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Association between syphilis seroprevalence and age among blood donors in Southern China: an observational study from 2014 to 2017

Xiaobing Wu,[1] Yang Guan,[2] Jianbin Ye,[1] Hanlin Fu,[3] Chunlai Zhang,[1] Lina Lan,[1] Fengxin Wu,[4] Fen Tang,[1] Feng Wang,[5] Yumao Cai,[1] Weiye Yu,[1] Tiejian Feng[1]

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For numbered affiliations see end of article.

Correspondence to
Xiaobing Wu; bingfsh@126.com

ABSTRACT

Objective This study investigated the association between syphilis seroprevalence and age among blood donors, and described the distribution of serological titres among syphilis-infected donors, aiming to confirm the syphilis epidemic characteristics and to promote effective interventions for older adults.

Methods Data were obtained from the Shenzhen Programme for Syphilis Prevention and Control in 2014–2017. Blood samples were screened using the ELISAs, and confirmed using the *Treponema pallidum* particle agglutination assay (TPPA) and toluidine red unheated serum test (TRUST).

Results Among 394 792 blood donors, 733 tested TPPA and TRUST positive (active infection), and 728 tested only TPPA positive (historical infection). The overall prevalence of syphilis seropositivity was 370.1 per 100 000 (95% CI 351.1 to 389.0 per 100 000); the prevalence of active infection was 185.7 per 100 000 (95% CI 172.2 to 199.1 per 100 000). People aged ≥45 years displayed a prevalence of 621.8 per 100 000 in syphilis seropositivity and 280.5 per 100 000 in active infection, which were 3.8 times and 2.4 times higher than that for people aged <25 years, respectively. The prevalence of syphilis seropositivity (χ^2_{trend}=311.9, p_{trend}<0.001) and active infection (χ^2_{trend}=72.1, p_{trend}<0.001) increased significantly with age. After stratification by gender and year of donation, the increasing trend of prevalence with age remained (p_{trend}<0.05), except for the prevalence of active infection in males and females in 2014. About 16.3% of donors with active infection and aged ≥45 years had a TRUST titre of ≥1:8, lower than that of patients aged <25 years (51.3%) and 25–34 years (34.1%).

Conclusions The findings confirm the high prevalence of syphilis among older adults, and suggest the need to increase awareness among healthcare providers and deliver more targeted prevention interventions for older adults to promote early testing.

Strengths and limitations of this study

- This study described the syphilis seroprevalence among nearly 400 000 blood donors, including syphilis seropositivity, active infection and distribution of serological titres.
- The testing process in this study, using ELISAs as a screening test and then using *Treponema pallidum* particle agglutination assay and toluidine red unheated serum test to confirm the serostatus, increased the accuracy of syphilis seroprevalence.
- Lack of information on syphilis seroprevalence between first-time donors and repeat donors was a limitation to this study.

INTRODUCTION

The global population is ageing as a combined result of the demographic transition from high to low levels of fertility and mortality.[1] Population ageing increases the total global disease burden, with approximately 23% attributable to disorders in people aged ≥60 years.[2] Chronic non-communicable diseases, including cardiovascular disease, malignant neoplasms and chronic respiratory diseases, are the leading contributors to disease burden in older people.[2] However, infectious diseases also considerably affect older people, as an increasing incidence of infectious diseases, such as HIV and syphilis, was shown from the recent surveillance data.[3–5] This large disease burden among older people calls for improvements in the healthcare system and more investments and programmes focusing on healthy ageing.[2]

Syphilis, caused by *Treponema pallidum*, is a chronic infection with diverse clinical manifestations occurring in distinct stages, and may lead to blindness, dementia, delirium and death, if not treated immediately or adequately.[6] Syphilis can also aid the passage for HIV to invade, reduce the CD4 T-cell levels and increase the viral load, thereby aggravating the harm caused by HIV.[7] Even though syphilis can be effectively treated with penicillin, about 36.4 million new cases occur annually.[8] In China, the syphilis epidemic has rapidly increased, with a 16.3% increase

per year during the first decade after the severe acute respiratory syndrome outbreak.[9] The reported incidence was slightly higher among females than males (ratio 1.00:0.92), but it varied significantly with age.[5] Younger people (aged 20–39 years) reported the highest syphilis incidence and accounted for the largest proportion of newly reported cases; however, the older age groups (aged ≥45 years) had the fastest growth in incidence, and males aged ≥60 years displayed a peak incidence of latent syphilis in the last decade.[5] With the accelerated ageing of the global population, the increasing syphilis epidemic among older adults is alarming.

Shenzhen, a special economic zone located in southern China and with a population of >10 million, is one of the cities that most affected by syphilis. The reported incidence of syphilis was over 60 per 100 000 in last 10 years, which was much higher than the national incidence.[5 10] Consistent with the aforementioned characteristics of varied age groups, a rapid increase in syphilis incidence among older adults was observed in Shenzhen.[11] Studies usually considered blood donors as a representative of the general population and used the prevalence data of blood donors for real-time surveillance and identification of high-risk groups.[12] Whether the syphilis seroprevalence among blood donors agrees with reported incidence characteristics remains to be studied. Shenzhen launched a comprehensive programme, the Shenzhen Programme for Syphilis Prevention and Control (SPSPC), in November 2013 to enhance syphilis screening among blood donors and five other subgroups (HIV voluntary counsellors, methadone maintenance treatment users, female sex workers, men who have sex with men and women of childbearing age), as well as case management, including diagnosis, treatment and follow-up, for syphilis-infected adults.[13] Based on the data from the SPSPC, this study aimed to examine differences in syphilis seroprevalence among blood donors and describe the distribution of serological titres among syphilis-infected donors with respect to age groups, to confirm the syphilis epidemic characteristics in southern China and support the design of effective interventions for older adults.

METHODS

Subjects and blood donation process

Blood donors were recruited by the Shenzhen Blood Center between 2014 and 2017. About 10 blood mobiles, with the Shenzhen Blood Center logo and the words 'non-remunerated blood donation', were dispatched around the city to increase the accessibility of blood donation. Volunteers could either go to the mobiles or to the blood centre directly.

Before donation, all potential donors needed to sign a donation registration form, complete a health history questionnaire, and undergo rapid testing and a brief physical examination. A concise introduction of blood use, donation procedure, laboratory testing, and legal and regulatory requirements was shown at the front of the registration form. Inform consent was obtained from the donors for the laboratory testing and use of the blood, the academic use of the data and the publication of the report. The health history questionnaire contained a total of 27 medical conditions that would permanently or temporarily prevent the donors from donation, including a series of chronic diseases and infectious diseases (eg, HIV, syphilis), transplant, high-risk behaviours (eg, homosexual behaviours, drug use), surgery, delivery, breast feeding. Predonation repaid testing included blood type, haemoglobin, hepatitis B surface antigen and alanine transaminase. Weight, blood pressure, heart rate and body temperature were measured. Clinical examination of the skin and limbs was conducted. People who conformed to the Whole Blood and Component Donor Selection Requirements (GB 18467–2001) could proceed to donate blood. All blood donors were non-remunerated. Light refreshment, a blood donation certification and a blood credit allowing free transfusion for donors or their direct relatives were provided as incentives. The donation process and blood management were fully in accordance with the Blood Donation Law of the People's Republic of China and the Blood Donation Regulation of the Shenzhen Special Economic Zone.

Serological testing

After donation, the blood samples were transferred to the Shenzhen Blood Center and underwent a series of laboratory testing. The ELISAs with two different reagents (Zhuhai Lizhu Bio-engineering, Zhuhai, China; DiaSorin S.p.A. UK Branch, UK) were performed simultaneously on all blood samples for syphilis screening. Syphilis-positive samples of one or both screening assays, with a form listing the donors' name, age and gender, were then transferred to the Shenzhen Center for Chronic Disease Control (SZCCC, a city-level prevention and control centre for sexually transmitted diseases (STDs)) under SPSPC guidelines. A treponemal test of *T. pallidum* particle agglutination (TPPA; Fujirebio, Tokyo, Japan) and a non-treponemal test of toluidine red unheated serum test (TRUST; Shanghai Rongsheng BioTech, Shanghai, China) were used at the SZCCC to confirm the infection status. TRUST-positive samples further underwent quantitative titre testing to monitor response to treatment. TPPA and TRUST results were sent back to the Shenzhen Blood Center within 2 days after the samples were received.

Definition of syphilis infection

Based on serological test results, syphilis seropositivity was divided into historical infection and active infection, which was consistent with the classification from previous studies.[12] Historical infection was defined as TPPA positive but TRUST negative and active infection as both TPPA and TRUST positive.[14] Syphilis seropositivity was defined as TPPA positive, including both TRUST negative and TRUST positive. Moreover, high-titre was defined as a quantitative titre of ≥1:8 in patients with active infection. For the purpose of this study, syphilis seropositivity, which represented the overall infection status among the target

population, and active infection and high-titre status which were correlated with disease activity, were analysed.

Statistical analysis

Data of donors' number among different subgroups (age, gender and year of donation) and syphilis testing results were sourced from the Shenzhen Blood Center and the SZCCC, respectively. Primary outcomes of interest were the prevalence of syphilis seropositivity and active infection among all blood donors in different age groups. There were four age groups, <25, 25–34, 35–44 years and ≥45 years, fully considering the age coverage of blood donors and age classification in previous studies.[15 16] We calculated the crude prevalence and its 95% CI. The χ^2 test for trend was used to assess the difference in prevalence among age groups. ORs and their 95% CIs were calculated when comparing the risk of syphilis seropositivity and active infection between the ≥45 years age group and other age groups. Line graphs were used to describe the changes in prevalence for both syphilis seropositivity and active infection among the age groups after stratification by gender and year of donation. Furthermore, we described the distribution of TRUST titres among the age groups and compared the difference using the χ^2 test for trend. Data were analysed using SPSS V.17.0 for Windows (IBM); p<0.05 was considered statistically significant in the χ^2 test.

Patient and public involvement statement

Patients and the public were not involved in developing the hypothesis or research questions, nor were they involved in developing plans for the design or implementation of this study. The staff of the Shenzhen Blood Center were responsible for telling syphilis-positive participants about the test results and providing referral services related to syphilis treatment and management by phone.

RESULTS

Demographic characteristics

From 2014 to 2017, a total of 394 792 donors were recruited by the Shenzhen Blood Center for non-remunerated blood donation. Among them, 67.4% were male and 85.0% were aged <45 years. The distribution of age was varied between genders (χ^2=11 249.0, p<0.001) and among years of donation (χ^2=1182.0, p<0.001). People aged 25–34 years accounted for the largest proportion of donors (table 1).

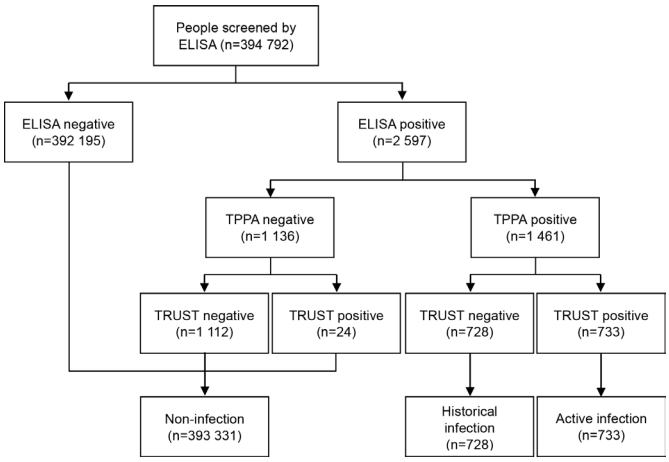

Figure 1 Flow chart for syphilis screening and confirmatory testing among blood donors. TPPA, *Treponema pallidum* particle agglutination assay; TRUST, toluidine red unheated serum test.

Prevalence of syphilis seropositivity and active infection

After ELISA testing, 2597 samples tested positive and were sent to the SZCCC for further examination. Among them, 733 (28.2%) were both TPPA and TRUST positive, 728 (28.0%) were only TPPA positive, and 1136 (43.7%) were false positive (figure 1). The overall prevalence of syphilis seropositivity was 370.1 per 100 000 (95% CI 351.1 to 389.0 per 100 000), and the prevalence of active infection was 185.7 per 100 000 (95% CI 172.2 to 199.1 per 100 000). The prevalence of syphilis seropositivity and active infection was higher among females than males (syphilis seropositivity: χ^2=60.4, p<0.001; active infection: χ^2=36.1, p<0.001) and showed a decreasing trend from 2014 to 2017 (syphilis seropositivity: χ^2_{trend}=27.1, p_{trend}<0.001; active infection: χ^2_{trend}=7.8, p_{trend}=0.005). People aged ≥45 years reported the highest prevalence of both syphilis seropositivity and active infection, which was 3.8 times (OR 3.8; 95% CI 3.1 to 4.6) and 2.4 times (OR 2.4; 95% CI 1.9 to 3.0) higher than that among people

Table 1 Characteristics of blood donors in different age groups in Shenzhen, 2014–2017

Variables	Aged <25 years (n=95 736), (%)	Aged 25–34 years (n=137 447), (%)	Aged 35–44 years (n=102 422), (%)	Aged ≥45 years (n=59 187), (%)	χ^2	P value
Gender					11 249.0	<0.001
Male	51 409 (19.3)	96 237 (36.2)	74 445 (28.0)	44 061 (16.6)		
Female	44 327 (34.5)	41 210 (32.0)	27 977 (21.7)	15 126 (11.8)		
Year of donation					1182.0	<0.001
2014	22 389 (25.3)	31 929 (36.0)	23 131 (26.1)	11 210 (12.6)		
2015	24 330 (25.7)	33 096 (35.0)	24 011 (25.4)	13 241 (14.0)		
2016	24 560 (24.0)	35 736 (34.9)	26 362 (25.7)	15 843 (15.5)		
2017	24 457 (22.4)	36 686 (33.7)	28 918 (26.5)	18 893 (17.3)		

aged <25 years, and 2.3 times (OR 2.3; 95% CI 2.0 to 2.6) and 1.8 times (OR 1.8; 95% CI 1.5 to 2.2) higher than that among people aged 25–34 years, respectively. Trend analysis showed that the prevalence of syphilis seropositivity (χ^2_{trend}=311.9, p_{trend}<0.001) and active infection (χ^2_{trend}=72.1, p_{trend}<0.001) increased significantly with age (table 2). After stratification by gender and year of donation, the increasing trend of prevalence with age remained (p_{trend}<0.05), except for the prevalence of active infection among males (χ^2_{trend}=0.923, p_{trend}=0.337) and females (χ^2_{trend}=0.224, p_{trend}=0.636) in 2014 (figure 2).

Distribution of TRUST titres

Among 733 donors with active infection, a TRUST titre of 1:1 accounted for the largest proportion (41.7%), followed by a titre of 1:2 (24.1%). About 27.0% had a TRUST titre of ≥1:8. The distribution of TRUST titres was varied among the age groups (figure 3). Patients aged ≥45 years comprised a large proportion of low titres at 1:1 and 1:2, and the proportion of high titres was only 16.3%, which was much smaller than that among patients aged <25 years (51.3%) and 25–34 years (34.1%). The proportion of high titre declined significantly with age (χ^2_{trend}=53.6, p_{trend}<0.001) (table 3).

DISCUSSION

This study identified that the overall prevalence of syphilis seropositivity among nearly 400 000 blood donors in 2014–2017 was 370.1 per 100 000, which was higher than that reported in the USA (54.6 per 100 000) and Brazil (135.5 per 100 000),[12 17] but lower than that reported in Ethiopia (732.4 per 100 000), Cameroon (3976.3 per 100 000) and India (1623.7 per 100 000).[18–20] The prevalence was similar to that in many cities in mainland China, such as Xi'an (359.6 per 100 000), Urumqi (359.3 per 100 000) and Kunming (381.2 per 100 000).[15,21] However, unlike some studies that used only one method (ie, ELISA) to confirm the syphilis infection status and report the prevalence,[15 19 21 22] this study used ELISA as a screening test and then used TPPA and TRUST to confirm the serostatus if screened positive. As is known, ELISA is a method used worldwide for syphilis screening, with a sensitivity of >95% and specificity of >99% according to the reagent evaluation.[23] TPPA is considered as the gold standard test in syphilis diagnosis. Surprisingly, only 56.3% of ELISA-positive patients in this study were confirmed by TPPA, meaning the positive predictive value (the value associated with sensitivity, specificity and disease prevalence) for ELISA on syphilis was below 60% among blood donors. The testing process in this study greatly reduced the number of false positives and increased the accuracy of syphilis seroprevalence.

To our knowledge, this study is the first in-depth study focusing on active infection and serological titre distribution of syphilis among blood donors in mainland China. Active infection is different from historical infection as the former indicates more transmission and late syphilis

Table 2 Prevalence of syphilis seropositivity and active infection among blood donors in different age groups

Age group	No of screened	Syphilis seropositivity				Active infection			
		No	Prevalence per 100 000 (95% CI)	χ^2_{trend}	P_{trend} value	No	Prevalence per 100 000 (95% CI)	χ^2_{trend}	P_{trend} value
Aged <25 years	95 736	158	165.0 (139.3 to 190.8)	311.9	<0.001	113	118.0 (96.3 to 139.8)	72.1	<0.001
Aged 25–34 years	137 447	376	273.6 (245.9 to 301.2)			211	153.5 (132.8 to 174.2)		
Aged 35–44 years	102 422	559	545.8 (500.7 to 590.9)			243	237.3 (207.5 to 267.0)		
Aged ≥45 years	59 187	368	621.8 (558.4 to 685.1)			166	280.5 (237.9 to 323.1)		

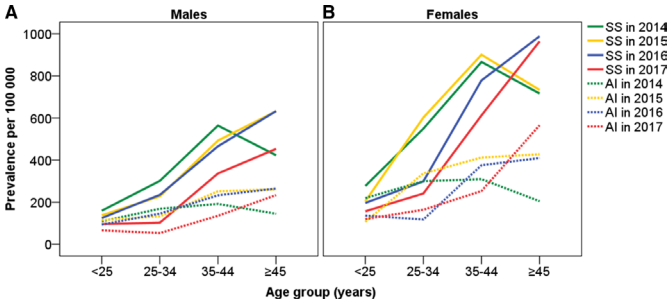

Figure 2 Prevalence of SS and AI in different age groups, 2014–2017. (A) Prevalence of SS and AI among males. (B) Prevalence of SS and AI among females. AI, active infection; SS, syphilis seropositivity.

if without timely and adequate treatment. The higher the serological titre, the more the risk of transmission (eg, mother-to-child transmission) and adverse outcomes.[24] This study documented that 50.2% (733/1461) of syphilis seropositive donors had active infection, and 13.6% (198/1461) had a TRUST titre of ≥1:8. Here, the proportion of high titres among syphilis seropositive patients was similar to that reported in the USA.[12]

This study found that syphilis prevalence significantly increased with age. Older adults aged ≥45 years displayed the highest prevalence of both syphilis seropositivity and active infection. More importantly, from the national surveillance data, people aged ≥60 years had a remarkably higher increase in reported incidence compared with those aged 45–60 years.[5] Hospitalised patients aged ≥70 years showed the highest syphilis prevalence (4.8%), followed by patients aged 61–70 years (3.9%) and those aged 51–60 years (3.2%), which was much different from that for HIV infection for which patients aged 31–40 years recorded the highest prevalence.[25] Based on the results of this study and previous studies, health awareness and syphilis prevention focusing on older adults are needed.

The higher prevalence among older adults might be due to several reasons. First, many older people are sexually active,[26] and their sexual health and behaviour affect syphilis transmission. Low self-perception of risk

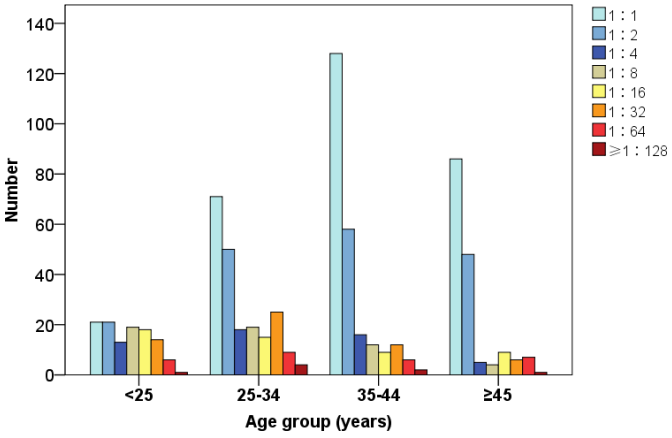

Figure 3 Distribution of TRUST titres among active infection donors in different age groups. TRUST, toluidine red unheated serum test.

and misconceptions or limited knowledge about syphilis and other STDs were frequently reported as reasons for condomless sex among older adults.[5 27] Second, older adults have been largely neglected by healthcare providers due to age-related stigma.[28] Sexual health services for HIV or STDs rarely focus on older adults, leaving this group behind in both testing and prevention. Third, presenting with a late diagnosis has been significantly associated with older age. Older people were more likely to be aware of their serostatus when in hospital or had an active offer for testing.[29] In this study, analysis of the TRUST results suggests that >90% of syphilis-infected people aged ≥45 years with TRUST negative or with low titres had a previous infection. However, late presentation is particularly worrying among older people because it further increases the risk of cardiovascular syphilis, neurosyphilis and paresis. As syphilis is a great imitator, doctors often ignore syphilis infection when diagnosing the elderly, leading to omission of syphilis testing and misdiagnosis of the disease.

Evidence suggests that the most significant factor affecting testing patterns in older adults is the active provision of the screening test.[29] Since the initiation of China's national syphilis control plan, syphilis screening has been widely integrated into HIV voluntary counselling and testing (VCT) services. More than 95% of people who received HIV testing services have undergone free syphilis testing.[30] Referral, treatment and follow-up services would be provided to those diagnosed with syphilis. In Shenzhen, more than half of VCT sites are set in community health service centres, where a separate room is arranged for counselling and testing service. However, due to the low awareness of self-testing, older adults rarely positively seek the services. Meanwhile, most health staff are unwilling to provide the service actively because of limited experience, lack of time, discomfort in discussing sexual behaviours and STDs with older adults, stigma and ageism.[28] Hence, enhanced training of healthcare providers and education of older adults are necessary.

Consistent with the results of some previous studies, the prevalences of both syphilis seropositivity and active infection were higher among females than males.[21 22] It may stem partly from the different physiology and anatomy of the genital organs between both sexes, leading to females being more likely to contract STDs in receptive vaginal sex behaviours.[31] Some studies have proved that the male-to-female transmission rate is higher than the female-to-male rate in certain STDs, such as HIV.[31 32] Besides, a proportion of females have multiple sex partners during their lifetime. A previous study has found that the syphilis prevalence among husbands of 2261 syphilis-infected pregnant women was <30%0.[33] Premarital or extramarital sexual partners may greatly increase the risk of syphilis infection among females. Additionally, serological response differs between males and females.[34] Females are more likely to be serofast (defined as remaining positive in a non-treponemal test and keeping the titre at a certain level (mostly 1:8 or below) after recommended therapy

Table 3 Proportion of high-titre among active infection donors in different age groups

Age group	TRUST titre <1:8, (%)	TRUST titre ≥1:8, (%)	χ^2_{trend}	P_{trend} value
Aged <25 years	55 (48.7)	58 (51.3)	53.6	<0.001
Aged 25–34 years	139 (65.9)	72 (34.1)		
Aged 35–44 years	202 (83.1)	41 (16.9)		
Aged ≥45 years	139 (83.7)	27 (16.3)		

TRUST, toluidine red unheated serum test.

and follow-up 1–3 years according to syphilis stage) when comparing with males,[35] leading to more females staying in the state of active infection. The exact mechanism underlying this difference is unclear, but it may be partly associated with the varied immune system between both sexes.[34] Furthermore, men who have sex with men are considered a major high-risk subgroup for syphilis infection and are permanently deferred from blood donation in China.[36] In this study, males were excluded if they reported they had ever engaged in homosexual behaviour in the health history questionnaire, which may be one of the reasons for the low syphilis prevalence among males.

Limitations

Our study has several limitations. First, limited financial and human resources restricted us in using a population-based design, which is considered as the gold standard in evaluating disease epidemics.[12] The choice of blood donors as population samples may result in potential bias, such as selection bias for age coverage and self-identified health conditions. Second, the syphilis seroprevalence among first-time donors was significantly higher than that among repeat donors.[12 15] This study did not collect the information of first-time donors and repeat donors, which may lead to underestimation of syphilis seroprevalence. Third, false-negative results attributable to the window period of syphilis infection may result in an underestimation of syphilis seroprevalence. However, the residual risk of syphilis infection is very low according to a residual risk analysis conducted in Shenzhen.[37]

Fourth, this study used two reagents in syphilis screening. Samples with one positive result or both positive results would be considered as problematic samples. This parallel testing method was strict and suitable for blood donors. However, we did not collect the data of each reagent and the positive predictive value cannot be calculated, respectively.

CONCLUSIONS

This study provides an in-depth analysis of the association between syphilis seroprevalence and age. Older adults showed a high prevalence of both syphilis seropositivity and active infection but a small proportion of high titres, which point towards the compelling need to heighten awareness among healthcare providers and deliver more targeted prevention interventions for older adults to promote early testing.

Author affiliations
[1]Department of STD Control and Prevention, Shenzhen Center for Chronic Disease Control, Shenzhen, China
[2]Department of Dermatology, Shenzhen Center for Chronic Disease Control, Shenzhen, China
[3]Department of Epidemiology and Health Statistics, Xiangya School of Public Health, Central South University, Changsha, China
[4]Department of Preventative Medicine, School of Public Health, Guangdong Medical University, Dongguang, China
[5]Department of STD Control Laboratory, Shenzhen Center for Chronic Disease Control, Shenzhen, China

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Contributors XW and TF contributed to designing the study, coordinating data collection and drafting the article. YG, JY, CZ and FT contributed to data collection, patient treatment and disease management. HF, LL and FW contributed to data collection and data analysis. FW contributed to syphilis testing and laboratory quality control. YC and WY contributed to making important comments of the manuscript. All authors read and approved the final draft of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval was obtained from the Ethics Committee of Shenzhen Center for Chronic Disease Control (No. 20180212).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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