approved by the Child Health Epidemiology Research Group and used for the recent global estimates. Six parameters, i.e., number of live births, number of stillbirths, proportion of pregnant women with positive test, at least one ANC visits, syphilis screening, and adequate treatment percentage should be given to estimate the prevalence of maternal syphilis and APOs. Based on literature reviews [25], the probabilities of associated APOs occurring without effective treatment were estimated as 52% for any adverse outcome, 21% for stillbirth/early fetal death (EFD), 9% for neonatal death, 6% for prematurity and low birth weight (LBW), and 16% for congenital syphilis (CS). The effectiveness of screening and treatment with penicillin in averting above APOs were 84%, 82%, 80%, 64% and 97% respectively [26]. After setting the relative error of 5%, point estimates of burden of syphilis-related APOs can be calculated by this algorithm automatically. Meanwhile, the APOs averted by current PMTCT efforts and ECS targets can also be estimated, which could be applied to assess the reductions of syphilis associated APOs.
Results

Screening and treatment for maternal syphilis in Shanghai

From 2001 to 2015, about 2.8 million pregnant women received serological screening for syphilis in Shanghai. The screening rate had been rising quickly from 63.0% to 90.0% in 2007, and reached a nearly full coverage of 99.6% in 2015. In total, there were 7149 maternal syphilis cases detected during the 15-year period. The highest prevalence of maternal syphilis was 0.38% in 2007, and then decreased to 0.20% in 2015. The proportion of adequate treatment among detected maternal syphilis cases was 96.8% in 2001, reduced to 69.8% in 2011 and rebounded to 83.6% in 2015.

Classified by resident status, the coverage of screening among non-resident pregnant women is lower than residents at the beginning, and the disparity began to shrink after 2005 and reached an almost full coverage to all pregnant women (Fig. 2a). It was found although the prevalence of maternal syphilis decreasing both in residents and non-residents, it was higher in the non-resident pregnant women (0.2%–0.6%) compared to the residents (0.1%–0.2%) (Fig. 2b). As for the treatment for maternal syphilis, no significant differences were found between residents and non-residents before 2010. However, the resident infected cases had a higher treatment percentage during 2011–2015 (from 79.7% to 92.4%) than the non-resident cases (from 66.2% to 80.8%) (Fig. 2c).

Estimation on associated adverse outcomes for maternal syphilis

According to the WHO syphilis associated APOs calculation, in total, 1195 maternal syphilis associated APOs were reported during 2001 to 2015 (Fig. 3a), including 503(42.5%) early fetal loss (EFL)/stillbirth, 223(18.8%) neonatal death, 195(16.5%) prematurity or LBW, and 263(22.2%) clinical evidence of congenital syphilis. The APOs happened among non-resident maternal syphilis cases accounted for the majority of the APOs in Shanghai varied from 61.4% to 84.8% (Table 1).

Estimation of syphilis associated APOs averted by the PMTCT program

If there were no PMTCT services in Shanghai, it was estimated that 3301 syphilis associated APOs would have occurred from 2001 to 2015 in Shanghai (Fig. 3b), including 1333(40.4%) EFL/stillbirth, 571(17.3%) neonatal death, 381(11.5%) prematurity or LBW, and 1016(30.8%) clinical evidence of CS. With the integrated PMTCT program, 2163 APOs has been averted during this 15-year period, including 852(39.4%) EFL/stillbirth, 356(16.4%) neonatal death, 190(8.8%) prematurity or LBW, and 765(35.4%) clinical evidence of CS. Both the resident and non-resident syphilis infected pregnant women were benefitted remarkably. It was observed that the gap between the numbers of syphilis associated APOs and ECS goals had been narrowed by years and the ECS goals was met in 2012 among resident pregnant women (Fig. 3c). Although stratified by residency, the ECS goals in non-resident syphilis infected women has yet to meet, the gap between current services and the goal had been reduced significantly in recent 5 years (Fig. 3d). The estimated effective rate of PMTCT for syphilis had been maintained at 76.9%–82.2% among resident women during recent four years.

Discussion

The prevalence of seropositivity for maternal syphilis in Shanghai ranged from 0.20% to 0.38% during 2001–2015, which is comparable to some high-income countries (Ireland [27] 0.29% in 2005–2012, Germany [28] 0.30% in 2010). Compared with other domestic provinces in China, it was much lower (Shenzhen City [15] 0.52% in 2005, Guangzhou City [29] 0.60% in 2008, Jilin City [30] 0.58% in 2010). Based on WHO syphilis associated APOs estimation model, a large number of APOs had been prevented effectively under the current PMTCT program.

Remarkable achievements have been attained through the implementation of PMTCT. Firstly, municipal and national PMTCT programs provide guidelines for standardized clinical practice and systematic management of maternal syphilis. Secondly, “Early Warning and Management System for Pregnancy Risks” [31] in Shanghai provides routine follow-up for pregnant women who are assessed as at high risk, including maternal syphilis. Thirdly, nearly 100% coverage of antenatal care guarantees the accessibility to diagnosis and treatment for maternal syphilis. Last but not least, information system for maternal syphilis helps surveillance and follow-up.

But PMTCT program in Shanghai is still facing a persistent growth of maternal syphilis. One of the reasons for this increase was the abolition of compulsory pre-marital health check-up (CPH) since 2003. It was reported that the coverage of CPH dropped from 60% in 2003 to nearly 0% in 2006 [32]. A study conducted by Chen Y and his colleagues reported that the infection rate of HPV and protozoon infection increased in ANC after 2003, which should be detected earlier in CPH [33]. Moreover, although the first ANC is regulated at 1st trimester, a big part of pregnant women, especially the non-residents women, wouldn’t attend ANC until the 2nd or 3rd trimester. One study in Shanghai found that only 67.9% of pregnant women could receive early ANC before 12 GW [34]. In addition, it was observed that proportion of adequate treatment undergone a decrease during 2011–2012 when the national integrated...
PMTCT program was initially implemented. During the shift and integration of municipal and national PMTCT surveillance systems, some treatment and newborn follow-up information might be missing, which could lead to the underestimation of the proportion of adequate treatment. With the improvement of national PMTCT system, this indicator rebounded to 83.6% in 2015. Even so, there were still gaps between the coverage in local and the goal of ECS (90%). To improve the accessibility of syphilis treatment, Shanghai health
Table 1  Estimation of Shanghai’s disease burden of syphilis associated APOs during 2001–2015

| Year | EFL/Stillbirth Resident | EFL/Stillbirth Non-resident | Neonatal death Resident | Neonatal death Non-resident | Prematurity/LBW Resident | Prematurity/LBW Non-resident | Congenital Syphilis Resident | Congenital Syphilis Non-resident | Total APOs Resident | Total APOs Non-resident |
|------|------------------------|---------------------------|-------------------------|---------------------------|-------------------------|---------------------------|-----------------------------|-----------------------------|-----------------|---------------------|
| 2001 | 9                      | 14                        | 4                       | 6                         | 3                       | 5                         | 5                           | 9                           | 22              | 35                  |
| 2002 | 8                      | 21                        | 3                       | 9                         | 3                       | 7                         | 4                           | 15                          | 18              | 52                  |
| 2003 | 5                      | 12                        | 2                       | 5                         | 2                       | 4                         | 2                           | 7                           | 11              | 29                  |
| 2004 | 8                      | 15                        | 4                       | 7                         | 3                       | 6                         | 4                           | 8                           | 18              | 36                  |
| 2005 | 8                      | 23                        | 4                       | 10                        | 3                       | 9                         | 4                           | 13                          | 19              | 55                  |
| 2006 | 7                      | 25                        | 3                       | 11                        | 3                       | 10                        | 3                           | 14                          | 17              | 21                  |
| 2007 | 13                     | 42                        | 6                       | 19                        | 5                       | 17                        | 6                           | 22                          | 30              | 100                 |
| 2008 | 8                      | 38                        | 3                       | 17                        | 3                       | 15                        | 3                           | 18                          | 18              | 89                  |
| 2009 | 7                      | 28                        | 3                       | 12                        | 3                       | 11                        | 3                           | 14                          | 17              | 20                  |
| 2010 | 9                      | 23                        | 4                       | 11                        | 4                       | 10                        | 5                           | 11                          | 22              | 55                  |
| 2011 | 9                      | 32                        | 4                       | 14                        | 4                       | 11                        | 5                           | 19                          | 21              | 77                  |
| 2012 | 7                      | 36                        | 3                       | 16                        | 3                       | 13                        | 2                           | 22                          | 16              | 87                  |
| 2013 | 6                      | 33                        | 3                       | 15                        | 3                       | 12                        | 1                           | 18                          | 14              | 78                  |
| 2014 | 7                      | 24                        | 3                       | 11                        | 3                       | 10                        | 2                           | 12                          | 16              | 56                  |
| 2015 | 5                      | 21                        | 2                       | 9                         | 2                       | 8                         | 2                           | 10                          | 11              | 49                  |
authority appointed additional thirty-two maternity hospitals as the “designed hospitals” for maternal syphilis medical care in 2016, where infected pregnant women could receive syphilis treatment, specialized antenatal care and safe delivery at the same facility.

We found that there were disparities in maternal syphilis screening, treatment between the resident and non-resident pregnant women. Meanwhile, it was observed that the proportion of estimated APOs incurred among these non-residents increased from 61.4% in 2001 to 81.7% in 2015. Due to poor reproductive health knowledge, unfamiliar with antenatal care system and low coverage of health insurance [35–37], the non-resident cases were the vulnerable group for on time screening and adequate treatment. Furthermore, the high mobility of these women also hinders their receiving regular ANCs. A previous study of ours found that although 49.7% of the non-resident women had adequately utilized antenatal care, only 19.7% of them visited ANC during the first trimester in Shanghai [38]. Therefore, more attentions should be paid to those vulnerable non-resident pregnant women and tailored interventions including health education, PMTCT promotion and point of care should be given to maximize the effects of PMTCT effects in Shanghai, and to reduce the inequity in maternal healthcare utilization.

Based on the comprehensive surveillance system, our study is able to describe the longitudinal trend of maternal syphilis and burden of APOs in Shanghai over 15 years. Still, there are some limitations in this study. First of all, the municipal report system and national PMTCT system were experiencing an alternation in 2011–2012, thus, data from different sources had showed slight inconsistence. Secondly, the fixed parameters in WHO estimation model was based on several studies carried out in other countries, which may influence the accuracy and validity of estimation when applying to Shanghai data.

Conclusions
This study found that screening of maternal syphilis has reached a full coverage both in residents and non-residents, and the prevalence of syphilis among pregnant women is consistently decreasing during the past 15 years. Attributing to the PMTCT program, large numbers of APOs associated with syphilis have been averted. More attentions should be paid to those vulnerable non-resident pregnant women to reduce the inequity on maternal healthcare.

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Availability of data and materials
Data can be available by contacting the authors.

Authors’ contributions
YL participated in study design, led the data collection and analysis, and drafted the manuscript. LPZ participated in study design, commented data and assisted with manuscript writing. LD and WLJ and LXQ were involved in data collection and data analysis. BX was responsible for this project and involved in study design, data analysis and manuscript writing. YL and LPZ having the same contribution and are both the first author for this manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study has been approved by the Institutional Review Board of School of Public Health, Fudan University (IRB#2016-03-05/78).

Consent for publication
The Author confirms that its publication has been approved by all co-authors.

Competing interests
The authors declare that they have no competing interests.

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