

## ORIGINAL ARTICLE

# Congenital syphilis in the Russian Federation: magnitude, determinants, and consequences

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*Sex Transm Infect* 2003;**79**:106–110

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**Objectives:** Reported cases of congenital syphilis in the Russian Federation increased 26-fold from 1991–9. Our objectives were to describe the frequency, risk factors, and consequences of delivering an infant with congenital syphilis among pregnant women with active syphilis.

**Methods:** In a retrospective record review using consecutive sampling of logs at maternity hospitals in five geographic areas, data were abstracted for 850 women with active syphilis during pregnancy who had completed  $\geq 20$  weeks' gestation. Further information was abstracted from records in antenatal clinics, dermatovenereology clinics, and paediatric hospitals. We assessed the frequency of confirmed or probable congenital syphilis, used logistic modelling to identify independent predictors for delivering a baby with congenital syphilis, and calculated the proportion of infants with congenital syphilis who experienced late fetal death (20–27 weeks), stillbirth ( $\geq 28$  weeks), or infant death.

**Results:** A total of 64% ( $n=544$ ) of 850 pregnant syphilis infected women delivered an infant with confirmed or probable congenital syphilis; 40% of the sample had no prenatal care. Among women with no prenatal care, 77% received either no treatment or inadequate treatment and 86% delivered an infant with congenital syphilis. Important independent and modifiable risk factors for delivery of an infant with congenital syphilis included receiving no prenatal care (adjusted OR 2.8, 95% CI 1.7 to 4.7) and having the first test for syphilis at  $\geq 28$  weeks' gestation (adjusted OR 4.0, 95% CI 2.6 to 6.0). Fatal outcomes were observed in 26% of infants with congenital syphilis, including late fetal death (7%), stillbirth (16%), or neonatal death (3%).

**Conclusions:** In the Russian Federation, the frequency of congenital syphilis is high, risk factors for congenital syphilis are modifiable, and the consequences of congenital syphilis are severe.

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Accepted for publication  
4 September 2002

Even one case of congenital syphilis is a sentinel public health event, since timely diagnosis and treatment of syphilis infected pregnant women should prevent transmission almost entirely.<sup>1</sup> When timely treatment of primary or secondary syphilis is not received, approximately 75% of syphilis infected pregnant women experience adverse outcomes, which may only become manifest months or years after birth.<sup>2</sup> Fetal and infant complications include stillbirth; miscarriage; skin, bone, blood, renal, hepatic, dental, and central nervous system disorders; and death.<sup>3,4</sup>

The unprecedented increase in congenital syphilis over the past decade in the Russian Federation occurred in the aftermath of sociopolitical and economic transformations following the Soviet Union's breakdown.<sup>5,6</sup> From 1991 to 1999, the number of cases of congenital syphilis increased 26-fold, from 29 to 743 cases.<sup>7,8</sup> This increase mirrors the 26-fold rise in syphilis rates among women aged 18 and above (from 1991, 8.04/100 000 to 1999, 209/100 000).<sup>7</sup> Decreases in syphilis rates in the late 1990s were partly explained by a drop-off in case finding and by a shift from use of the public towards private health services, which are less likely to report cases.<sup>9,10</sup> In order to be reported as a congenital syphilis case in Russia, infants must be symptomatic, have persistent serological abnormalities, or receive a diagnosis of syphilitic stillbirth. The requirement of clinical and/or serological findings may cause the true burden of congenital syphilis in the Russian Federation to be underestimated. The World Health Organization (WHO) definition classifies infants born to either untreated or inadequately treated mothers as probable cases, since most infants with congenital syphilis are asymptomatic at birth<sup>2</sup> and because maternal non-compliance with recommendations for follow up is common.<sup>11</sup> We used the WHO case definition to facilitate international contextualisation of our findings.

The aims of this investigation were to describe the frequency of delivery of an infant with confirmed or probable congenital syphilis among women with active syphilis during pregnancy; to identify risk factors for delivery of an infant with congenital syphilis; and to describe frequency of unfavourable pregnancy outcomes among syphilis infected women.

## METHODS

A retrospective cohort design was used for this study, which was conducted by collaborators from the Ministry of Health of the Russian Federation, the Russian Federal Central Institute of Skin and Venereal Diseases, the Moscow City Health Committee, the Russian Association for the Prevention of Sexually Transmitted Infections "SANAM" (non-governmental organisation) in Moscow, the Moscow Oblast (equivalent to "province") Dermatovenereology Dispensary, the St Petersburg State Medical University, the Novgorod City Dermatovenereology Dispensary, the Novgorod Oblast Dermatovenereology Dispensary, the Novgorod Oblast Health Committee and the State Medical Institute, the Ryazan Oblast Dermatovenereology Dispensary, United States Agency for International Development (USAID), the Soros Foundation Open Society Institute, and the US Centers for Disease Control and Prevention (CDC). This study was approved by an ethics committee representing the Russian Ministry of Health and by the CDC internal review board.

The study population included women with a positive test for syphilis during pregnancy from two metropolitan (Moscow and St Petersburg) and three non-metropolitan areas (Novgorod, Moscow Oblast, and Ryazan). Participants delivered at 20 weeks' gestation or later in a participating maternity hospital between January 1995 and October 1999. In the Russian

Federation, the great majority of pregnant women give birth in hospital settings, syphilis testing is typically performed in centralised laboratories, and pregnant women who access prenatal care receive multiple tests during pregnancy. Initially, 1071 women with a positive non-treponemal test for syphilis (usually a Wassermann test) or a treponemal test (known as immunofluorescence reaction, which is comparable to the FTA-ABS (fluorescent treponemal antibody absorption test)) were presumptively enrolled. Each site consecutively sampled from 100–300 eligible women delivering before October 1999. Investigators developed lists of women with a diagnosis of syphilis during pregnancy by reviewing laboratory and admission logs from maternity hospitals and dermatovenereology dispensaries (DVDs). Abstractors collected standardised data from medical records in maternity hospitals, DVDs, prenatal clinics, and paediatric hospitals. Some sites identified the needed sample using 1 year of medical records, while others needed up to 5 years. All analyses are reported for the multisite data, since site specific analyses demonstrated similar findings among all sites. Analyses were restricted to the 850 women with evidence of active syphilis during the most recent pregnancy, including: (1) those with first known occurrence of syphilis during the most recent pregnancy ( $n=613$ , 72.1%), and (2) women with previous syphilis who had no record of previous treatment ( $n=103$ ), laboratory indications of lack of resolution of infection (a qualitative two unit increase in non-treponemal test,  $n = 98$ ); or laboratory (positive one unit increase in non-treponemal test) and clinical evidence of lack of resolution of infection ( $n = 36$ ).

Demographic, social, behavioural, and clinical risk factors for congenital syphilis were considered. Outcomes included inadequate treatment of mother for syphilis and congenital syphilis in the infant. We used the WHO case definition for congenital syphilis (same as CDC definition).<sup>12</sup> An infant was classified as a probable case when: (1) it was born to an inadequately treated or untreated mother (regardless of signs in the infant); (2) an infant had a positive serological test for syphilis and any one of the following: evidence of congenital syphilis on physical examination, placental changes, necropsy confirmation. An infant was classified as a confirmed case when *Treponema pallidum* was identified by dark field microscopy (often unavailable), direct fluorescent antibody (DFA), or other stains from lesions, placenta, umbilical cord, or necropsy. An infant was classified as a “syphilitic stillbirth” if fetal death occurred at 28 weeks’ gestation or later and the mother had untreated or inadequately treated syphilis at delivery. By WHO criteria, in case of a syphilitic stillbirth, a fetus should weigh more than 500 g and death should occur after 20 weeks. However, since fetal weights were unavailable and criteria for stillbirth in the Russian Federation require a gestational age of 28 weeks or greater, we only included as probable cases stillbirths occurring at 28 weeks or later. We do present data on late fetal deaths (from 20–27 weeks). Findings from physical examinations and placental evaluation were considered. There was no evidence in medical records that x rays of long bones were performed.

Adequate treatment of syphilis during pregnancy was defined as documentation of parenteral penicillin G administration. According to the CDC guidelines for the treatment of sexually transmitted diseases (STD), parenteral penicillin G is the preferred treatment for all stages of syphilis and the choice of long acting or short acting penicillin should be determined by disease stage and clinical signs.<sup>13</sup> Whereas the WHO and CDC treatment guidelines recommend long acting benzathine penicillin G for primary, secondary, and all forms of latent syphilis during pregnancy,<sup>13–14</sup> treatment standards in the Russian Federation included either long acting or daily doses of short acting (aqueous or procaine) penicillin G preparations.<sup>15</sup> Therefore, we defined adequate treatment as administration of long acting or short acting penicillin G regimens, completed at least 30 days before delivery.

All data were entered using Russian EPI-INFO software and then converted to SAS. Mantel-Haentzel,  $\chi^2$  relative risks, and

95% confidence intervals were used to perform bivariate analysis of risk factors for congenital syphilis. Logistic modelling was used to identify independent risk factors for delivery of an infant with congenital syphilis.

## RESULTS

The population of 850 women with active syphilis during pregnancy was fairly diverse; 77% were ages 20 and over, 19% were non-residents of the city or town in which they delivered, 19% were unmarried, and 72% were unemployed or homemakers. The reported prevalence of multiple partners among those with complete behavioural data was 20% (100/511), and HIV testing was documented for 90% of the sample (table 1). Unfortunately, information regarding use of alcohol and drugs during pregnancy was largely missing from the medical record. We found that 57% of pregnant women with active syphilis received either no prenatal care (40%) or care at 21 weeks’ gestation or later (17%).

Although early testing and treatment of pregnant women with syphilis is a mainstay of preventing its transmission to their newborns, 45% of such women were tested at 28 weeks of gestation or later (table 2). Most women were tested with non-treponemal tests only (637/759, 79%, data not shown); confirmation by treponemal tests was infrequent. Among pregnant women with active syphilis, 6% had primary syphilis and 34% had secondary syphilis; clinical signs of syphilis were recorded in the medical record for 26% (219/850, data not shown) of the sample. A minority of cases of active syphilis (12%) were diagnosed in DVDs; the majority (56%) were diagnosed in women’s health clinics and maternity hospitals. The

**Table 1** Characteristics of study population among women with active syphilis during pregnancy, Russia ( $n=850$ )

Characteristic	Number of mothers	Percentage of total
Age (years) at delivery		
$\leq 19$	195	22.9
$\geq 20$	655	77.1
Place of residence		
Resident	672	79.1
Non-resident	165	19.4
Homeless	13	0.5
Marital status		
Married/living as married	673	79.2
Single	159	18.7
Unknown	18	2.1
Employment status*		
Manual labour	84	9.9
Professional	105	12.4
Student/pupil	42	5.0
Homemaker	305	36.0
Unemployed	301	35.5
Unknown	11	1.3
Number of sex partners		
1	411	48.4
2–5	84	9.9
6+	16	1.9
Unknown	339	39.9
Prenatal care		
Yes	505	59.4
No	342	40.2
Missing/unknown	3	0.4
Time of first prenatal care visit		
No prenatal care	342	40.2
$\leq 20$ weeks	325	38.2
$\geq 21$ weeks	146	17.2
Missing	37	4.4
HIV testing		
Yes	761	89.5
No	59	6.9
Missing	30	3.5

\*Total sample decreased due to missing data.

**Table 2** Syphilis characteristics among women with active syphilis during pregnancy, Russia (n=850)

Characteristic	Number of mothers	Percentage of total
Timing of first test for syphilis during pregnancy		
≤27 weeks	411	54.9
≥28 weeks	377	45.1
Previous diagnosis of syphilis*		
Yes	237	27.9
No	613	72.1
Stage of syphilis diagnosis during pregnancy*		
Any primary	32	5.9
Any secondary	183	33.6
Early latent	320	58.8
Late latent/unknown duration	9	1.7
Setting for diagnosis		
Women's health setting	474	55.8
Any DVD consultation	100	11.8
Other/missing	276	32.5
Antibiotic treatment administered		
Yes	469	55.2
No	381	44.8
Record states ambulatory or inpatient treatment		
Ambulatory	156	18.4
Inpatient	280	32.9
Both	30	3.5
Neither/missing	384	45.2
Penicillin treatment administered		
Yes	351	41.3
No	499	58.7
Delivers infant with confirmed or probably congenital syphilis		
Yes	544	64.0
No	306	36.0
Added prophylactic treatment†		
Yes	306	36.0
Inadequate	25	2.9
No/missing	488/31	61.1

\*Total n decreased due to missing data; †"prophylactic" antibiotic treatment refers to injectable penicillin G administered on an outpatient basis after completing the initial course of curative therapy. The added course is recommended for syphilis infected pregnant women by national policy in the Russian Federation to prevent transmission to the fetus.

medical record specified that some treatment was received—either a listed antibiotic regimen (parenteral penicillin, cephalosporin, erythromycin) or a general statement that "syphilis treatment was administered"—for 55% of the total sample. Among the 469 women who received some treatment, only 45% had a fourfold fall in antibody titres or reversion to negative. Penicillin administration was documented for only 41% of the total sample. Failure to receive penicillin was greatest for women who had no prenatal care (77%, 264/342).

A total of 64% (n = 544) of the sample had infants who were confirmed or probable cases of congenital syphilis (table 2). Included as cases were infants with one or more of the following: serological and clinical abnormalities (chancres, lymphadenopathy, leucoderma, alopecia, or characteristic mucocutaneous lesions, n = 112), visualisation of spirochaetes (n = 1), birth to untreated or inadequately treated mothers (n = 499), and stillbirth (n = 62).

A number of significant predictors were identified (table 3). The risk of delivery of a baby with congenital syphilis was significantly greater for women who were non-residents (women who are not legal residents of the city or town in which they deliver may not have full access to health coverage for prenatal care and for delivery costs) (83%) or homeless (89%) than for residents (62%, p<0.001). Among women who had no prenatal care, 86% delivered an infant with congenital syphilis, whereas women who had early prenatal care (≤20 weeks' gestation) had a much lower risk of congenital syphilis (41%, p<0.001). Similarly, women whose first serological test for syphilis occurred at 28 weeks' gestation or later (83%) were nearly twice as likely to deliver a baby with congenital syphi-

**Table 3** Risk factors for delivery of an infant with congenital syphilis among pregnant women with active syphilis giving birth, Russia (n=715)

Characteristic	Percentage (number) of those in risk group who are cases of congenital syphilis	Statistical significance
Age (years) at delivery		
≤19	67.5 (102)	Not significant
≥20	66.0 (368)	
Married/living as married*		
Yes	65.2 (381)	Not significant
No	71.9 (92)	
Place of residence		
Resident	61.8 (349)	p<0.001
Non-resident	83.0 (117)	
Homeless	88.9 (8)	
Prenatal care		
Yes	53.9 (234)	p<0.001
No	85.7 (240)	
Time of 1st prenatal visit		
≤20 weeks	41.2 (134)	p for trend <0.001
≥21 weeks	63.0 (87)	
No prenatal visits	85.7 (240)	
Number of visits		
≥4 visits	53.4 (150)	p for trend <0.001
≤3 visits	77.6 (45)	
No prenatal visits	85.7 (240)	
Timing of first test for syphilis during pregnancy		
≤27 weeks	45.9 (147)	p<0.001
≥28 weeks	83.4 (272)	
Stage of syphilis diagnosis during pregnancy*		
Any primary	48.4 (15)	p<0.001
Any secondary	41.5 (56)	
Early latent	52.9 (137)	
Late latent	66.7 (6)	
Setting for syphilis diagnosis		
Dermatovenerology dispensary	47.6 (40)	p<0.001
Women's health setting	60.1 (230)	
Other	82.3 (204)	
Symptoms syphilis in mother		
Yes	48.0 (82)	p<0.001
No	72.1 (392)	
Type treatment*		
Both	33.3 (8)	p for trend <0.01
Ambulatory	40.4 (46)	
Inpatient	53.9 (145)	
Treatment before pregnancy		
Yes	67.6 (71)	Not significant
No	66.1 (403)	
Laboratory evidence of resolution		
Yes	60.8 (183)	p<0.01
No	70.3 (291)	

\*Restricted to women who received treatment.

lis as those whose first test occurred earlier (46%, p<0.001). The setting for diagnosis of syphilis was important: women diagnosed in women's health (60%) or other settings (82%) were significantly more likely to deliver a baby with congenital syphilis than women who were diagnosed in a DVD setting (48%, p<0.001). Women who had laboratory evidence of resolution of infection also had a significantly lower risk (p<0.01). Among the subgroup of women receiving treatment, those receiving both ambulatory and inpatient treatment had the lowest risk (33%), followed by those receiving ambulatory treatment alone (40%), and the highest risk among those receiving treatment occurred in those receiving inpatient treatment alone (54%, p for trend <0.01). After adjustment for maternal age, non-resident status, and being unmarried, we found three independent risk factors for the delivery of an infant with congenital syphilis: failure to receive prenatal care (adjusted OR 2.8, 95% CI 1.7 to 4.7), testing for syphilis at 28 weeks' gestation or later (OR 4.0, 95% CI 2.6 to 6.0), and latent, as opposed to primary or secondary, syphilis (OR 3.7, 95% CI 2.4 to 5.7).

**Table 4** Pregnancy outcomes by adequacy of treatment, evidence of resolution of maternal infection, and whether infant met case definition for congenital syphilis, Russia (n=634)\*

	Late fetal death 20+weeks		Induced abortion 20+weeks		Live birth		Stillbirth		Born alive, then died	
	No	%	No	%	No	%	No	%	No	%
Parenteral penicillin treatment										
No	27	7.6	42	11.8	215	60.2	61	17.1	12	3.4
Yes	11	4.0	55	19.9	199	71.8	9	3.3	3	1.1
Lab evidence of resolution										
No	31	7.5	75	18.1	231	55.8	65	15.7	12	2.9
Yes	7	3.2	22	10.0	183	83.2	5	2.3	3	1.4
Infant met congenital syphilis case definition										
Yes	27	7.0	43	11.1	242	62.5	62	16.0	13	3.4
No	11	4.5	54	21.9	172	69.6	8	3.2	2	0.8

\*Total sample decreased because one site had missing data on stillbirths.

Our evaluation of pregnancy outcomes, including fetal or infant death, was restricted to four of the five sites, since for one of the sites data on stillbirth were largely missing. Among women in our study population whose infants met the case definition for congenital syphilis, 26% had an outcome of fetal or infant death: 16% had stillbirths, 7% had fetal deaths (note that all 23% of these would be classified as syphilitic stillbirths using WHO criteria), and 3% had infants who were born alive and then died (table 4). The risk of stillbirth was similarly high among analyses restricted to those women without medical record documentation of parenteral penicillin G therapy (17%) and those without laboratory evidence of resolution of infection (16%).

## DISCUSSION

In our study population in the Russian Federation, the frequency of congenital syphilis is high, major risk factors for congenital syphilis are modifiable, and consequences of congenital syphilis are severe. Although congenital syphilis should be largely preventable, more than six of 10 syphilis infected women delivered an infant with congenital syphilis. The majority, nearly 60%, of syphilis infected women received either no or late prenatal care. The risk of congenital syphilis was extremely high among women who received no prenatal care: nine out of 10 delivered an infant with congenital syphilis. We found that one half of syphilis infected pregnant women had their first test for syphilis at 28 weeks of gestation or later, thus making it more difficult for them to complete the recommended treatment 1 month before delivery.

Among women with active syphilis during pregnancy, less than half received the recommended treatment with parenteral penicillin G. Failure to receive treatment was associated with women's healthcare seeking behaviours: three out of every four women who did not obtain prenatal care failed to receive penicillin treatment. The consequences of not receiving penicillin treatment were severe: pregnancy outcome was death—fetal death, stillbirth, or infant death—for more than one fourth of these women.

A comparison of our findings with national survey data revealed an important difference between high risk syphilis infected pregnant women and the general population. Data from the recent USAID supported Russian Women's Reproductive Health Survey indicate that only 5% of the general population of women received no prenatal care at their most recent pregnancy,<sup>16</sup> a percentage that pales before the 40% in our study population. Syphilis infected women who seek no or late prenatal care receive late testing and late treatment, which in turn does not allow the needed several months before delivery that would be necessary for serological evidence of resolution of infection. We found that less than half of women with treatment had serological evidence of such resolution.

Our findings regarding the epidemiology of congenital syphilis in the Russian Federation are comparable to previous reports describing outbreaks of congenital syphilis in the United States, which suggest that among syphilis infected pregnant women, the frequency of delivery of an infant with congenital syphilis ranges from 25% to 64%.<sup>17-19</sup> Recognised risk factors include lack of prenatal care, late entry into prenatal care, failure to repeat syphilis testing early during the third trimester, previous delivery of an infant with congenital syphilis, previous stillbirth, use of injecting drugs, exchange of sex for drugs or money, having an unwanted pregnancy, young age, rural residence, being unmarried, and having no father's name on the birth certificate.<sup>18-26</sup> We found several related risk factors—namely, lack of prenatal care and serological testing for syphilis after 28 weeks' gestation, in our study population. Our findings regarding high rates of fetal or infant death among untreated or inadequately treated mothers in the Russian Federation are also similar to those previously reported.<sup>27</sup>

Although certain biases in measurement of risk factors are unavoidable because this study was retrospective, Russian national experts agree that the most important risk factors—characteristics of prenatal care, testing and treatment, and residential status of mother—were validly measured by medical records. Unfortunately, substance abuse could not be assessed because of missing data. Our findings may be minimally influenced by selection bias, because the performance of the non-treponemal Wasserman tests could not be retrospectively confirmed and because confirmatory testing was not routinely performed. Thus, we may have enrolled some pregnant women who had false positive results. However, the observed high incidence of fetal and infant death suggests it is unlikely that a substantial number of false positives were enrolled. In the event that some participants had false positive results, the incidence of congenital syphilis would have been underestimated.

This study provided new, objective, systematic, quantitative information about the epidemiology of congenital syphilis in the Russian Federation. Clearly, early diagnosis and appropriate treatment of syphilis infected mothers—the mainstay of congenital syphilis prevention—cannot occur when 60% of at-risk women do not access early prenatal care. Barriers to early access of prenatal care by syphilis infected women and to receipt of adequate treatment should be identified, so that interventions which include disenfranchised and non-resident populations can be developed. Current regulations in the Russian Federation stipulate that only dermatovenereologists are authorised to treat syphilis infected pregnant women. To strengthen congenital syphilis prevention in the Russian Federation, it will be critical to strengthen collaborations between obstetricians, dermatovenereologists, and paediatricians, as well as between academic and public health sectors. As a result of recommendations generated by this evaluation, national policy reforms have been initiated.

### Key messages

- Surprisingly, two thirds of babies born to pregnant women with active syphilis meet the case definition for congenital syphilis
- Major risk factors for congenital syphilis are largely preventable; one of the strongest is receiving no or late prenatal care (57% of syphilis infected pregnant women)
- Consequences of congenital syphilis are severe, as 26% of infants born to infected mothers have fatal outcomes (stillbirth, late fetal death, or neonatal death)
- Serious attention now to prevention of mother to child transmission of syphilis is critical during this time of rapid HIV expansion in eastern Europe.
- Critical strategies for strengthening prevention of congenital syphilis are similar to those needed for strengthening prevention of mother to child transmission of HIV: timely testing, diagnosis, and treatment of infected mothers in prenatal care settings

In an era of rapid HIV expansion in eastern Europe, perinatal transmission of HIV would also be expected to rise in the Russian Federation.<sup>28</sup> One of the mainstays of preventing mother to child transmission of syphilis is identical to that of preventing mother to child transmission of HIV: timely testing, diagnosis, and appropriate treatment of infected mothers in prenatal care settings. Immediate, conscientious attention to implementation of recommendations to strengthen prevention of perinatal transmission of syphilis can be expected to help build the infrastructure that will be essential for preventing perinatal transmission of HIV.

### ACKNOWLEDGEMENTS

Sources of funding: Division of STD Prevention, Centers for Disease Control and Prevention, and the US Agency for International Development (Moscow Mission).

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LT participated in and contributed substantially to the conception and design, to standardised implementation, to analysis and interpretation of data, to drafting the article and to revising it critically for important intellectual content; ES participated in and contributed substantially to the conception and design, to standardised implementation, to analysis and interpretation of data, to drafting the article and to revising it critically for important intellectual content; KS participated in and contributed substantially to the conception and design, to standardised implementation, to analysis and interpretation of data, to drafting the article and to revising it critically for important intellectual content; AS participated in and contributed substantially to the conception and design, to standardised implementation, to analysis and interpretation of data, to drafting the article and to revising it critically for important intellectual content; CR participated in and contributed substantially to the conception and design, to standardised implementation, to analysis and interpretation of data, to drafting the article and to revising it critically for important intellectual content; SH participated in and contributed substantially to the conception and design, to standardised implementation, to analysis and interpretation of data, to drafting the article and to revising it critically for important intellectual content.

None of the authors had any conflicts of interest in connection with this paper.

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