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Short Communication

Syphilis in pregnancy, congenital syphilis, and factors associated with mother-to-child transmission in Itapeva, São Paulo, 2010 to 2014

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Abstract

Introduction: This study describes cases of syphilis in pregnancy (SiP) and congenital syphilis (CS) and identifies factors associated with mother-to-child transmission in patients in Itapeva from January 1, 2010 to December 31, 2014. **Methods:** Using SiP and CS notification forms and medical records, a cross-sectional study involving 149 pregnant women was conducted. **Results:** Annual SiP detection rates ranged from 16.3-31.4/1000 live births. Most women had prenatal care started at the first trimester of pregnancy with ≥6 visits. Mother-to-child transmission rate was 69.7%. CS incidence rates varied from 9.1-22.3/1000 live births. **Conclusions:** The results suggest low quality of prenatal care.

Keywords: Congenital syphilis. Syphilis in pregnancy. Vertical transmission. Prenatal care. Risk factors.

The World Health Organization established the goal of reducing congenital syphilis (CS) incidence to <0.5 cases per 1,000 live births (LB) by 2015[1]. Brazil has not met this goal. Reporting Diseases Information System (*Sistema de Informações de Agravos de Notificação, SINAN*) data show an increase in detection rates of syphilis in pregnancy (SiP) in Brazil, from 3.7/1,000 LB in 2010 to 11.2/1,000 in 2015[2]. CS incidence rates also increased from 2.4/1,000 LB in 2010 to 6.5/1,000, in 2015[2]. In São Paulo (SP), in Southeast Brazil, SiP detection rates increased from 3.7/1,000 LB in 2010 to 11.3/1,000 in 2015, and CS incidence rates increased from 1.9/1,000 LB in 2010 to 5.4/1,000 in 2015[2].

Itapeva, a city with approximately 92,000 inhabitants (2013), located in Southwest SP, the least developed region in the state, had the highest detection rates of acquired syphilis in the state: 113.9 cases/100,000 inhabitants, 2.5 times the average of the state (44.8 cases/100,000), in 2014[3].

This study aimed to 1) describe sociodemographic characteristics and prenatal care of pregnant women with syphilis; 2) estimate SiP detection rates, CS incidence, and mother-to-child transmission rate; 3) describe clinical-laboratory characteristics, healthcare, and outcomes of newborns of mothers with SiP; and 4) identify factors associated with CS, in Itapeva, SP.

This cross-sectional study included all cases of SiP and CS identified in Itapeva between 1/1/2010 and 12/31/2014. Cases were identified by municipal surveillance and active search in primary healthcare units (*Unidades Básicas de Saúde*), maternal and child care center (*Centro Materno Infantil,* CMI), specialized outpatient clinic (*Serviço de Ambulatório Especializado,* SAE), and the single hospital in the city (*Santa Casa de Misericórdia de Itapeva,* SCMI). In 2014, a list of women with positive syphilis test was obtained from the laboratory responsible for conducting the tests for the public health system (*Sistema Único de Saúde*) and the SCMI. We collected data on demographic and clinical-laboratory characteristics of pregnant women, prenatal care and delivery, and their outcomes (LB, miscarriages, and stillbirths). Data sources were SiP and CS notification records and prenatal care and hospital records.

The study adopted the 2007 Ministry of Health (MoH) definitions and treatment recommendations for SiP and CS, which were in force during the study period.

Data were entered into a Microsoft Excel 2010 spreadsheet and analyzed using STATA, version 13.0 (StataCorp LP, College Station, Texas, USA). We conducted a descriptive analysis of the variables of interest and calculated the annual SiP detection rates (number of SiP cases divided by the number of LB); the annual CS incidence rates (number of confirmed CS cases divided by

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the number of LB); and the rate of mother-to-child transmission of syphilis (number of confirmed CS cases divided by the total number of LB, stillbirths, and miscarriages of mothers with SiP). To assess the association between CS and variables of interest, a bivariate analysis was conducted. Prevalence ratios (PR) and respective 95% confidence intervals (CIs) were calculated. Variables with $p<0.20$ were included in a multiple analysis using a Poisson regression model with robust variance. The significance level was set at 5%.

The project was approved by the Itapeva Health Department, SCMI, and the Research Ethics Committee of the University of São Paulo Medical School (CAPPesq, 168/14).

Table 1 presents the sociodemographic and prenatal care data of the 149 women with SiP included in the study. The mean age was 24.3 years; most women (69.2%) had ≤8 years of education and were homemakers (67.8%). Most women (94.6%) had prenatal care, 56.8% were <13 weeks pregnant at their first visit, 75.9% had ≥6 prenatal visits, and 58.9% did not miss any appointment. Among the 141 pregnant women who had prenatal care, 137 (97.2%) had at least one syphilis test, and 80.3% of them were tested within ≤15 days of their first visit. A routine, rapid screening test for syphilis was introduced in Itapeva in 2012 and performed for only 47 (31.5%) participants. The Venereal Disease Research Laboratory (VDRL) was the first test performed for most women, and it was positive in 128 (93.4%) cases. Of the nine pregnant women with a negative first test, eight were tested a second time by the VDRL, among whom four were positive. The four pregnant women with two negative tests did not repeat the serology during pregnancy. Thus, 88.6% (132/149) of women had syphilis diagnosed during pregnancy (57% in the first trimester), and 11.4% were diagnosed at childbirth/miscarriage (**Table 1**).

An active laboratory search identified six SiP cases not identified by health services. Only 42.2% (62/149) of SiP cases identified in this study were notified to surveillance authorities.

Of the 132 women with syphilis diagnosed during pregnancy, 128 (97%) received a medical prescription for treatment. The time between diagnosis and prescription ranged from 0-195 days (mean, 34.8). Among the 128 women who received a prescription, 120 (93.8%) effectively used the medication, and treatment was adequate in 89.8%. Among the 120 women who effectively used the prescribed medication, 85% had ≥1 serological test after treatment, but only 31.7% had monthly VDRL after treatment, as recommended. Retreatment was prescribed for 24 women and 18 (75%) effectively received the medication; however, only seven had a VDRL test after retreatment. For 107 (83.6%) of the 128 women who received treatment prescriptions, the time between the last prescription and delivery was >30 days (**Table 1**). Over half (56.4%) of the women's sexual partners were provided syphilis treatment, among whom the treatment was adequate in 86.1% cases.

SiP detection rates were 17.2/1,000 LB (2010), 16.3 (2011), 21.9 (2012), 17.5 (2013), and 31.4 (2014).

Seven of the 132 (5.3%) women diagnosed with SiP subsequently had negative treponemal tests and were considered as false-positive VDRL. All seven received syphilis treatment during pregnancy and were diagnosed with systemic lupus erythematosus after delivery.

The 149 pregnancies resulted in two miscarriages, three stillbirths, and 147 LB (three twins). Based on MoH criteria, CS was confirmed in 101 of 147 LB. We assumed the two miscarriages and three stillbirths were due to CS, even without serological tests, biopsy, or necropsy, since maternal syphilis was diagnosed at the time of delivery/curettage. Mother-to-child transmission rate was 69.7% (106/152).

In this study, CS incidence rates were 15.1/1,000 LB (2010), 12.1 (2011), 15.6 (2012), 9.1 (2013), and 22.3 (2014), higher than the rates estimated by surveillance data: 12.2/1,000 LB (2010), 9.9 (2011), 7.8 (2012), 6.3 (2013), and 9.8 (2014).

Among the 147 LB, 30.8% were preterm infants (<37 weeks of pregnancy); 35.6% had low birth weight (<2,500 g), and 52.8% had clinical signs of CS at birth (**Table 2**). Syphilis clinical signs were anemia, splenomegaly, and hepatomegaly (each sign occurred in 54 newborns, 72%); jaundice in 31 (41.3%); osteochondritis in 18 (24%); skin lesions in 12 (16%); pseudo paralysis in seven (9.3%); and serosanguineous rhinitis in two (2.7%).

VDRL was performed in 92.3% of newborns and 67.1% tested positive (**Table 2**). Cerebrospinal fluid (CSF) examination was performed in 52.4% of newborns, and 45 (59.2%) of them had abnormal CSF (all presented pleocytosis and increased protein; two had positive VDRL).

Syphilis treatment was administered soon after birth for 57% newborns. Most infants (97.6%) started treatment in the first two days of life; only one started treatment after >30 days. There were five neonatal deaths for CS (**Table 2**).

Considering the adequacy (or not) of both maternal and partners' treatment, 101 LB had confirmed CS; 21 (20.8%) of them were not treated at birth, even though 10 had clinical signs consistent with CS. All 21 children were followed-up in the SAE. Twenty were evaluated within a mean of 30 days after hospital discharge; three received syphilis treatment in the SAE. One child was evaluated only at two years of age, when VDRL was positive, and was then treated. Another child, asymptomatic at birth, had VDRL titers higher than maternal titers, but the mother rejected the child's treatment and quit the follow-up. All other children were not treated based on their VDRL results.

Children's assessment at two years of age showed 91.6% (130/142) were cured without sequelae, 10 (7%) had sequelae (one had pulmonary stenosis, two had global developmental delay, three had epilepsy, and four had pseudoparalysis and global development delay), and two died from causes unrelated to CS (**Table 2**).

In the analyses of the association of CS with the variables of interest, seven women with false-positive VDRL and one newborn with unknown outcome were excluded. Therefore, the analyses included 141 pregnant women; the twin pregnancies were considered only once.

CS was confirmed in 103 of the 141 LB, miscarriages, and stillbirths in mothers with SiP included in this analysis (prevalence, 73.1%; 95% CI, 64.9-80.2). In the bivariate

TABLE 1: Sociodemographic characteristics, prenatal care, and syphilis diagnosis and treatment of the 149 women with syphilis in pregnancy identified in Itapeva, São Paulo, from 2010 to 2014.

Characteristics	N	(%)
Age (years) (n=149)		
Mean (SD)	24.3 (6.6)	
Median (min – max)	24 (14 – 45)	
Skin color (n=149)		
white	124	(83.2)
black or brown	25	(16.8)
Level of education (n=146[1])		
incomplete elementary education	54	(37.0)
incomplete secondary education	49	(33.6)
complete secondary education	40	(27.4)
complete higher education	3	(2.0)
Place of residence (n=149)		
rural	10	(6.7)
urban	139	(93.3)
Occupation (n=149)		
homemakers	101	(67.8)
other	48	(32.2)
Number of sexual partners (n=113[1])		
<3	57	(50.4)
≥3	55	(48.6)
Smoked during pregnancy (n=131[1])	52	(39.7)
Drank alcohol during pregnancy (n=130[1])	26	(20.0)
Used illicit drugs during pregnancy (n=132[1])	18	(13.6)
HIV serology (n=148[1])		
positive	2	(1.4)
not done	5	(3.4)
HPV diagnosis during pregnancy (n=97 [1])	10	(10.3)
Diabetes mellitus during pregnancy (n=140[1])	6	(4.3)
Hypertension during pregnancy (n=142[1])	10	(7.0)
Had prenatal care (n=149)	141	(94.6)
Gestational age at the first prenatal visit (n=139[1])		
first trimester (≤13 weeks)	79	(56.8)
second trimester (14 – 27 weeks)	56	(40.3)
third trimester (≥28 weeks)	4	(2.9)
Number of prenatal visits (n=141[2])		
<6	34	(24.1)
≥6	107	(75.9)
Mean (SD)	7,8 (2,9)	
Median (min – max)	8 (1 - 15)	

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Absences in prenatal visits (n=141[2])		
0	83	(58.9)
≥1	58	(41.1)
Mean (SD)	1.3 (2.0)	
Had a non-treponemal syphilis serological test during pregnancy (n=141[2])	137	(97.2)
Positive result in the first serological test (n=137[3])	128	(93.4)
Gestational age at the time of the first syphilis serology (n=137[3])		
before the diagnosis of pregnancy	3	(2.2)
first trimester (≤13 weeks)	85	(62.0)
second trimester (14 – 27 weeks)	36	(26.3)
third trimester (≥28 weeks)	13	(9.5)
Time between the first prenatal care visit and the first serological test (n=137[3])		
≤15 days	110	(80.3)
16 – 30 days	6	(4.4)
31 – 60 days	7	(5.1)
61 – 90 days	3	(2.2)
>90 days	11	(8.0)
Had a treponemal test during prenatal care (n=149)	116	(77.9)
Gestational age at syphilis diagnosis (n=149)		
before pregnancy	3	(2.0)
first trimester (≤13 weeks)	85	(57.0)
second trimester (14 – 27 weeks)	31	(20.8)
third trimester (≥28 weeks)	13	(8.7)
at the time of delivery or curettage	17	(11.4)
Antibody titers in the first positive VDRL (n=149)		
≤1:4	64	(43.0)
>1:4	85	(57.0)
Clinical presentation of syphilis (n=105[1])		
primary	21	(20.0)
secondary or latent with <1 year's duration	59	(56.2)
latent with >1 year's duration	22	(20.9)
tertiary	3	(2.9)
Received a prescription of treatment during pregnancy (n=132[4])	128	(97.0)
Time between diagnosis and treatment prescription (n=128[5]) (days)		
≤7	22	(17.2)
8 – 15	18	(14.1)
16 – 30	45	(35.1)
31 – 60	22	(17.2)
61 – 90	8	(6.3)
>90	13	(10.1)

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Gestational age at the time of treatment prescription (n=128[5]) (weeks)		
≤13	50	(39.1)
14 – 27	57	(44.5)
≥28	21	(16.4)
Prescribed treatment regimen (n=128[5])		
Benzathine penicillin 2,400,000 IU	9	(7.0)
Benzathine penicillin 4,800,000 IU	6	(4.7)
Benzathine penicillin 7,200,000 IU	113	(88.3)
Received the prescribed treatment (n=128[5])	120	(93.8)
Treatment prescribed was adequate (n=128[5])	115	(89.8)
First treatment prescribed was ≥30 days before delivery (n=128[5])	115	(89.8)
Number of serological tests after treatment (n=120[6])		
0	18	(15.0)
1	33	(27.5)
≥2	69	(57.5)
Had monthly VDRL testing after treatment (n=120[6])	38	(31.7)
Received a retreatment prescription (n=120[6])	24	(20.0)
Received the prescribed retreatment (n=24[7])	18	(75.0)
Had a VDRL test after retreatment (n=18[8])	7	(38.9)
Last treatment prescribed was ≥30 days before delivery (n=128[5])	107	(83.6)
Partner was treated (n=140[1])	79	(56.4)
Partner's treatment regimen (n=79[9])		
Benzathine penicillin 2,400,000 IU	8	(10.2)
Benzathine penicillin 4,800,000 IU	5	(6.3)
Benzathine penicillin 7,200,000 IU	66	(83.5)
Partner's treatment was adequate (n=79[9])	68	(86.1)
Reason for not treating the partner (n=60[1])		
partner had no contact with the pregnant woman	23	(38.3)
partner was not called/communicated with	10	(16.7)
partner did not attend	1	(1.6)
partner refused treatment	7	(11.7)
partner with non-reactive serology test	15	(25.0)
patient changed partner	4	(6.7)

[1]Number of participants with available information; [2]Number of pregnant women who had prenatal care; [3]Number of pregnant women who had a nontreponemal test during prenatal care; [4]Number of pregnant women diagnosed during pregnancy; [5]Number of pregnant women who received treatment prescription; [6]Number of pregnant women who actually received the prescribed treatment; [7]Number of pregnant women who received a retreatment prescription; [8]Number of pregnant women who effectively received retreatment; [9]Number of partners who were treated.

SD: standard deviation; **HPV:** human papillomavirus; **VDRL:** Venereal Disease Research Laboratory.

analysis, a higher frequency of CS was observed in children of smokers, mothers who attended <6 prenatal visits, and mothers with late diagnoses (**Table 3**).

In the multiple regression, a statistically significant association between "gestational age at diagnosis" and "smoking during pregnancy" was observed. Among 76 women with gestational age <13 weeks at diagnosis, 22 (29%) were smokers, whereas among 48 women with gestational age >13 weeks at diagnosis, 29 (60.4%) were smokers (p=0.001, excluding 17 women without data on smoking). Hence, two final models were obtained: one with the variable "smoking" and another with "gestational age at diagnosis." In the first model, CS was independently associated with <6 prenatal visits (adjusted PR [aPR]=1.29, 95% CI, 1.05-1.57, p=0.014) and smoking

TABLE 2: Clinical-laboratory characteristics at birth, syphilis diagnosis, treatment, and outcomes of 147 live newborns of mothers with syphilis during pregnancy in Itapeva, São Paulo, from 2010 to 2014.

Characteristics	N	(%)
Gestational age at birth (n=143[1])		
<24 weeks	2	(1.4)
24 – 30 weeks	9	(6.3)
31 – 36 weeks	33	(23.1)
37 – 38 weeks	34	(23.8)
39 – 42 weeks	63	(44.0)
>42 weeks	2	(1.4)
Birth weight (n=146[1])		
normal (≥2,500 g)	94	(64.4)
low birth weight (1,500 – 2,499 g)	41	(28.1)
very low birth weight (1,000 – 1,499 g)	6	(4.1)
extremely low birth weight (<1,000 g)	5	(3.4)
Mean (SD)	2,825.3 (761.2)	
Median (min - max)	2,955 (443 – 4,390)	
Presence of clinical signs of syphilis at birth (n=142[1])	75	(52.8)
VDRL test results (n=143[1])		
≤1:4	66	(46.1)
>1:4	30	(21.0)
negative	36	(25.2)
not done	11	(7.7)
Cerebrospinal fluid analysis (n=145[1])		
Normal	31	(21.4)
Altered	45	(31.0)
Not done	69	(47.6)
Received specific treatment for syphilis (n=142[1])	81	(57.0)
Age at the beginning of treatment (n=81[2])		
0 days	74	(91.4)
1 day	5	(6.2)
3 days	1	(1.2)
34 days	1	(1.2)
Drug used for syphilis treatment (n=81[2])		
crystalline penicillin	43	(53.1)
procaine penicillin	2	(2.5)
crystalline penicillin + procaine penicillin	36	(44.4)
Outcome at the time of hospital discharge/notification (n=147)		
live	142	(96.6)
death from CS	5	(3.4)
Outcome at two years of age (n=142[3])		
cure without sequelae	130	(91.6)
healing with sequelae	10	(7.0)
death	2	(1.4)

[1]Number of infants with available information; [2]Number of newborns who received treatment for syphilis (81); [3]Number of infants live at the time of hospital discharge or notification (142).

SD: standard deviation; **CS:** congenital syphilis.

TABLE 3: Bivariate analysis of the factors associated with congenital syphilis in Itapeva, São Paulo, from 2010 to 2014.

Variables	Total	CS				
	n	n	%	PR	95% CI (PR)	p
Mother's skin color						0.505
white	118	85	72.0	1		
black or brown	23	18	78.3	1.09	0.85 – 1.39	
Age (years)						0.250
<25	82	63	76.8	1		
≥25	59	40	67.8	0.88	0.71 – 1.09	
Mother's educational attainment (years) (n=139)						0.691
≤8	73	52	71.2	1		
>8	66	49	74.2	1.04	0.85 – 1.28	
Number of sexual partners (n=107)						0.087
<3	52	41	78.8	1		
≥3	55	35	63.6	0.81	0.63 – 1.03	
Smoking during pregnancy (n=124)						0.001
no	73	44	60.3	1		
yes	51	44	86.3	1.43	1.15 – 1.78	
Use of alcohol during pregnancy (n=123)						0.399
no	97	67	69.1	1		
yes	26	20	76.9	1.11	0.87 – 1.43	
Use of illicit drugs during pregnancy (n=125)						0.179
no	92	62	67.4	1		
yes	33	26	78.8	1.17	0.93 – 1.47	
Gestational age at the first prenatal visit (n=132) (weeks)						0.238
<14	75	51	68.0	1		
≥14	57	44	77.2	1.14	0.92 – 1.40	
Number of prenatal visits (n=134)						<0.001
≥6	101	66	65.3	1		
<6	33	30	90.9	1.39	1.16 – 1.66	
Antibody titers in the first positive VDRL						0.053
≤1:4	58	37	63.8	1		
>1:4	83	66	79.5	1.25	1.00 – 1.56	
Gestational age at diagnosis						0.009
before pregnancy or ≤13 weeks	83	53	63.9	1		
14 – 27 weeks	29	25	86.2	1.35	1.09 – 1.68	
≥28 weeks or during delivery/curettage	29	25	86.2	1.35	1.09 – 1.68	

CS: congenital syphilis; **PR:** prevalence ratio, **CI:** confidence interval; **VDRL:** Venereal Disease Research Laboratory.

during pregnancy (aPR=1.36, 95% CI, 1.09-1.70, p=0.007). In the second model, CS was independently associated with <6 prenatal visits (aPR=1.30, 95% CI, 1.07-1.58, p=0.007), late diagnosis (second trimester: aPR=1.34, 95% CI, 1.08-1.68; third trimester/at delivery: aPR=1.17, 95% CI, 0.90-1.52, p=0.033), and antibody titers >1:4 in the first positive VDRL test (aPR=1.26, 95% CI, 1.01-1.58, p=0.042).

In this study, SiP annual detection rates in Itapeva (from 16.3 to 31.4/1,000 LB) were higher than mean rates in SP and Brazil (9.3 and 10.4/1000 LB, respectively, in 2014)[2]. CS annual incidence rates (from 9.1 to 22.3/1,000 LB) were also higher than rates in SP and Brazil (5.4 and 4.7/1,000 LB, respectively, in 2014)[2] and higher than rates estimated by municipal surveillance. Mother-to-child transmission rate

was high (69.7%), even though most women had prenatal care (94.6%), started prenatal care in the first trimester (56.8%), and attended ≥6 visits (75.9%).

This study identified 10 (6.6%) miscarriages, stillbirths, and neonatal deaths for CS; another 10 children had long-term sequelae related to CS. Early diagnosis and treatment of SiP, ideally before the 20th week of pregnancy may reduce fetal losses and infant deaths. However, in Itapeva, only 39.1% of women received treatment prescription in the first trimester.

The results point to the low quality of prenatal care as a key factor for the high CS rates in Itapeva. Many CS cases would have been prevented if the MoH recommendations for SiP were fully adopted. Other Brazilian studies also showed that prenatal care did not ensure an early SiP diagnosis, nor the timely and adequate treatment of pregnant women and their sexual partners, and did not prevent miscarriages, stillbirths, and deaths related to CS[3-10]. In SP state, from 2007 to 2014, there were 1,012 fetal losses due to CS (126 deaths, and 886 miscarriages and stillbirths)[5].

An increase in acquired syphilis cases may have also contributed to the increase in SiP and CS cases[5].

The care of newborns of mothers with SiP did not follow the MoH protocol either. VDRL was not performed for 7.7% of newborns, and 20.8% of newborns with confirmed CS did not receive specific treatment at birth. In SP state, in 2013, 44.5% of CS cases were not treated according to the protocol, and 29% of children with CS did not receive the recommended treatment[5]. Other studies have also pointed to a failure to perform recommended tests for newborns with CS, particularly VDRL in the CSF and radiological examinations[5-6].

In this study, smoking during pregnancy, attending <6 prenatal visits, starting prenatal care after the 13th week of pregnancy, and high VDRL antibody titers (>1:4) were independently associated with CS. Other Brazilian studies also found an association of CS with a low number of prenatal visits[5-6,11-13]. Low number of serological tests[6] and a lack of tests in the first trimester[6] were also associated with higher CS risk.

Higher CS rates in newborns of smokers were also reported previously[4,14]. Smoking affects the placental barrier and may increase mother-to-child transmission[4].

It is important to note that low VDRL titers (≤1:4) have clinical significance[15]. In a study in Belo Horizonte, 18.9% of the mothers of children with CS had VDRL titers ≤1:4 during pregnancy[6].

This study had limitations inherent to using secondary data, particularly underreporting, although an active search in the health services and laboratory increased its sensitivity. Other limits are the coverage and quality of information from medical records and notification reports.

Despite the protocols established by the MoH and the availability of syphilis diagnoses and treatment in health services responsible for prenatal care, CS elimination remains a challenge. Emphasizing SiP and CS importance to healthcare workers, managers, and the general population, improving prenatal care quality with inclusion and co-responsibility of sexual partners, and the use of methods such as rapid diagnostic tests that allows early and appropriate diagnosis and treatment of both pregnant women and sexual partners, are critical.

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Conflict of interest

The authors declare that there is no conflict of interest.

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