The Evaluation of Preventive and Control Measures on Congenital Syphilis in South China: A Time Series Modelling Study

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Research Article

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Abstract

Background:
The re-emergence of congenital syphilis (CS) was witnessed since the 1990s over the globe, including China. The country, therefore, carried out the prevention and control measures in an all-around way in 2010, including large-scale syphilis screening for pregnant women, providing standard treatment and follow-up management for both infected mothers and their infants, as well as the supportive strategies from the government as the response. However, there is a lack of the published evaluation for these measures when the deadline of the final goal (CS notification rate < 15/100,000 livebirths by 2025) is approaching. This study evaluates the effectiveness of CS control measures based on the change of the notification rate from 2005 to 2020 and predicts the CS case number in the following year in Guangdong, one of the provinces which used to have the highest CS notification rate in China.

Methods:
The interrupted time series analysis was conducted to compare changes in slope and level of CS notification rate from 2005 to 2020 in Guangdong Province and its three regions with different economic development levels. The year 2012 was identified as the intervention point, the time when Guangdong Province officially launched a bunch of measures. The autoregressive integrated moving average model was established to predict the CS case number of Guangdong Province in 2021.

Results:
A total of 12,687 CS cases were reported from 2005 to 2020. The notification rate of CS had been increasing in Guangdong Province until 2012 (128.55/100,000 livebirths), followed by a constant downward trend. It hit the lowest point in 2020 (5.76/100,000 livebirths), which was lower than the national goal set for 2025 (15/100,000 livebirths). The effectiveness of preventive and control measures was proved by the significant change in slope of the notification rate which was found in both of the whole province and two less-developed regions (-18.18, 95% CI: -25.63 to -10.75, -10.49, 95% CI: -13.13 to -7.86 and −32.89, 95% CI: -41.67 to -24.10, respectively). In the developed region where the notification rate had already been decreasing in the pre-program period, implementing these measures also aided in hastening the rate of descent. The CS case number in 2021 was predicted to be 48, which remains a low-level epidemic.

Conclusions:
The comprehensive preventive and control measures have assisted Guangdong Province to control CS and exceed the goal that China set for 2025 ahead of schedule. As these measures worked effectively in
places with varying levels of development and produced satisfying outcomes in regions with limited resources, it could be feasible to be generalized in other Low-and-Middle-Income countries where CS is still a public health concern.

**Background**

Congenital syphilis (CS) is a type of syphilis that can be transmitted from mother to child during pregnancy and brings the heaviest disease burden comparing with other types[1]. The CS has re-emerged in the world over the last few decades and lead to adverse birth outcomes (ABO) in up to 80% of CS cases[2, 3]. More than 500,000 cases of CS were reported globally in 2016, resulting in over 200,000 stillbirths and neonatal deaths[4]. This disease, on the other hand, can be effectively prevented and eventually eliminated through a variety of cost-effective interventions, such as early screening in antenatal care and immediate treatment[4]. Eliminating CS could benefit not only in reducing ABO attributable to syphilis but in improving the maternal health, contributing in the achievement of Sustainable Development Goals (SDG) of the United Nations.[5]. World Health Organization (WHO) therefore initiated a series of programs, such as the *Global health sector strategy on sexually transmitted infections 2016–2021*.

China has also experienced the resurgence since the 1990s. The notification rate of CS jumped from 0.53/100,000 live births to 64.41/100,000 live births over the last two decades, with an annual increase of 49.2%[5]. To respond to the rising epidemic, China piloted “*Regulations for the prevention of mother-to-child transmission of AIDS, syphilis and hepatitis B*” in 2010 [7], as well as “*The National Program of Syphilis Control and Prevention 2010–2020*” [6] Both of the policies had controlling CS notification rate under 15/100,000 livebirths by 2025 as one of their goals. What they had in common was the CS preventive and control measures, specifically: a) integrating the health education or consultation with antenatal care for pregnant women and encourage their partners to get tested b) implementing PMTCT services (including syphilis screening and treatment) for the infected mother and infants; c) standardizing the follow-up management and treatment for infants of CS positive mothers and d) supporting measures from the government. As of 2019, more than 10 countries and regions, had been validated as having eliminated CS by adopting the similar interventions, such as Thailand and Cuba[8, 9]. The intervention package was also addressed in the national syphilis control guideline of some developed countries with minor epidemic[10, 11]. WHO specifically emphasized the measure of “a strongly committed government” to ensure the effectiveness of CS control strategy[12], but the importance of the government’s role was not strongly emphasized by countries mentioned above. Instead, this was a critical component in China’s policies, namely the supportive measures provided by the government, including the supervision and data management, the sufficient financial subsidy, and the capacity building of health professionals, which are considered as the fundamental of implementing interventions.

China set the overall goal of achieving a CS notification rate of less than 15/100,000 live births in 2025, which were earlier than that of WHO (in 2030).
However, only few provincial evaluations were publicly published at the moment, two of which reported that neither of them achieved the mid-term goal (less than 30/100,000 livebirths by 2015) [13, 14]. Therefore, it is essential to conduct the latest evaluation to find out whether the core measures truly worked, especially in places with serious CS epidemic.

Time-series methods established upon historical data to both extract the underlying time-dependent structure and forecast the future developments. They have been commonly performed for the analysis of data for sexually transmitted disease[15, 16]. For example, interrupted time series analysis (ITSA) is a widely used approach to assess the effect of interventions introduced at the population level over a clearly defined period [17]. It has been increasingly popular in the evaluation of health policies related to PMTCT and HIV control [18, 19]. Also, another time series method, autoregressive integrated moving average models (ARIMA) could overcome the seasonal fluctuation of a linear trend and random error, which has been successfully applied to forecast the incidence of various infectious diseases [16].

Therefore, this study aims to provide the most recent assessment of CS preventive and control measures in Guangdong province, the province suffered the sever CS epidemic in South China, by conducting an ITSA and ARIMA model based on data from the national case-based surveillance system. The findings could serve as instructive scientific evidence for both domestic and international health sectors to develop more targeted strategies for CS elimination in the future, contributing to the SDGs of the UN.

Methods

Study Setting

Guangdong Province was selected as the study setting since it was one of the provinces with the highest CS notification rate in early 2000s [20]. Having the largest number of migrants in China[21] also added extra pressure to CS control and prevention[22]. We stratified all the 21 cities in Guangdong into three regions based on their geographic location and economic development status, namely, the Pearl River Delta (PRD) region, East & West wings, and the northern ecological development zone[23]. Specifically, PRD is the most developed region, whose the per capita GDP was almost 3 times more than that of the north zone[24]. This study explored the impact of CS preventive and control measures in Guangdong at both provincial and regional levels so that a more comprehensive evaluation can be provided.

Study design and data source

The interrupted time-series (ITS) design was used to estimate the change in CS notification rate before and after the implementation. Data about CS which contained annual and municipal case numbers from 2005–2020 was derived from the national case-based surveillance system by colleges of Dermatology Hospital, Southern Medical University, who had the permission to assess the data. Only the local confirmed cases were included in this study. The data of the annual live births were generated from Guangdong Health Statistical Yearbook (2005–2019). The information about economic development was obtained from Guangdong Statistic Book (2005–2019).
Outcomes

The main outcome of this study was the CS notification rate (1/100,000 livebirths) before and after the implementation of CS preventive and control measures.

Statistical analysis

The interrupted times series analysis

The ITSA was performed to detect changes in the slope and level of CS notification rate after releasing the program. A significant difference in changes between the pre-program period (2005–2011) and the post-program period (2012–2020) will indicate a significant impact of measures implemented [25].

ITSA requires the linearity and the non-autocorrelation of the data. The former was confirmed by Cochran-Armitage test ($P<0.001$) and the 1st -order autocorrelation was detected by conducting Cumby-Huizinga test, then corrected by Newey-West regression ($P>0.05$). Variables included in models were a) time, ranging from 1 to 16, representing the year 2005 to 2020; b) intervention is a dummy variable, which was code as 0 before the intervention and 1 after the intervention; c) post time, is the time count variable after the intervention. It was coded as 0 before intervention and the first observation after intervention and as 1 starting from the second observation afterwards. $\varepsilon_t$ is the residual at time $t$, which represents the variation that is not explained by the regression model. The segmented regression model was specified below:

$$Y_t = \beta_0 + \beta_1 \times \text{time} + \beta_2 \times \text{intervention} + \beta_3 \times \text{post time} + \varepsilon_t$$

Where $Y_t$ is the CS notification rate, $\beta_0$ represents the CS epidemic level at the time when the first observation was obtained (2005); $\beta_1$ represents the slope change estimate of CS notification rate number before implementing the intervention while $\beta_2$ represents the slope change before and after the implementation; $\beta_2$ represents the level change of CS notification rate after the intervention took place.

The year 2012 was identified as the intervention point when Guangdong Health Commission officially announced the implementation of “Regulations for the prevention of mother-to-child transmission of AIDS, syphilis and hepatitis B” and “The National Program of Syphilis Control and Prevention 2010–2020”, which contained 4 main preventive and control measures mentioned before[26, 27].

ARIMA model

ARIMA model has good prediction accuracy for various infectious diseases including syphilis[28], hence it was applied here to forecast the CS epidemic trend in 2021. The stationary sequence is the precondition of ARIMA analysis, however, the monthly notification rate was not available in this study and the annual values were too few to establish the model, the monthly case number was used instead. The stationary was then validated by the Augmented Dickey-Fuller test ($P<0.05$) after the 1st order log differential. The data from 2005–2019 was used to construct the model and that of 2020 was for the verification. The general form of the model is ARIMA ($p,d,q) \times (P,D,Q)$, where $p$, $d$, $q$ and $P$, $D$, $Q$ represent the order of the
autoregressive, integrated, moving average parts of non-seasonal and seasonal components respectively and s represents the length of the seasonal period (s = 12 for 12 months in this study)[29]. These parameters were estimated by autocorrelation function (ACF) graph and partial autocorrelation (PACF) graph[30] and chosen by the minimum Akaike's information criterion (AIC). Coefficients were calculated using the maximum likelihood estimation method (MLE). A white noise sequence of residuals was confirmed by the Box-Ljung test (P > 0.05). Diagnostic checking parameters, including the mean absolute error (MAE), root mean square error (RMSE), mean absolute percentage error (MAPE) were the indicators to evaluate the goodness-of-fit of the model.

The ITSA was performed in STATA Ver 15.1(Stata Crop 2011) and the optimal ARIMA model was selected using forecast::auto.arima() function in R software version 4.1.0 (R project for statistical computing, Vienna, Austria). The test for the regression coefficient was two-sided, α = 0.05. The map of CS notification rate distribution was drawn by ArcGIS 10.8 (Environmental Systems Research Institute Inc, Redlands, CA, USA.)

**Results**

**CS epidemic analysis**

A total of 12,687 confirmed CS cases were reported from 2005–2020 in Guangdong Province. The increasing trend of notification rate remained until 2007 when it began to decline slightly before reaching the peak in 2011 (128.55 cases/ 100,000 live births). It kept decreasing afterwards with the lowest notification rate was met in 2020 (5.75 cases/100,000 livebirths). Table 1 depicts the CS notification rate in Guangdong Province during the whole duration. A 95.52% decrease was observed after CS prevention and control measures were implemented. According to our result, Guangdong province achieved the goal set for CS control in the program (< 15 / 100,000 livebirths in 2025) ahead of time.
Table 1
The CS case number and notification rate of Guangdong Province, 2005–2020

| Year | Number of live births | Number of confirmed cases | Notification rate, 1/100,000 livebirths |
|------|------------------------|---------------------------|----------------------------------------|
| 2005 | 826,754                | 601                       | 72.69                                  |
| 2006 | 856,062                | 953                       | 111.32                                 |
| 2007 | 933,180                | 1,152                     | 123.45                                 |
| 2008 | 1,076,485              | 1,182                     | 109.80                                 |
| 2009 | 1,104,865              | 1,203                     | 108.88                                 |
| 2010 | 1,160,645              | 1,301                     | 112.09                                 |
| 2011 | 1,209,687              | 1,555                     | 128.55                                 |
| 2012 | 1,365,005              | 1,471                     | 107.76                                 |
| 2013 | 1,335,902              | 1,056                     | 79.05                                  |
| 2014 | 1,279,995              | 834                       | 65.16                                  |
| 2015 | 1,285,983              | 535                       | 41.60                                  |
| 2016 | 1,328,820              | 322                       | 24.23                                  |
| 2017 | 1,528,465              | 204                       | 13.35                                  |
| 2018 | 1,317,907              | 140                       | 10.62                                  |
| 2019 | 1,292,526              | 96                        | 7.43                                   |
| 2020 | 1,406,854              | 81                        | 5.76                                   |

(Note: Notification rate = number of confirmed cases/numbers of live birth*10,000)

We explored the geographic distribution of CS notification rate from 2005 to 2020 (See Fig. 1). The notification rate in most cities rose from 2005 and reached the peak around 2012, after when the case number started to fall, which coincided with

Figure 2 indicated that the CS notification rate mostly clustered at PRD in 2005 and then moved to the North Zone and East & west wings before the implementation (2011), when the notification rate was generally higher than in 2005. In 2020, all the cities witnessed a low-level epidemic, comparing with the other two years.

Specifically, the CS notification rate in PRD has been decreasing since 2007 while that of the other two regions had a slight increase, peaking around 2011 (See Fig. 3). The distinctive difference in CS
notification rate among these three regions can be observed, indicating that PRD has achieved the lowest CS notification rate among all the regions since 2015.

The effectiveness of CS preventive and control measures

Before the implementation, the average notification rate of Guangdong Province was 110.87 cases/100,000 live births and then dropped by 67.80% in the post-program period, namely 39.03 cases/100,000 live births. This change depicts the statistical significance. \( \beta_2 = -41.50, 95\% CI: -67.14 \text{ to } -15.85, P = 0.004 \). The slope change of CS notification rate was −18.19 before and after the measures were implemented, \( \beta_3 = -18.19, 95\% CI: -25.63 \text{ to } -10.75, P < 0.001 \), implying a significant declining trend. Figure 3 illustrated the difference in the changes of slope and level before and after the implementation.

In terms of three regions, the level change of notification rate was statistically significant \( P < 0.05 \) in PRD and the north development zone. The obvious change of slope was only found in non-PRD regions, which both showed an increasing pre-program trend and turned to be declining in the post-program period (See Fig. 5).

The parameter estimation results of all the interrupted time series analysis were all shown in Table 2.
Table 2
Results of multiple linear regression parameter estimations

| Variables                  | Coefficient | Standard error | t     | 95% CI              | P     |
|----------------------------|-------------|----------------|-------|--------------------|-------|
| **Guangdong Province**     |             |                |       |                    |       |
| Intercept                  | 87.46       | 14.77          | 5.92  | 55.29 to 119.64    | < 0.001 |
| time                       | 5.52        | 2.95           | 2.11  | -0.19 to 11.23     | 0.057 |
| intervention               | -41.59      | 11.77          | -3.52 | -67.24 to -15.94   | 0.004 |
| post-time                  | -18.04      | 3.36           | -5.36 | -25.38 to -10.71   | < 0.001 |
| **PRD**                    |             |                |       |                    |       |
| Intercept                  | 248.47      | 48.18          | 5.16  | 143.50 to 353.45   | < 0.001 |
| time                       | -3.38       | 8.67           | -0.39 | -22.28 to 15.51    | 0.703 |
| intervention               | -104.22     | 33.13          | -3.15 | -176.39 to -32.04  | 0.008 |
| post-time                  | -14.47      | 48.18          | -1.57 | -34.60 to 5.65     | 0.143 |
| **East & West wings**      |             |                |       |                    |       |
| Intercept                  | 9.81        | 4.40           | 2.23  | -0.22 to 19.39     | 0.046 |
| time                       | 4.44        | 1.14           | 3.89  | 1.95 to 6.93       | 0.002 |
| intervention               | 10.94       | 6.29           | 1.74  | -2.76 to 24.65     | 0.107 |
| post-time                  | -10.49      | 1.21           | -8.67 | -13.13 to -7.86    | < 0.001 |
| **North ecological development zone** | | | | | |
| Intercept                  | 19.19       | 6.31           | 3.04  | 5.43 to 32.94      | 0.010 |
| time                       | 16.91       | 2.01           | 8.40  | 12.52 to 21.29     | < 0.001 |
| intervention               | -45.54      | 15.07          | -3.02 | -78.39 to -12.68   | 0.011 |
| post-time                  | -32.88      | 4.03           | -8.15 | -41.67 to -24.09   | < 0.001 |

Considering that the values of CS notification rate among three regions vary greatly, a semi-logarithmic line graph (Fig. 6) was made to compare their rate at which the CS incidence decline over time. It demonstrated that the notification rate of PRD dropped at a similar rate with that of the North zone after 2012 and showed a more obvious decrease since 2017. Hence, although the slope change of PRD was not considered as significant, a nearly fastest rate of decline was observed in the post-program period. The East & West wings had a relatively stable trend, which explained the insignificance of its level change. **The forecasting of CS case number in Guangdong Province**
Table S1 (Additional file) displayed the monthly CS case number, based on which the time sequence diagram (Additional file, Figure S1) was created. In line with the diagram, the monthly CS case number from 2005–2020 was not stationary and needed to be stabilized to establish ARIMA \((p,d,q) \times (P, D, Q)\) s model. Therefore, the 1st order log differential was performed and the new diagram was presented in Figure S2 (Additional file). ACF and PACF graph was also listed in Figure S3 (Additional file). The optimal model ARIMA \((0,1,1) \times (1,0,2)\)\(^{[12]}\) was selected based on AIC criteria and its prediction accuracy was confirmed by a white noise residuals sequence (Box-Ljung test: \(P>0.05\)). The model presented a satisfying fitting result (See Fig. 7.) and predicted the CS case number in 2021 as 48, of which the monthly case number all located within 95% CI. The forecasting result was presented in Table S2 (Additional file).

| Time series                  | Optimal Model            | Goodness-of-fit | Ljung-Box test |
|-----------------------------|--------------------------|-----------------|----------------|
|                             | (0,1,1) \times (1,0,2)\(^{[12]}\) | 0.36            | 0.43           |

### Discussion

Multiple policies with a bunch of CS preventive and control measures were conducted at the same period (2010–2020), which involved integrating the syphilis screening with health education, the standard treatment for pregnant women and the follow-up of infants of CS patients, alongside supportive strategies from the government. These policies targeted at eliminating MTCT of syphilis and turned out to be effective in Guangdong Province, as evidenced by the significant difference in CS notification rate before and after the implementation. The CS new cases would be fewer in the following year.

Particularly, at the provincial level, the notification rate of CS rose from 72.69 to 128.55/ 100,000 livebirths in the pre-program period, reflecting the heavy disease burden which the re-emergence brought.\(^{[1]}\) Also, some researchers believed that the upgrade of the national reporting system for infectious diseases which reduced underreporting partially contributed to the increase \(^{[31]}\). After implementing the CS control measures, Guangdong Province showed 95.52% of decline in CS notification rate from 2012 to 2020. The significant change in slope and level demonstrated the effectiveness that these core measures contributed to.

In terms of the regional level, it was not surprising to find the most severe CS epidemic in PRD, the region with the highest GDP \(^{[32]}\). It was a consensus decades ago that the developed regions tended to suffer a heavier disease burden of CS\(^{[33]}\) and urban citizens were more vulnerable than rural ones because of their more frequent high-risk sexual behaviour\(^{[34]}\). However, a clear decreasing trend in CS notification rate of PRD was witnessed since 2007 and it became the region with the lowest CS notification rate in
In 2015, 3 years after the implementation. Digging into the reason of this progress, we discovered that PRD owned over 60% of GDP and 70% of top-tier hospitals over the province[35, 36], implying the abundant medical resources and the great capacity to prevent and control the disease. For instance, Shenzhen, one of the most developed cities in the province, launched the Program of Prevention of Mother-to-Child Transmission of Syphilis in Shenzhen (PPSS) in 2002, which involved free syphilis test for pregnant women, treatment for positive individuals and 18 months’ follow-up for their babies[37]. It cost almost 2800 million Yuan in total (around 431.7 million US dollars) [38] and resulted in a 91.3% decrease in CS notification rate from 2002 to 2011[39]. Therefore, since the epidemic of PRD had already been controlled before 2012, presenting a constant downward trend, insignificant change in slope was detected. However, the progress cannot be neglected because of its nearly fastest among all the regions and the lowest notification rate after 2015. Moreover, the CS case is predicted to be 48.

These all indicated that the measures they took earlier were sustainably effective and long-term rewarding.

In contrast, two less-developed regions (East & west wings and North ecological development zone) both had a rising trend of CS notification rate before the implementation. This could presumably bring a heavier disease burden as they possessed fewer medical resources and poorer public health capacity than PRD. In line with Guangdong province Statistic Bureau [32], the north ecological development zone had the lowest GDP and pregnancy screening rate and the fewest hospitals but the highest mortality rate of newborns among all the three regions, followed by East & west wings. These suggested its weak capacity to prevent and control the CS.

Additionally, recent research found that pregnant women in underdeveloped regions had a higher risk of contracting syphilis. This was because that their husbands who might be ‘return migrants’ from urban to rural areas, possibly had untreated syphilis or high-risk sexual behaviour due to the lack of awareness of the disease. It was thus likely that they transmitted the disease to their wife, leading to the occurrence of CS[40]. In this study, the north ecological development zone had the highest net emigration[41], implying a large number of migrant returnees. This should have explained why its CS notification rate was higher than the east & west wings, where the population mobility was less active. LMICs such as Tanzania[42], Mozambique[43] and Nepal [44] have also identified this phenomenon as a potential source of additional CS cases. However, the situation in both two regions started to improve when the preventive and control measures were launched and ended up with a low-level epidemic trend. This proved that the measures worked effectively not only in developed regions but also the resource-constrained settings.

However, CS is still endemic in many other LMICs, accounting for the most cases globally[12]. These countries also faced similar challenges with two underdeveloped regions in our study, such as limited medical resources, the weak public health capacity and the large number of migrants, as previously mentioned [12, 45]. WHO pointed out that there was a lack of guidelines for health service providers in LMICs to prevent this disease. Given that Guangdong Province already had control CS epidemic even in
its underdeveloped regions through preventive and control measures, it is possible to generalize them in countries facing the same barriers as Guangdong.

Specifically, the dominant interventions that Guangdong conducted, in particular, providing syphilis-related health education to pregnant women, large-scale screening, standard treatment, as well as the follow-up or the referral of infected mother and their infants, have been already considered as cost-effective by WHO[12]. However, a series of supporting measures from the government was the fundamental of the implementation. It addressed improving the surveillance system, assuring financial subsidy, strengthening the capacity building and so on. To be detailed, the regular supervision was conducted following the order of “provincial-municipal-county level”. The central government allocated particular subsidy to CS control every year in accordance with the number of people in need[46]. All above were referred as “governance commitment” that was called for by WHO [12]. Hence, if countries with CS epidemic could carry out all these measures above, a positive result could be rewarded in the end.

The generalization of these measures would also be considered as part of international cooperation, which is of great importance for global CS elimination. Additionally, more problems would be also found out when localizing, which can help them to remove obstacles and get closer to the CS elimination eventually.

**Limitations**

Several limitations existed in this study. First, more than 18 observations were usually recommended for ITSA[47]. However, the data before 2005 in this study was unable to obtain because of the upgrade of the national reporting system and we thus have only 16 observations. Despite this, multiple factors such as the sample size per time point, location of intervention in the time series, also need to be taken into consideration when applying ITSA[48]. The sample size per time point of this research came from over 12,000 CS cases and the intervention point was located right in the middle of the whole duration. These could both increase the power of ITSA, which compensated for the impact of insufficient observations[48]. Second, the effects of confounding factors such as population mobility could not be examined because of the limited information. Further research at the individual level is therefore suggested. Third, since the monthly live births number was unable to access, it was replaced by CS case number to construct the ARIMA model. Hence, a minor difference might exist between results using these two indicators. Finally, this study only analysed the data of Guangdong Province, therefore more consideration will be required when making the general conclusion about the effectiveness of these measures in the whole country.

**Conclusions**

In conclusion, as CS preventive and control measures have greatly contributed to control the epidemic in Guangdong Province, which has achieved the goal for 2025 earlier than planned, there is also the probability of generalizing it in other LMICs, particularly in those which still have an upward epidemic
trend but with the constrained resource. The satisfying outcome could be expected in regions that face similar challenges as less-developed regions of this study, including the lack of resources, the risk of CS spreading that brought by migrant returnees and the poor CS awareness of both health workers and the public. In that case, all the countries, especially LMICs, could move closer to WHO's goal of eliminating congenital syphilis in 2030.

**Abbreviations**

ABO: Adverse Births Outcomes;
ACF: Autocorrelation Function
AIC: Akaike's Information Criterion
ARIMA: Autoregressive Integrated Moving Average Model
CS: Congenital syphilis;
GDP: Gross Domestic Product;
ITSA: Interrupted Times Series Analysis;
LMICs: Low- and Middle-Income Countries;
MAE: Mean Absolute Error
MAPE: Mean Absolute Percentage Error
MLE: Maximum Likelihood Estimation Method
PACF: Partial Autocorrelation Function
PMTCT: Prevention of Mother to Child Transmission;
PMCHT: Preventing Mother to child HIV transmission;
PPSS: Program of Prevention of Mother-to-Child Transmission of Syphilis in Shenzhen;
PRD: Pearl River Delta;
RMSE: root mean square error
UN: the United Nations
WHO: World Health Organization
Declarations

Ethics approval and consent to participate

The data used in this study was second-handed and all the identical information was removed in the process of analysis. Therefore, the ethical approval would not be a necessity here.

Consent for publication

Not applicable

Availability of data and materials

The dataset analysed during the current study are not publicly available as it was derived from the national system and only staff with permission have assessment. If data is truly needed, please contact the corresponding author Wang Cheng.

Competing interests

All of the authors declared that they had no competing interest.

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Authors' contributions

Conceptualization, Xijia Tang, Shangqing Tang, Wen Chen and Li Ling; Data curation, Peizhen Zhao and Cheng Wang; Formal analysis, Xijia Tang, Shangqing Tang; Funding acquisition, Cheng Wang and Li Ling; Investigation, Peizhen Zhao and Cheng Wang; Methodology, Xijia Tang, Shangqing Tang; Project administration, Cheng Wang and Li Ling; Resources, Cheng Wang; Supervision, Cheng Wang and Li Ling; Validation, Xijia Tang, Shangqing Tang and Peizhen Zhao; Writing – original draft, Xijia Tang, Shangqing Tang; Writing – review & editing, Xijia Tang, Shangqing Tang, Wen Chen and Li Ling

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**Figures**
Figure 1

The geographical distribution of congenital syphilis notification rate in each city of Guangdong province from 2005 to 2020. Blue color represented Pearl River Delta, green color represented the north ecological development zone and orange color represented the east & west wings.
Figure 2

The geographical distribution of CS notification rate in Guangdong province in 2005(a), 2011(b) and 2020(c). The darker colour indicates the higher notification rate.
Figure 3

The annual congenital syphilis notification rate of Guangdong Province and three regions from 2005-2020.
Figure 4

Interrupted time series plot of annual change of congenital syphilis notification rate in Guangdong Province, before and after the implementation of the CS control measures. The intervention year was 2012. The slope and level change were both significant, p<0.05.
Interrupted time series plot of congenital syphilis notification rate change of three regions in Guangdong Province. The intervention year was 2012. The level change in PRD (Figure 4a) and North ecological development zone (Figure 4c) were both significant, P<0.05; the slope change in the North ecological development zone (Figure 4c) and East & west wings (Figure 4b) were both significant, P<0.05.

**Figure 5**
Figure 6

The semi-logarithm line graph of the regional congenital syphilis notification rate from 2005-2019.
Figure 7

Monthly CS case number from 2005 to 2019 as reported (in black) and fitted by the optimal ARIMA model (in blue). ARIMA-based forecast of CS case number was presented in sky-blue color and displayed a 95% prediction interval (grey ribbon).

Supplementary Files

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