

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Association between syphilis prevalence and age: an analysis of surveillance data among blood donors in southern China, 2014-2017

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024393
Article Type:	Research
Date Submitted by the Author:	24-May-2018
Complete List of Authors:	Wu, Xiaobing; Shenzhen Center for Chronic Disease Control Guan, Yang; Shenzhen Center for Chronic Disease Control, Guangdong Ye, Jianbin; Shenzhen Center for Chronic Disease Control Fu, Hanlin; XiangYa School of Public Health, Central South University, Department of Epidemiology and Health Statistics Zhang, Chunlai; Shenzhen Center for Chronic Disease Control Lan, Lina; Shenzhen Center for Chronic Disease Control Wu, Fengxin; School of Public Health, Guangdong Medical University Tang, Fen; Shenzhen Center for Chronic Disease Control Wang, Feng; Shenzhen Center for Chronic Disease Control Cai, Yumao; Shenzhen Center for Chronic Disease Control Yu, Weiye; Shenzhen Center for Chronic Disease Control Feng, Tiejian; Shenzhen Center for Chronic Disease Control, Department of STD control and prevention
Keywords:	Syphilis, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts

Title page**Association between syphilis prevalence and age: an analysis of surveillance data among blood donors in southern China, 2014-2017**

Xiaobing Wu,¹ Yang Guan,¹ Jianbin Ye,¹ Hanlin Fu,² Chunlai Zhang,¹ Lina Lan,¹ Fengxin Wu,³ Fen Tang,¹ Feng Wang,¹ Yumao Cai,¹ Weiye Yu,¹ Tiejian Feng¹

Author affiliations

¹Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control, No.2021 Buxin Road, Luohu District, Shenzhen City, Guangdong Province, People's Republic of China

²Xiangya School of Public Health, Central South University, NO. 238 Shang Ma Yuan Ling Xiang, Kaifu District, Changsha, Hunan Province, People's Republic of China

³School of Public Health, Guangdong Medical University, No.1 Xincheng Boulevard, Songshan Lake, National High Technology Industrial Development Zone, Dongguan City, Guangdong Province, People's Republic of China

Corresponding Author:

Tiejian Feng, MD

Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control

Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong Province, Mainland China

E-mail: fengtiej@126.com

Telephone number: +86-755-25618781

First author:

Xiaobing Wu, PhD

Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control

Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong

Province, People's Republic of China

E-mail: bingfsh@126.com

Telephone number: +86-755-25106861

Co-author:

Yang Guan, MD

Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
Chronic Disease Control

Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
Province, People's Republic of China

E-mail: gygyimi@126.com

Telephone number: +86-755-25632714

Co-author:

Jianbin Ye, BSc

Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
Chronic Disease Control

Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
Province, People's Republic of China

E-mail: 842413681@qq.com

Telephone number: +86-755-25632714

Co-author:

Hanlin Fu, PhD

Xiangya School of Public Health, Central South University

Postal address: NO. 238 Shang Ma Yuan Ling Xiang, Kaifu District, Changsha, Hunan
Province, People's Republic of China

E-mail: 694400861@qq.com

Telephone number: +86-15111341391

Co-author:

Chunlai Zhang, BSc

1
2
3 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
4 Chronic Disease Control

5
6 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
7 Province, People's Republic of China

8
9 E-mail: szzhchl@163.com

10
11 Telephone number: +86-755-25632714
12
13

14
15 **Co-author:**

16 Lina Lan, MPH

17
18 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
19 Chronic Disease Control

20
21 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
22 Province, People's Republic of China

23
24 E-mail: 8262268@qq.com

25
26 Telephone number: +86-755-25608017
27
28

29
30 **Co-author:**

31 Fengxin Wu, BSc

32 School of Public Health, Guangdong Medical University

33
34 Postal address: No.1 Xincheng Boulevard, Songshan Lake, National High Technology
35 Industrial Development Zone, Dongguan City, Guangdong Province, People's Republic
36 of China

37
38 E-mail: 1162887843@qq.com

39
40 Telephone number: +86-13650232046
41
42

43
44 **Co-author:**

45 Fen Tang, BSc

46
47 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
48 Chronic Disease Control

49
50 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
51 Province, People's Republic of China

52
53 E-mail: 791950577@qq.com
54
55

1
2
3 Telephone number: +86-755-25632714
4
5

6 **Co-author:**

7
8 Feng Wang, MSc

9
10 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
11 Chronic Disease Control

12
13 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
14 Province, People's Republic of China

15
16 E-mail: biowangfeng@163.com

17
18 Telephone number: +86-755-25619065
19
20
21

22 **Co-author:**

23
24 Yumao Cai, MPH

25
26 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
27 Chronic Disease Control

28
29 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
30 Province, People's Republic of China

31
32 E-mail: 64165469@qq.com

33
34 Telephone number: +86-755-25632714
35
36
37

38 **Co-author:**

39
40 Weiye Yu, MD

41
42 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
43 Chronic Disease Control

44
45 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
46 Province, People's Republic of China

47
48 E-mail: ywy2002@126.com

49
50 Telephone number: +86-755-25531338
51
52

53 **Word Counts:** 299 words (abstract); 2658 words (text);

54 **Tables:** 3 tables;

55
56 **Figures:** 3 figures.
57
58
59
60

ABSTRACT

Objective: This study investigated the associations between syphilis prevalence and age among blood donors, and described the distribution of serological titres among syphilis-infected donors, aiming at confirming the syphilis epidemic characteristics and promoting effective interventions for older adults.

Methods: Data were obtained from the Shenzhen Program for Syphilis Prevention and Control in 2014-2017. Blood samples were screened using the enzyme-linked immunosorbent assay (ELISA), and confirmed using the *Treponema pallidum* particle agglutination assay (TPPA) and toluidine red unheated serum test (TRUST).

Results: Among 394 792 blood donors, 733 were TPPA and TRUST positive, and 728 were only TPPA positive. The overall prevalence of syphilis infection was 370.1 per 100 000 [95% confidence interval (CI), 351.1-389.0 per 100 000]; the prevalence of active infection was 185.7 per 100 000 (95% CI, 172.2-199.1 per 100 000). People aged ≥ 45 years displayed a prevalence of 621.8 per 100 000 in syphilis infection 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. The prevalence of syphilis infection ($\chi^2_{\text{trend}} = 311.9$, $p_{\text{trend}} < 0.001$) and active infection ($\chi^2_{\text{trend}} = 72.1$, $p_{\text{trend}} < 0.001$) increased significantly with age. After stratification of gender and year of donation, the increasing trend of prevalence with age remained ($p_{\text{trend}} < 0.05$), except for the prevalence of active infection in males ($\chi^2_{\text{trend}} = 0.923$, $p_{\text{trend}} = 0.337$) and females ($\chi^2_{\text{trend}} = 0.224$, $p_{\text{trend}} = 0.636$) in 2014. About 16.3% of patients aged ≥ 45 years had a TRUST titre of $\geq 1:8$, 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 prevalence among nearly 400 000 blood donors, including syphilis infection, active infection, and distribution of serological titres.
- ▶ Using trend analysis after stratification of gender and year of donation to examine the association between syphilis prevalence and age, the results confirmed the increasing trend of prevalence with age.
- ▶ Lack of information on syphilis prevalence between first-time donors and repeat donors is a limitation to this study.

MAIN TEXT

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 human immunodeficiency virus (HIV) and syphilis, was shown from recent surveillance data.³⁻⁵ This large disease burden in older people calls for improvements in the healthcare system and more investments and programs 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, death, etc., 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 of HIV.⁷ Even though syphilis can be effectively treated by penicillin, about 36.4 million new cases occur annually.⁸ In China, the syphilis epidemic has rapidly increased, with 16.3% increase per year during the first decade after the SARS outbreak.⁹ The reported incidence was slightly higher among females than males (ratio, 1.00 to 0.92), but it varied significantly with age.⁵ The younger people (20-39 years) reported the highest syphilis incidence and accounted for the largest proportion of newly reported cases; however, the older age groups (≥ 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, located in southern China and next to Hong Kong, is a large city with a population of >10 million.¹⁰ It was the first city in China to make donated blood meet

1
2
3 the demand for clinical use.¹¹ After China initiated the 10-year plan for syphilis
4 prevention and control, Shenzhen launched a comprehensive program, the Shenzhen
5 Program for Syphilis Prevention and Control (SPSPC), in November 2013 to enhance
6 syphilis screening among blood donors and other five subgroups [HIV voluntary
7 counsellors, methadone maintenance treatment users, female sex workers, men who
8 have sex with men(MSM), and women of childbearing age], as well as case
9 management, including diagnosis, treatment, and follow-up, for syphilis-infected
10 adults.¹² The reported syphilis incidence remained relatively stable since 2008.
11 However, consistent with the aforementioned characteristics of varied age groups, a
12 rapid growth of syphilis incidence was observed among older adults in Shenzhen.¹³
13 Studies usually considered blood donors as the representative of general population
14 and used the prevalence data of blood donors for real-time surveillance and
15 identification of high-risk groups.¹⁴ Whether the syphilis seroprevalence among
16 blood donors agrees with reported incidence characteristics remains to be studied.
17 Therefore, this study aimed to examine differences in syphilis prevalence among
18 blood donors and describe the distribution of serological titres among
19 syphilis-infected donors with respect to age groups, to confirm the syphilis epidemic
20 characteristics in southern China and support the design of effective interventions for
21 older adults.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37

38 **METHODS**

39 **Subjects and blood donation process**

40 Blood donors were recruited by the Shenzhen Blood Center between 2014 and 2017.
41 More than 10 blood mobiles, with the Shenzhen Blood Center logo and the words
42 'non-remunerated blood donation', were dispatched around the city to increase the
43 accessibility of blood donation. Volunteers could go to the mobiles or to the blood
44 centre directly.
45
46
47
48
49
50

51 Before donation, all potential donors needed to complete a detailed health history
52 questionnaire, sign a donation registration form, undergo weight, blood pressure and
53 heart rate measurement, and have a rapid test for blood type, hemoglobin, hepatitis
54 B surface antigen and alanine transaminase. People who conformed to the Whole
55
56
57
58
59
60

1
2
3 Blood and Component Donor Selection Requirements (GB 18467-2001) could
4 proceed to donate blood. All blood donors were non-remunerated. A light
5 refreshment, a blood donation certification, and a blood credit allowing free
6 transfusion for donors or their direct relatives were provided as incentives. The
7 donation process and blood management were fully in accordance with the Blood
8 Donation Law of the People's Republic of China and Blood Donation Regulation of the
9 Shenzhen Special Economic Zone.
10
11
12
13
14
15

16 Serological testing

17
18 After donation, the blood samples were transferred to the Shenzhen Blood Center
19 and underwent a series of laboratory testing. The enzyme-linked immunosorbent
20 assay (ELISA; Zhuhai Lizhu Bio-engineering Co., Ltd., Zhuhai, China) was performed on
21 all blood samples for syphilis screening. Syphilis-positive samples, with a form listing
22 the donors' name, age, and gender, were then transferred to the Shenzhen Center for
23 Chronic Disease Control [SZCCC, a city-level prevention and control centre for
24 sexually transmitted diseases (STDs)] under SPSPC guidelines. A treponemal test of
25 *Treponema pallidum* particle agglutination (TPPA; Fujirebio Inc., Tokyo, Japan) and a
26 non-treponemal test of toluidine red unheated serum test (TRUST; Shanghai
27 Rongsheng BioTech Co., Ltd., Shanghai, China) were used in the SZCCC to confirm the
28 infection status. TRUST-positive samples further underwent a quantitative titre
29 testing to monitor response to treatment. TPPA and TRUST results were sent back to
30 the Shenzhen Blood Center in 2 days after the samples were received.
31
32
33
34
35
36
37
38
39
40
41
42

43 Definition of syphilis infection

44 Based on serological testing results, syphilis infection was divided into two categories:
45 historical infection and active infection. Historical infection was defined as TPPA
46 positive but TRUST negative, and active infection as both TPPA and TRUST positive.¹⁵
47 The overall syphilis infection was defined as TPPA positive, including both historical
48 and active infection. Moreover, high-titre was defined as active infection patients
49 with a quantitative titre of $\geq 1:8$.
50
51
52
53
54
55

56 Statistical analysis

Primary outcomes of interest were prevalence of syphilis infection and active infection among all blood donors in different age groups. There were four age groups, <25 years, 25-34 years, 35-44 years, and ≥ 45 years, fully considering the age coverage of blood donors and age classification in previous studies.^{16,17} We calculated the crude prevalence and its 95% confidence interval (CI). The chi-squared (χ^2) test for trend was used to assess the prevalence difference among age groups. Line graphs were used to describe the change in prevalence for both syphilis infection and active infection among the age groups after stratification of gender and year of donation. Odds ratios (ORs) and their 95% CIs were calculated when comparing the risk of syphilis infection and active infection between the ≥ 45 years age group and other age groups. Furthermore, we described the distribution of TRUST titres among age groups and compared the difference using the χ^2 test. Data were analysed using SPSS 17.0 for Windows; $p < 0.05$ was considered statistically significant in the χ^2 test.

RESULTS

Demographic characteristics

Between 2014 and 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 <45 years. The proportion of male donors increased significantly by age ($\chi^2_{\text{trend}} = 8301.1$, $p_{\text{trend}} < 0.001$), and the number of donations in each age group increased over the studied years ($\chi^2_{\text{trend}} = 932.3$, $p_{\text{trend}} < 0.001$) (Table 1).

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

Variables	Aged <25 years (n=95736)	Aged 25-34 years (n=137447)	Aged 35-44 years (n=102422)	Aged ≥ 45 years (n=59187)	χ^2_{trend}	p_{trend} value
Gender					8301.1	<0.001
Male	51409(53.7%)	96237(70.0%)	74445(72.7%)	44061(74.4%)		
Female	44327(46.3%)	41210(30.0%)	27977(27.3%)	15126(25.6%)		
Year of donation					932.3	<0.001
2014	22389(23.4%)	31929(23.2%)	23131(22.6%)	11210(18.9%)		
2015	24330(25.4%)	33096(24.1%)	24011(23.4%)	13241(22.4%)		
2016	24560(25.7%)	35736(26.0%)	26362(25.7%)	15843(26.8%)		
2017	24457(25.5%)	36686(26.7%)	28918(28.2%)	18893(31.9%)		

Prevalence of syphilis infection and active infection

After ELISA testing, 2597 samples were 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 infection was 370.1 per 100 000 (95% CI, 351.1-389.0 per 100 000), and the prevalence of active infection was 185.7 per 100 000 (95% CI, 172.2-199.1 per 100 000). The prevalence of syphilis infection (478.1 vs 317.9 per 100 000, $\chi^2 = 60.4$, $p < 0.001$) and active infection (244.9 vs 157.1 per 100 000, $\chi^2 = 36.1$, $p < 0.001$) was higher among females than males and showed a decreasing trend from 2014 to 2017 (syphilis infection: $\chi^2_{\text{trend}} = 27.1$, $p_{\text{trend}} < 0.001$; active infection: $\chi^2_{\text{trend}} = 7.8$, $p_{\text{trend}} = 0.005$). People aged ≥ 45 years reported the highest prevalence of both syphilis infection and active infection, which was 3.8 times (OR = 3.8, 95% CI = 3.1-4.6) and 2.4 times (OR = 2.4, 95% CI = 1.9-3.0) higher than that among people aged < 25 years, and 2.3 times (OR = 2.3, 95% CI = 2.0-2.6) and 1.8 times (OR = 1.8, 95% CI = 1.5-2.2) higher than that among people aged 25-34 years, respectively. Trend analysis shown that the prevalence of syphilis infection ($\chi^2_{\text{trend}} = 311.9$, $p_{\text{trend}} < 0.001$) and active infection ($\chi^2_{\text{trend}} = 72.1$, $p_{\text{trend}} < 0.001$) increased significantly with age (Table 2). After stratification of gender and year of donation, the increasing trend of prevalence with age remained ($p_{\text{trend}} < 0.05$), except for the prevalence of active infection in males ($\chi^2_{\text{trend}} = 0.923$, $p_{\text{trend}} = 0.337$) and females ($\chi^2_{\text{trend}} = 0.224$, $p_{\text{trend}} = 0.636$) in 2014 (Figure 2).

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

Age groups	Number of screened	Syphilis infection				Active infection			
		Number	Prevalence per 100 000 (95%CI)	χ^2_{trend}	p_{trend} value	Number	Prevalence per 100 000 (95%CI)	χ^2_{trend}	p_{trend} value
Aged < 25 years	95736	158	165.0(139.3-190.8)	311.9	< 0.001	113	118.0(96.3-139.8)	72.1	< 0.001
Aged 25-34 years	137447	376	273.6(245.9-301.2)			211	153.5(132.8-174.2)		
Aged 35-44 years	102422	559	545.8(500.7-590.9)			243	237.3(207.5-267.0)		
Aged ≥ 45 years	59187	368	621.8(558.4-685.1)			166	280.5(237.9-323.1)		

Distribution of TRUST titres

Among 733 patients 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 $\geq 1:8$. 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%) (Table 3).

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

TRUST titres	Aged < 25 years (n=113)	Aged 25-34 years (n=211)	Aged 35-44 years (n=243)	Aged ≥ 45 years (n=166)	χ^2	p value
$< 1:8$	55 (48.7%)	139 (65.9%)	202 (83.1%)	139 (83.7%)	61.7	< 0.001
$\geq 1:8$	58 (51.3%)	72 (34.1%)	41 (16.9%)	27 (16.3%)		

DISCUSSION

This study identified that the overall prevalence of syphilis infection among nearly 400 000 blood donors in 2014-2017 was 370.1 per 100 000, which was higher than that reported in the United States (54.6 per 100 000) and Brazil (135.5 per 100 000),^{14,18} 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).¹⁹⁻²¹ 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).^{16,22} However, unlike some studies using only one method (i.e., ELISA) to confirm the syphilis infection status and report the prevalence,^{16,20,22,23} this study used ELISA as a screening test and then used TPPA and TRUST to confirm the serostatus if screened positive. Surprisingly, only 56.3% of ELISA-positive patients were confirmed by TPPA. The testing process in this study greatly increased the accuracy of syphilis prevalence. Furthermore, this study found that 50.2% (733/1461) of syphilis-infected donors were active infection patients, among which 27.0% (198/733) had a TRUST titre of $\geq 1:8$. To our knowledge, this is the first in-depth study focusing on active infection and serological titre

1
2
3 distribution of syphilis among blood donors in mainland China. Here, the proportion
4 of high titres among active infection patients was similar to that reported in the
5 United States.¹⁴
6
7

8
9
10 This study found that syphilis prevalence significantly increased with age. Older
11 adults aged ≥ 45 years displayed the highest prevalence of both syphilis infection and
12 active infection. More importantly, from the national surveillance data, people aged
13 ≥ 60 years had a remarkably higher increase in reported incidence compared with
14 those aged 45-60 years.⁵ Hospitalised patients aged ≥ 70 years showed the highest
15 syphilis prevalence (4.8%), followed by patients aged 61-70 years (3.9%) and those
16 aged 51-60 years (3.2%).²⁴ Given the results from this study and previous studies,
17 health awareness and syphilis prevention focusing on older adults are needed.
18
19
20
21
22
23

24
25 The higher prevalence in older adults might be due to several reasons. First, many
26 older people are sexually active,²⁵ and their sexual health and behaviour affect
27 syphilis transmission. Low self-perception of risk and misconceptions or limited
28 knowledge about syphilis and other STDs were frequently reported as reasons for
29 condomless behaviours among older adults.^{5,26} Second, older adults have been
30 largely neglected by healthcare providers due to age-related stigma.²⁷ Sexual health
31 services for HIV or STDs rarely focus on older adults, leaving this group behind in
32 both testing and prevention. Third, presenting with a late diagnosis has been
33 significantly associated with older age. Older people were more likely to be aware of
34 their serostatus when in hospital or an active offer of a testing.²⁸ In this study,
35 analysis of the TRUST titre distribution suggests that $> 80\%$ of people aged ≥ 45 years
36 with low TRUST titres had a previous infection. However, late presentation is
37 particularly worrying among older people because it further increases the risk of
38 cardiovascular syphilis, neurosyphilis, paresis, etc. As syphilis is a great imitator,
39 doctors often ignore syphilis infection when diagnosing the elderly, leading to
40 omission of syphilis testing and misdiagnosis of the disease.
41
42
43
44
45
46
47
48
49
50
51
52

53
54 Evidence suggests that the most significant factor affecting testing patterns in older
55 adults is providing the screening test actively.²⁸ Since the initiation of China's national
56
57
58
59
60

1
2
3 syphilis control plan, syphilis screening has been widely integrated into HIV voluntary
4 counselling and testing (VCT) services. More than 95% of people who received HIV
5 testing services have undergone free syphilis testing.²⁹ Referral, treatment, and
6 follow-up services would be provided to those diagnosed with syphilis. In Shenzhen,
7 more than half of VCT sites are set in community health service centres, where a
8 separate room is arranged for counselling and testing service. However, due to the
9 low awareness of self-testing, older adults rarely positively seek the services.
10
11 Meanwhile, most health staff are unwilling to provide the service actively because of
12 limited experience, lack of time, discomfort in discussing sexual behaviours and STDs
13 with older adults, stigma, ageism, etc.²⁷ Hence, enhanced training of healthcare
14 providers and education of older adults are necessary.
15
16
17
18
19
20
21
22

23
24 As mentioned, the prevalence of both syphilis infection and active infection were
25 higher among females than males, consistent with the results of some previous
26 studies.^{22,23} The physiology and anatomy of the genital organs are much different
27 between both sexes. Females are more likely to contract STDs in receptive vaginal sex
28 behaviours.³⁰ The male-to-female transmission rate is higher than the
29 female-to-male rate in certain STDs, such as HIV.^{30,31} Besides, a proportion of females
30 have premarital or extramarital sexual partners. A previous study has found that
31 syphilis prevalence among husbands of 2261 syphilis-infected pregnant women was <
32 30%.³² Additionally, being serofast (or remaining positive in a non-treponemal test
33 and having a titre with less than a fourfold decline in ≥ 1 year after recommended
34 therapy) is common among syphilis patients.³³ The serofast rate is higher among
35 females than males (42.8% vs 28.6%),³⁴ leading to more females staying in the state
36 of active infection. The exact mechanism of this difference is unclear, but it may be
37 partly associated with the varied immune system between both sexes.³⁴ MSM are
38 considered to be a major high-risk subgroup of syphilis infection and are permanent
39 deferral of blood donation in China.³⁵ In this study, males were excluded if they
40 reported they had ever had homosexual behaviours or had multiple sex partners in
41 health history questionnaire, which may be one of the reasons for the low syphilis
42 prevalence in males.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.¹⁴ 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, this study did not distinguish the syphilis prevalence between first-time donors and repeat donors, which may lead to underestimation of syphilis disease burden. In previous studies, the syphilis prevalence among first-time donors was significantly higher than that among repeat donors.^{14,16} Third, false-negative results attributable to the window period of syphilis infection may result in an underestimation of syphilis prevalence. However, the residual risk of syphilis infection is very low according to a residual risk analysis in Shenzhen.³⁶

Conclusions

This study provides an in-depth analysis of the associations between syphilis prevalence and age. Older adults showed a high prevalence of both syphilis infection 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.

Acknowledgements The authors would like to thank Qiong Yu and Xi Chen from Shenzhen Blood Center for their support in data collection and blood sample transportation. The authors also give thanks to all the blood donors for taking part in this study.

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.

Funding This work was supported by the Shenzhen Science and Technology Innovation Commission (grant number JCYJ20160428145537703) and the Sanming Project of Medicine in Shenzhen (No. SZSM201611077).

Competing interests The authors declare no competing interest.

Patient consent Not applicable.

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 sharing statement Data are available by emailing XW(bingfsh@126.com).

REFERENCES

1. Department of Economic and Social Affairs, Population Division, United Nations. *World Population Ageing: 1950-2050*. <http://www.un.org/esa/population/publications/worldageing19502050/> (accessed 22 May 2018)
2. Prince MJ, Wu F, Guo Y, et al. The burden of disease in older people and implications for health policy and practice. *Lancet* 2015; 385: 549-62.
3. Tavoschi L, Gomes Dias J, Pharris A, et al. New HIV diagnoses among adults aged 50 years or older in 31 European countries, 2001-15: an analysis of surveillance data. *Lancet HIV* 2017; 4: e514-21.
4. Mahy M, Autenrieth CS, Stanecki K, et al. Increasing trends in HIV prevalence among people aged 50 years and older: evidence from estimates and survey data. *AIDS* 2014; 28: S453-9.
5. Gong X, Yue X, Teng F, et al. Syphilis in China from 2000 to 2013: epidemiological

- trends and characteristics. *Chin J Dermatol* 2014; 47: 310-5. (in Chinese)
6. Workowski KA and Bolan GA. Sexually transmitted disease treatment guidelines, 2015. *MMWR Recomm Rep* 2015; 64: 34-49.
 7. Kotsafti O, Pappas V, Kourkounti S, et al. Early syphilis affects markers of HIV infection. *Int J STD AIDS* 2016; 27: 739-45.
 8. Newman L, Rowley J, Vander Hoorn S, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One* 2015; 10: e0143304.
 9. Yang S, Wu J, Ding C, et al. Epidemiological features of and changes in incidence of infectious disease in China in the first decade after the SARS outbreak: an observational trend study. *Lancet Infect Dis* 2017; 17: 716-25.
 10. Wu X, Hong F, Lan L, et al. Poor awareness of syphilis prevention and treatment knowledge among six different populations in south China. *BMC Public Health* 2016; 16: 287.
 11. Health and Family Planning Commission of Shenzhen Municipality. Shenzhen Blood Center.
http://www.sz.gov.cn/wsj/jgz/zsjg/200809/t20080909_35864.htm (accessed 22 May 2018).
 12. Wu XB, Zhang CL, Lan LN, et al. Syphilis infection among five different groups of people and analysis of treatment situation in Shenzhen. *China Tropical Medicine* 2015; 15: 830-2. (in Chinese)
 13. Lan LN, Wu XB, Zhang CL, et al. Epidemiological analysis of syphilis in Shenzhen from 2004 to 2013. *China Tropical Medicine* 2015; 15: 700-3. (in Chinese)
 14. Kane MA, Bloch EM, Bruhn R, et al. Demographic determinants of syphilis seroprevalence among U.S. blood donors, 2011-2012. *BMC Infect Dis* 2015; 15: 63.
 15. Chen YY, Qiu XH, Zhang YF, et al. A better definition of active syphilis infection. *Clin Chim Acta* 2015; 444: 1-2.
 16. Liu J, Huang Y, Wang J, et al. The increasing prevalence of serologic markers for syphilis among Chinese blood donors in 2008 through 2010 during a syphilis epidemic. *Transfusion* 2012; 52: 1741-9.
 17. Vera L, Milka D, Nurith SL, et al. Prevalence and incidence of syphilis among

- 1
2
3 volunteer blood donors in Israel. *J Blood Transfus* 2014; 2014: 154048.
- 4
5 18. Baiao AM, Kupek E, Petry A. Syphilis seroprevalence estimates of Santa Catarina
6 blood donors in 2010. *Rev Soc Bras Med Trop* 2014; 47: 179-85.
- 7
8 19. Abate M, Wolde T. Seroprevalence of Human Immunodeficiency Virus, Hepatitis
9 B Virus, Hepatitis C Virus, and Syphilis among Blood Donors at Jigjiga Blood Bank,
10 Eastern Ethiopia. *Ethiop J Health Sci* 2016; 26: 153-60.
- 11
12 20. Dionne-Odom J, Mbah R, Rembert NJ, et al. Hepatitis B, HIV, and Syphilis
13 seroprevalence in pregnant women and blood donors in Cameroon. *Infect Dis*
14 *Obstet Gynecol* 2016; 2016: 4359401.
- 15
16 21. Rawat A, Diwaker P, Gogoi P, et al. Seroprevalence & changing trends of
17 transfusion-transmitted infections amongst blood donors in a Regional Blood
18 Transfusion Center in north India. *Indian J Med Res* 2017; 146: 642-5.
- 19
20 22. Chen Y, Liu Z, Zhang Q, et al. Trend in prevalence of syphilis among voluntary
21 blood donors in Xi'an, China from 2006 to 2010. *Int J Infect Dis* 2014; 19: 98-9.
- 22
23 23. Li C, Xiao X, Yin H, et al. Prevalence and prevalence trends of transfusion
24 transmissible infections among blood donors at four Chinese regional blood
25 centers between 2000 and 2010. *J Transl Med* 2012; 10: 176.
- 26
27 24. Cao WW, Zhou RR, Qu X, et al. Prevalence of hepatitis B virus, hepatitis C virus,
28 human immunodeficiency virus and *Treponema pallidum* infections in
29 hospitalized patients before transfusion in Xiangya hospital Central South
30 University, China from 2011 to 2016. *BMC Infect Dis* 2018; 18: 145.
- 31
32 25. Gott CM. Sexual activity and risk-taking in later life. *Health Soc Care Community*
33 2001; 9: 72-8.
- 34
35 26. Tillman JL, Mark HD. HIV and STI testing in older adults: an integrative review. *J*
36 *Clin Nurs* 2015; 24: 2074-95.
- 37
38 27. Davis T, Teaster PB, Thornton A, et al. Primary care providers' HIV prevention
39 practices among older adults. *J Appl Gerontol* 2016; 35: 1325-42.
- 40
41 28. Adekeye OA, Heiman HJ, Onyeabor OS, et al. The new invincibles: HIV screening
42 among older adults in the U.S.. *PLoS One* 2012; 7: e43618.
- 43
44 29. Chen YF, Ding JP, Yan HJ, et al. The current status of syphilis prevention and
45 control in Jiangsu province, China: a cross-sectional study. *PLoS One* 2017; 12:
46 e0183409.
- 47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
- 2
- 3 30. Varghese B, Maher JE, Peterman TA, et al. Reducing the risk of sexual HIV
- 4 transmission: quantifying the per-act risk for HIV on the basis of choice of
- 5 partner, sex act, and condom use. *Sex Transm Dis* 2002; 29: 38-43.
- 6
- 7
- 8 31. Kim JH. HIV transmissions by stage and sex role in long-term concurrent sexual
- 9 partnerships. *Acta Biotheor* 2015; 63: 33-54.
- 10
- 11 32. Wu XB, Hong FC, Peng DY, et al. Syphilis infection status and the associated
- 12 factors among partners of married syphilis-infected pregnant women in
- 13 Shenzhen. *Chin J Dis Control Prev* 2016; 20: 1278-81. (in Chinese)
- 14
- 15 33. Seña AC, Zhang XH, Li T, et al. A systematic review of syphilis serological
- 16 treatment outcomes in HIV-infected and HIV-uninfected persons: rethinking the
- 17 significance of serological non-responsiveness and the serofast state after
- 18 therapy. *BMC Infect Dis* 2015; 15: 479.
- 19
- 20 34. Tong ML, Lin LR, Liu GL, et al. Factors associated with serological cure and the
- 21 serofast state of HIV-negative patients with primary, secondary, latent, and
- 22 tertiary syphilis. *PLoS One* 2013; 8: e70102.
- 23
- 24 35. Shi L, Wang J, Liu Z, et al. Blood donor management in China. *Transfus Med*
- 25 *Hemother* 2014; 41:273-282.
- 26
- 27 36. Yang AL, Wang SX, Wei TL, et al. Treponema pallidum infection and residual risk
- 28 of blood transmission of syphilis among voluntary blood donors in Shenzhen
- 29 from 2008 to 2012. *J Mod Lab Med* 2013; 28: 122-124. (in Chinese)
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

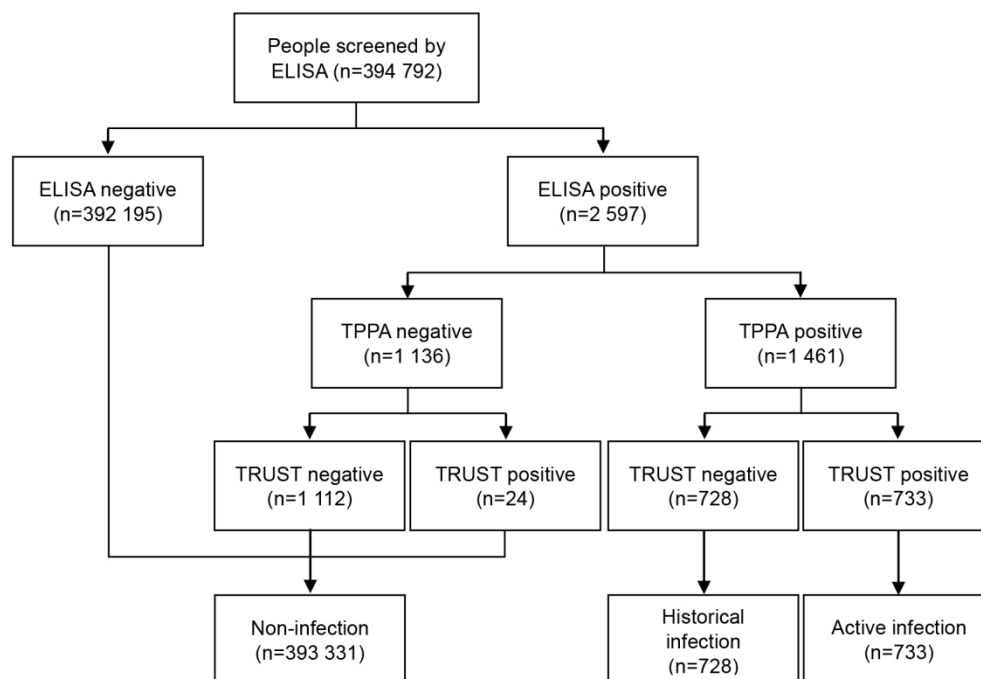


Figure 1 Flowchart for syphilis screening and confirmatory testing among blood donors. ELISA, enzyme-linked immunosorbent assay; TPPA, Treponema pallidum particle agglutination assay; TRUST, toluidine red unheated serum test.

157x116mm (300 x 300 DPI)

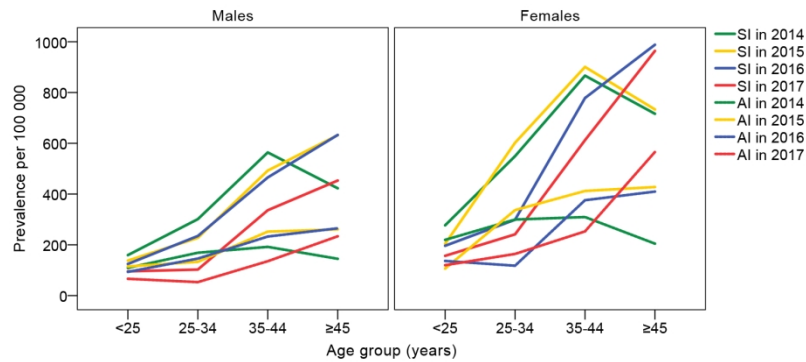


Figure 2 Prevalence of syphilis infection and active infection in different age groups, 2014-2017. (A) Prevalence of syphilis infection and active infection among males. (B) Prevalence of syphilis infection and active infection among females. SI: syphilis infection; AI: active infection

166x78mm (300 x 300 DPI)

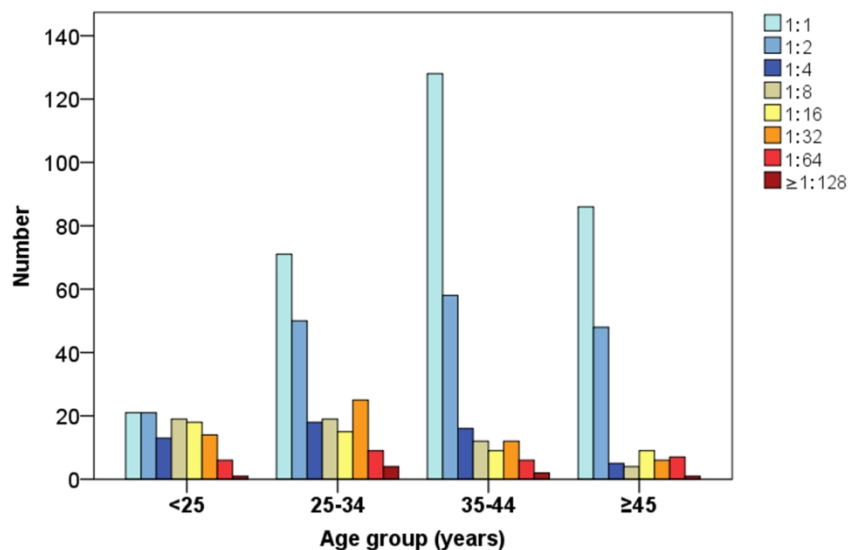


Figure 3 Distribution of TRUST titres among active infection donors in different age groups.

159x91mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	P1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	P8
Methods			
Study design	4	Present key elements of study design early in the paper	P8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P8-9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	P8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P9
Bias	9	Describe any efforts to address potential sources of bias	P9
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	P10
		(b) Describe any methods used to examine subgroups and interactions	P10
		(c) Explain how missing data were addressed	Not applicable
		(d) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P11
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	P20
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P10
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	P11,21
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P11-12, 21,22
		(b) Report category boundaries when continuous variables were categorized	P10
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	P11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	P12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P15
Generalisability	21	Discuss the generalisability (external validity) of the study results	P15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024393.R1
Article Type:	Original research
Date Submitted by the Author:	24-Oct-2018
Complete List of Authors:	Wu, Xiaobing; Shenzhen Center for Chronic Disease Control Guan, Yang; Shenzhen Center for Chronic Disease Control, Guangdong Ye, Jianbin; Shenzhen Center for Chronic Disease Control Fu, Hanlin; XiangYa School of Public Health, Central South University, Department of Epidemiology and Health Statistics Zhang, Chunlai; Shenzhen Center for Chronic Disease Control Lan, Lina; Shenzhen Center for Chronic Disease Control Wu, Fengxin; School of Public Health, Guangdong Medical University Tang, Fen; Shenzhen Center for Chronic Disease Control Wang, Feng; Shenzhen Center for Chronic Disease Control Cai, Yumao; Shenzhen Center for Chronic Disease Control Yu, Weiye; Shenzhen Center for Chronic Disease Control Feng, Tiejian; Shenzhen Center for Chronic Disease Control, Department of STD control and prevention
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Sexual health, Public health
Keywords:	Syphilis, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts

Title page

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

Xiaobing Wu,¹ Yang Guan,¹ Jianbin Ye,¹ Hanlin Fu,² Chunlai Zhang,¹ Lina Lan,¹ Fengxin Wu,³ Fen Tang,¹ Feng Wang,¹ Yumao Cai,¹ Weiye Yu,¹ Tiejian Feng¹

Author affiliations

¹Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control, No.2021 Buxin Road, Luohu District, Shenzhen City, Guangdong Province, People's Republic of China

²Xiangya School of Public Health, Central South University, NO. 238 Shang Ma Yuan Ling Xiang, Kaifu District, Changsha City, Hunan Province, People's Republic of China

³School of Public Health, Guangdong Medical University, No.1 Xincheng Boulevard, Songshan Lake, National High Technology Industrial Development Zone, Dongguan City, Guangdong Province, People's Republic of China

Corresponding Author:

Tiejian Feng, MD

Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control

Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong Province, Mainland China

E-mail: fengtiej@126.com

Telephone number: +86-755-25618781

First author:

Correspondence to Xiaobing wu; bingfsh@126.com and Tiejian Feng; fengtiej@126.com

1
2
3 Xiaobing Wu, PhD

4
5 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic
6
7 Disease Control

8
9 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong

10
11 Province, People's Republic of China

12
13 E-mail: bingfsh@126.com

14
15 Telephone number: +86-755-25106861

16
17
18 **Co-author:**

19
20 Yang Guan, MD

21
22 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic
23
24 Disease Control

25
26 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong

27
28 Province, People's Republic of China

29
30 E-mail: gygyimi@126.com

31
32 Telephone number: +86-755-25632714

33
34
35 **Co-author:**

36
37 Jianbin Ye, BSc

38
39 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic
40
41 Disease Control

42
43 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong

44
45 Province, People's Republic of China

46
47 E-mail: 842413681@qq.com

48
49 Telephone number: +86-755-25632714

50
51
52 **Co-author:**

53
54 Hanlin Fu, PhD

55
56 Xiangya School of Public Health, Central South University

1
2
3 Postal address: NO. 238 Shang Ma Yuan Ling Xiang, Kaifu District, Changsha City, Hunan
4
5 Province, People's Republic of China

6
7 E-mail: 694400861@qq.com

8
9 Telephone number: +86-15111341391
10

11
12 **Co-author:**

13
14 Chunlai Zhang, BSc

15
16 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic
17
18 Disease Control

19
20 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong

21
22 Province, People's Republic of China

23
24 E-mail: szzhchl@163.com

25
26 Telephone number: +86-755-25632714
27

28
29 **Co-author:**

30
31 Lina Lan, MPH

32
33 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic
34
35 Disease Control

36
37 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong

38
39 Province, People's Republic of China

40
41 E-mail: 8262268@qq.com

42
43 Telephone number: +86-755-25608017
44

45
46 **Co-author:**

47
48 Fengxin Wu, BSc

49
50 School of Public Health, Guangdong Medical University

51
52 Postal address: No.1 Xincheng Boulevard, Songshan Lake, National High Technology

53
54 Industrial Development Zone, Dongguan City, Guangdong Province, People's Republic of
55
56 China

1
2
3 E-mail: 1162887843@qq.com
4

5 Telephone number: +86-13650232046
6
7

8
9 **Co-author:**

10 Fen Tang, BSc

11
12 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic
13 Disease Control
14

15
16 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
17

18 Province, People's Republic of China

19 E-mail: 791950577@qq.com

20 Telephone number: +86-755-25632714
21
22
23
24

25
26 **Co-author:**

27 Feng Wang, MSc

28
29 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic
30 Disease Control
31

32 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
33

34 Province, People's Republic of China

35 E-mail: biowangfeng@163.com

36 Telephone number: +86-755-25619065
37
38
39
40
41

42
43 **Co-author:**

44 Yumao Cai, MPH

45
46 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic
47 Disease Control
48

49 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
50

51 Province, People's Republic of China

52 E-mail: 64165469@qq.com

53 Telephone number: +86-755-25632714
54
55
56
57
58
59
60

Co-author:

Weiye Yu, MD

Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic
Disease Control

Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong

Province, People's Republic of China

E-mail: ywy2002@126.com

Telephone number: +86-755-25531338

Word Counts: 298 words (abstract); 2974 words (text);

Tables: 3 tables;

Figures: 3 figures.

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 Program for Syphilis Prevention and Control in 2014-2017. Blood samples were screened using the enzyme-linked immunosorbent assay (ELISA), 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 infection was 370.1 per 100 000 [95% confidence interval (CI), 351.1-389.0 per 100 000]; the prevalence of active infection was 185.7 per 100 000 (95% CI, 172.2-199.1 per 100 000). People aged ≥ 45 years displayed a prevalence of 621.8 per 100 000 in syphilis infection 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 infection ($\chi^2_{\text{trend}} = 311.9$, $p_{\text{trend}} < 0.001$) and active infection ($\chi^2_{\text{trend}} = 72.1$, $p_{\text{trend}} < 0.001$) increased significantly with age. After stratification by gender and year of donation, the increasing trend of prevalence with age remained ($p_{\text{trend}} < 0.05$), 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 $\geq 1:8$, 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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Strengths and limitations of this study

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

MAIN TEXT

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 human immunodeficiency virus (HIV) and syphilis, was shown from recent surveillance data.³⁻⁵ This large disease burden among older people calls for improvements in the healthcare system and more investments and programs 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, death, etc., 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 16.3% increase per year during the first decade after the severe acute respiratory syndrome (SARS) outbreak.⁹ The reported incidence was slightly higher among females than males (ratio, 1.00 to 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.

1
2
3
4
5 Shenzhen, a special economic zone located in southern China and with a population
6 of >10 million, is one of the cities that most affected by syphilis. The reported incidence
7 of syphilis was over 60 per 100 000 in last 10 years, which was much higher than the
8 national incidence.^{5,10} Consistent with the aforementioned characteristics of varied age
9 groups, a rapid increase in syphilis incidence was observed among older adults in
10 Shenzhen.¹¹ Studies usually considered blood donors as a representative of the general
11 population and used the prevalence data of blood donors for real-time surveillance and
12 identification of high-risk groups.¹² Whether the syphilis seroprevalence among blood
13 donors agrees with reported incidence characteristics remains to be studied. Shenzhen
14 launched a comprehensive program, the Shenzhen Program for Syphilis Prevention and
15 Control (SPSPC), in November 2013 to enhance syphilis screening among blood donors
16 and five other subgroups [HIV voluntary counsellors, methadone maintenance
17 treatment users, female sex workers, men who have sex with men(MSM), and women
18 of childbearing age], as well as case management, including diagnosis, treatment, and
19 follow-up, for syphilis-infected adults.¹³ Based on the data from the SPSPC, this study
20 aimed to examine differences in syphilis seroprevalence among blood donors and
21 describe the distribution of serological titres among syphilis-infected donors with
22 respect to age groups, to confirm the syphilis epidemic characteristics in southern China
23 and support the design of effective interventions for older adults.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 **METHODS**

42 **Subjects and blood donation process**

43
44 Blood donors were recruited by the Shenzhen Blood Center between 2014 and 2017.
45 About 10 blood mobiles, with the Shenzhen Blood Center logo and the words
46 'non-remunerated blood donation', were dispatched around the city to increase the
47 accessibility of blood donation. Volunteers could either go to the mobiles or to the
48 blood centre directly.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Before donation, all potential donors needed to complete a health history questionnaire,
4 sign a donation registration form, and undergo a rapid testing and a brief physical
5 examination. The health history questionnaire contained a total of 27 medical
6 conditions that would permanently or temporarily prevent the donors from donation,
7 including a series of chronic diseases and infectious diseases (e.g., HIV, syphilis),
8 transplant, high-risk behaviours (e.g., homosexual behaviours, drug use), surgery,
9 delivery, breastfeeding, etc. Pre-donation repaid testing included blood type,
10 haemoglobin, hepatitis B surface antigen, and alanine transaminase. Weight, blood
11 pressure, heart rate and body temperature were measured and clinical examination of
12 the skin and limbs was conducted. People who conformed to the Whole Blood and
13 Component Donor Selection Requirements (GB 18467-2001) could proceed to donate
14 blood. All blood donors were non-remunerated. A light refreshment, a blood donation
15 certification, and a blood credit allowing free transfusion for donors or their direct
16 relatives were provided as incentives. The donation process and blood management
17 were fully in accordance with the Blood Donation Law of the People's Republic of China
18 and the Blood Donation Regulation of the Shenzhen Special Economic Zone.

34 Serological testing

35
36 After donation, the blood samples were transferred to the Shenzhen Blood Center and
37 underwent a series of laboratory testing. The enzyme-linked immunosorbent assay
38 (ELISA; Zhuhai Lizhu Bio-engineering Co., Ltd., Zhuhai, China) was performed on all blood
39 samples for syphilis screening. Syphilis-positive samples, with a form listing the donors'
40 name, age, and gender, were then transferred to the Shenzhen Center for Chronic
41 Disease Control [SZCCC, a city-level control and prevention centre for sexually
42 transmitted diseases (STDs)] under SPSPC guidelines. A treponemal test of *Treponema*
43 *pallidum* particle agglutination (TPPA; Fujirebio Inc., Tokyo, Japan) and a
44 non-treponemal test of toluidine red unheated serum test (TRUST; Shanghai Rongsheng
45 BioTech Co., Ltd., Shanghai, China) were used at the SZCCC to confirm the infection
46 status. TRUST-positive samples further underwent a quantitative titre testing to monitor
47
48
49
50
51
52
53
54
55
56

1
2
3 response to treatment. TPPA and TRUST results were sent back to the Shenzhen Blood
4 Center within 2 days after the samples were received.
5
6
7

8 **Definition of syphilis infection**

9
10 Based on serological testing results, syphilis infection was divided into two categories:
11 historical infection and active infection. Historical infection was defined as TPPA positive
12 but TRUST negative and active infection as both TPPA and TRUST positive.¹⁴ Overall
13 syphilis infection was defined as TPPA positive, including both historical and active
14 infection. Moreover, high-titre was defined as a quantitative titre of $\geq 1:8$ in patients
15 with active infection.
16
17
18
19
20
21
22

23 **Statistical analysis**

24
25 Primary outcomes of interest were the prevalence of syphilis infection and active
26 infection among all blood donors in different age groups. There were four age groups,
27 <25 years, 25-34 years, 35-44 years, and ≥ 45 years, fully considering the age coverage of
28 blood donors and age classification in previous studies.^{15,16} We calculated the crude
29 prevalence and its 95% confidence interval (CI). The chi-squared (χ^2) test for trend was
30 used to assess the prevalence difference among age groups. Odds ratios (ORs) and their
31 95% CIs were calculated when comparing the risk of syphilis infection and active
32 infection between the ≥ 45 years age group and other age groups. Line graphs were
33 used to describe the changes in prevalence for both syphilis infection and active
34 infection among the age groups after stratification by gender and year of donation.
35
36 Furthermore, we described the distribution of TRUST titres among the age groups and
37 compared the difference using the χ^2 test for trend. Data were analysed using SPSS 17.0
38 for Windows; $p < 0.05$ was considered statistically significant in the χ^2 test.
39
40
41
42
43
44
45
46
47
48
49
50

51 **Patient and public involvement statement**

52 Patients and the public were not involved in developing the hypothesis or the research
53 questions, nor were they involved in developing plans for the design or implementation
54
55
56

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 ($\chi^2 = 11249.0$, $p < 0.001$) and among years of donation ($\chi^2 = 1182.0$, $p < 0.001$). People aged 25-34 years accounted for the largest proportion of donors (**Table 1**).

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

Variables	Aged <25 years (n=95736)	Aged 25-34 years (n=137447)	Aged 35-44 years (n=102422)	Aged ≥45 years (n=59187)	χ^2	<i>p</i> value
Gender					11249.0	<0.001
Male	51409(19.3%)	96237(36.2%)	74445(28.0%)	44061(16.6%)		
Female	44327(34.5%)	41210(32.0%)	27977(21.7%)	15126(11.8%)		
Year of donation					1182.0	<0.001
2014	22389(25.3%)	31929(36.0%)	23131(26.1%)	11210(12.6%)		
2015	24330(25.7%)	33096(35.0%)	24011(25.4%)	13241(14.0%)		
2016	24560(24.0%)	35736(34.9%)	26362(25.7%)	15843(15.5%)		
2017	24457(22.4%)	36686(33.7%)	28918(26.5%)	18893(17.3%)		

Prevalence of syphilis infection 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 infection was 370.1 per 100 000 (95% CI, 351.1-389.0 per 100 000), and the prevalence of active infection was 185.7 per 100 000 (95% CI, 172.2-199.1 per 100 000). The prevalence of syphilis infection and active infection was higher among

1
2
3 females than males (syphilis infection: $\chi^2 = 60.4$, $p < 0.001$; active infection: $\chi^2 = 36.1$, $p <$
4 0.001) and showed a decreasing trend from 2014 to 2017 (syphilis infection: $\chi^2_{\text{trend}} =$
5 27.1, $p_{\text{trend}} < 0.001$; active infection: $\chi^2_{\text{trend}} = 7.8$, $p_{\text{trend}} = 0.005$). People aged ≥ 45 years
6 reported the highest prevalence of both syphilis infection and active infection, which
7 was 3.8 times (OR = 3.8, 95% CI = 3.1-4.6) and 2.4 times (OR = 2.4, 95% CI = 1.9-3.0)
8 higher than that among people aged < 25 years, and 2.3 times (OR = 2.3, 95% CI = 2.0-2.6)
9 and 1.8 times (OR = 1.8, 95% CI = 1.5-2.2) higher than that among people aged 25-34
10 years, respectively. Trend analysis showed that the prevalence of syphilis infection
11 ($\chi^2_{\text{trend}} = 311.9$, $p_{\text{trend}} < 0.001$) and active infection ($\chi^2_{\text{trend}} = 72.1$, $p_{\text{trend}} < 0.001$) increased
12 significantly with age (Table 2). After stratification by gender and year of donation, the
13 increasing trend of prevalence with age remained ($p_{\text{trend}} < 0.05$), except for the
14 prevalence of active infection among males ($\chi^2_{\text{trend}} = 0.923$, $p_{\text{trend}} = 0.337$) and females
15 ($\chi^2_{\text{trend}} = 0.224$, $p_{\text{trend}} = 0.636$) in 2014 (Figure 2).
16
17
18
19
20
21
22
23
24
25
26
27
28

29 **Table 2** Prevalence of syphilis infection and active infection among blood donors in different age
30 groups

Age groups	Number of screened	Syphilis infection				Active infection			
		Number	Prevalence per 100 000 (95%CI)	χ^2_{trend}	p_{trend} value	Number	Prevalence per 100 000 (95%CI)	χ^2_{trend}	p_{trend} value
Aged < 25 years	95736	158	165.0(139.3-190.8)	311.9	< 0.001	113	118.0(96.3-139.8)	72.1	< 0.001
Aged 25-34 years	137447	376	273.6(245.9-301.2)			211	153.5(132.8-174.2)		
Aged 35-44 years	102422	559	545.8(500.7-590.9)			243	237.3(207.5-267.0)		
Aged ≥ 45 years	59187	368	621.8(558.4-685.1)			166	280.5(237.9-323.1)		

44 Distribution of TRUST titres

45
46 Among 733 donors with active infection, a TRUST titre of 1:1 accounted for the largest
47 proportion (41.7%), followed by a titre of 1:2 (24.1%). About 27.0% had a TRUST titre of
48 $\geq 1:8$. The distribution of TRUST titres was varied among the age groups (Figure 3).
49
50

51 Patients aged ≥ 45 years comprised a large proportion of low titres at 1:1 and 1:2, and
52 the proportion of high titres was only 16.3%, which was much smaller than that among
53 patients aged < 25 years (51.3%) and 25-34 years (34.1%). The proportion of high-titre
54
55
56
57
58
59

declined significantly with age ($\chi^2_{\text{trend}} = 53.6$, $p_{\text{trend}} < 0.001$) (Table 3).

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

Age groups	TRUST titre < 1 : 8	TRUST titre \geq 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 \geq 45 years	139 (83.7%)	27 (16.3%)		

DISCUSSION

This study identified that the overall seroprevalence of syphilis infection among nearly 400 000 blood donors in 2014-2017 was 370.1 per 100 000, which was higher than that reported in the United States (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 (i.e., 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 >98% 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 was below 60%. 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

1
2
3 serological titre distribution of syphilis among blood donors in mainland China. Active
4 infection is different from historical infection as the former indicates more transmission
5 and late syphilis if without timely and adequate treatment. The higher the serological
6 titre, the more the risk of transmission (e.g., mother-to-child transmission) and adverse
7 outcomes.²⁴ This study documented that 50.2% (733/1461) of syphilis-infected donors
8 had active infection patients, and 13.6% (198/1461) had a TRUST titre of $\geq 1:8$. Here, the
9 proportion of high titres among syphilis infection patients was similar to that reported in
10 the United States.¹²

11
12
13
14
15
16
17
18
19
20 This study found that syphilis prevalence significantly increased with age. Older adults
21 aged ≥ 45 years displayed the highest prevalence of both syphilis infection and active
22 infection. More importantly, from the national surveillance data, people aged ≥ 60 years
23 had a remarkably higher increase in reported incidence compared with those aged
24 45-60 years.⁵ Hospitalised patients aged ≥ 70 years showed the highest syphilis
25 prevalence (4.8%), followed by patients aged 61-70 years (3.9%) and those aged 51-60
26 years (3.2%), which was much different from that for HIV infection for which patients
27 aged 31-40 years recorded the highest prevalence.²⁵ Based on the results of this study
28 and previous studies, health awareness and syphilis prevention focusing on older adults
29 are needed.

30
31
32
33
34
35
36
37
38
39
40 The higher prevalence in older adults might be due to several reasons. First, many older
41 people are sexually active,²⁶ and their sexual health and behaviour affect syphilis
42 transmission. Low self-perception of risk and misconceptions or limited knowledge
43 about syphilis and other STDs were frequently reported as reasons for condomless sex
44 among older adults.^{5,27} Second, older adults have been largely neglected by healthcare
45 providers due to age-related stigma.²⁸ Sexual health services for HIV or STDs rarely focus
46 on older adults, leaving this group behind in both testing and prevention. Third,
47 presenting with a late diagnosis has been significantly associated with older age. Older
48 people were more likely to be aware of their serostatus when in hospital or had an
49
50
51
52
53
54
55
56

1
2
3 active offer for testing.²⁹ In this study, analysis of the TRUST results suggests that > 90%
4 of syphilis-infected people aged ≥ 45 years with TRUST negative or with low titres had a
5 previous infection. However, late presentation is particularly worrying among older
6 people because it further increases the risk of cardiovascular syphilis, neurosyphilis,
7 paresis, etc. As syphilis is a great imitator, doctors often ignore syphilis infection when
8 diagnosing the elderly, leading to omission of syphilis testing and misdiagnosis of the
9 disease.
10
11

12
13
14
15
16
17
18 Evidence suggests that the most significant factor affecting testing patterns in older
19 adults is providing the screening test actively.²⁹ Since the initiation of China's national
20 syphilis control plan, syphilis screening has been widely integrated into HIV voluntary
21 counselling and testing (VCT) services. More than 95% of people who received HIV
22 testing services have undergone free syphilis testing.³⁰ Referral, treatment, and
23 follow-up services would be provided to those diagnosed with syphilis. In Shenzhen,
24 more than half of VCT sites are set in community health service centres, where a
25 separate room is arranged for counselling and testing service. However, due to the low
26 awareness of self-testing, older adults rarely positively seek the services. Meanwhile,
27 most health staff are unwilling to provide the service actively because of limited
28 experience, lack of time, discomfort in discussing sexual behaviours and STDs with older
29 adults, stigma, ageism, etc.²⁸ Hence, enhanced training of healthcare providers and
30 education of older adults are necessary.
31
32
33
34
35
36
37
38
39
40
41
42

43
44 Consistent with the results of some previous studies, the prevalence of both syphilis
45 infection and active infection were higher among females than males.^{21,22} It may stem
46 partly from the different physiology and anatomy of the genital organs between both
47 sexes, leading to females being more likely to contract STDs in receptive vaginal sex
48 behaviours.³¹ Some studies have proved that the male-to-female transmission rate is
49 higher than the female-to-male rate in certain STDs, such as HIV.^{31,32} Besides, a
50 proportion of females have premarital or extramarital sexual partners. A previous study
51
52
53
54
55
56

1
2
3 has found that the syphilis prevalence among husbands of 2261 syphilis-infected
4 pregnant women was < 30%.³³ Additionally, being serofast [defined as remaining
5 positive in a non-treponemal test and keeping the titre at a certain level (mostly 1:8 or
6 below) after recommended therapy and follow-up at least 1 year for primary syphilis, 2
7 years for secondary syphilis and 3 years for late syphilis] is common among syphilis
8 patients.³⁴ The serofast rate is higher among females than males (42.8% vs. 28.6%),³⁵
9 leading to more females staying in the state of active infection. The exact mechanism
10 underlying this difference is unclear, but it may be partly associated with the varied
11 immune system between both sexes.³⁵ Furthermore, MSM are considered to be a major
12 high-risk subgroup for syphilis infection and are permanently deferred from blood
13 donation in China.³⁶ In this study, males were excluded if they reported they had ever
14 engaged in homosexual behaviour in the health history questionnaire, which may be
15 one of the reasons for the low syphilis prevalence among males.
16
17
18
19
20
21
22
23
24
25
26
27
28

29 Limitations

30 Our study has several limitations. First, limited financial and human resources restricted
31 us in using a population-based design, which is considered as the gold standard in
32 evaluating disease epidemics.¹² The choice of blood donors as population samples may
33 result in potential bias, such as selection bias for age coverage and self-identified health
34 conditions. Second, this study did not distinguish the syphilis seroprevalence between
35 first-time donors and repeat donors, which may lead to underestimation of syphilis
36 disease burden. In previous studies, the syphilis seroprevalence among first-time donors
37 was significantly higher than that among repeat donors.^{12,15} Third, false-negative results
38 attributable to the window period of syphilis infection may result in an underestimation
39 of syphilis prevalence. However, the residual risk of syphilis infection is very low
40 according to a residual risk analysis conducted in Shenzhen.³⁷
41
42
43
44
45
46
47
48
49
50
51

52 Conclusions

53 This study provides an in-depth analysis of the association between syphilis
54
55
56
57
58
59
60

1
2
3 seroprevalence and age. Older adults showed a high prevalence of both syphilis
4 infection and active infection but a small proportion of high titres, which point towards
5 the compelling need to heighten awareness among healthcare providers and deliver
6 more targeted prevention interventions for older adults to promote early testing.
7
8
9

10
11
12
13
14 **Acknowledgements** The authors would like to thank Qiong Yu and Xi Chen from the
15 Shenzhen Blood Center for their support in data collection and blood sample
16 transportation. The authors also give thanks to all the blood donors for taking part in
17 this study.
18
19
20

21
22
23 **Contributors** XW and TF contributed to designing the study, coordinating data collection
24 and drafting the article. YG, JY, CZ and FT contributed to data collection, patient
25 treatment and disease management. HF, LL and FW contributed to data collection and
26 data analysis. FW contributed to syphilis testing and laboratory quality control. YC and
27 WY contributed to making important comments of the manuscript. All authors read and
28 approved the final draft of the manuscript.
29
30
31
32
33

34
35
36 **Funding** This work was supported by the Science, Technology and Innovation
37 Commission of Shenzhen Municipality (grant number JCYJ20160428145537703) and the
38 Sanming Project of Medicine in Shenzhen (No. SZSM201611077).
39
40
41
42

43 **Competing interests** The authors declare no competing interest.
44
45

46 **Patient consent** Not applicable.
47
48

49
50
51 **Ethics approval** Ethics approval was obtained from the Ethics Committee of Shenzhen
52 Center for Chronic Disease Control (No. 20180212).
53
54
55

1
2
3 **Provenance and peer review** Not commissioned; externally peer reviewed.
4
5

6
7 **Data sharing statement** Data are available by emailing XW(bingfsh@126.com).
8
9

10 11 12 **REFERENCES** 13

- 14 1. Department of Economic and Social Affairs, Population Division, United Nations.
15 *World Population Ageing: 1950-2050*.
16 <http://www.un.org/esa/population/publications/worldageing19502050/> (accessed
17 7 October 2018)
18
19
- 20 2. Prince MJ, Wu F, Guo Y, et al. The burden of disease in older people and
21 implications for health policy and practice. *Lancet* 2015; 385: 549-62.
22
23
- 24 3. Tavoschi L, Gomes Dias J, Pharris A, et al. New HIV diagnoses among adults aged 50
25 years or older in 31 European countries, 2001-15: an analysis of surveillance data.
26 *Lancet HIV* 2017; 4: e514-21.
27
28
- 29 4. Mahy M, Autenrieth CS, Stanecki K, et al. Increasing trends in HIV prevalence among
30 people aged 50 years and older: evidence from estimates and survey data. *AIDS*
31 2014; 28: S453-9.
32
33
- 34 5. Gong X, Yue X, Teng F, et al. Syphilis in China from 2000 to 2013: epidemiological
35 trends and characteristics. *Chin J Dermatol* 2014; 47: 310-5. (in Chinese)
36
37
- 38 6. Workowski KA and Bolan GA. Sexually transmitted disease treatment guidelines,
39 2015. *MMWR Recomm Rep* 2015; 64: 34-49.
40
41
- 42 7. Kotsafti O, Pappas V, Kourkounti S, et al. Early syphilis affects markers of HIV
43 infection. *Int J STD AIDS* 2016; 27: 739-45.
44
45
- 46 8. Newman L, Rowley J, Vander Hoorn S, et al. Global estimates of the prevalence and
47 incidence of four curable sexually transmitted infections in 2012 based on
48 systematic review and global reporting. *PLoS One* 2015; 10: e0143304.
49
50
- 51 9. Yang S, Wu J, Ding C, et al. Epidemiological features of and changes in incidence of
52 infectious disease in China in the first decade after the SARS outbreak: an
53
54
55
56

- 1
2
3 observational trend study. *Lancet Infect Dis* 2017; 17: 716-25.
4
5 10. Wu X, Hong F, Lan L, et al. Poor awareness of syphilis prevention and treatment
6 knowledge among six different populations in south China. *BMC Public Health* 2016;
7 16: 287.
8
9 11. Lan LN, Wu XB, Zhang CL, et al. Epidemiological analysis of syphilis in Shenzhen from
10 2004 to 2013. *China Tropical Medicine* 2015; 15: 700-3. (in Chinese)
11
12 12. Kane MA, Bloch EM, Bruhn R, et al. Demographic determinants of syphilis
13 seroprevalence among U.S. blood donors, 2011-2012. *BMC Infect Dis* 2015; 15: 63.
14
15 13. Wu XB, Zhang CL, Lan LN, et al. Syphilis infection among five different groups of
16 people and analysis of treatment situation in Shenzhen. *China Tropical Medicine*
17 2015; 15: 830-2. (in Chinese)
18
19 14. Chen YY, Qiu XH, Zhang YF, et al. A better definition of active syphilis infection. *Clin*
20 *Chim Acta* 2015; 444: 1-2.
21
22 15. Liu J, Huang Y, Wang J, et al. The increasing prevalence of serologic markers for
23 syphilis among Chinese blood donors in 2008 through 2010 during a syphilis
24 epidemic. *Transfusion* 2012; 52: 1741-9.
25
26 16. Vera L, Milka D, Nurith SL, et al. Prevalence and incidence of syphilis among
27 volunteer blood donors in Israel. *J Blood Transfus* 2014; 2014: 154048.
28
29 17. Baiao AM, Kupek E, Petry A. Syphilis seroprevalence estimates of Santa Catarina
30 blood donors in 2010. *Rev Soc Bras Med Trop* 2014; 47: 179-85.
31
32 18. Abate M, Wolde T. Seroprevalence of Human Immunodeficiency Virus, Hepatitis
33 B Virus, Hepatitis C Virus, and Syphilis among Blood Donors at Jigjiga Blood Bank,
34 Eastern Ethiopia. *Ethiop J Health Sci* 2016; 26: 153-60.
35
36 19. Dionne-Odom J, Mbah R, Rembert NJ, et al. Hepatitis B, HIV, and Syphilis
37 seroprevalence in pregnant women and blood donors in Cameroon. *Infect Dis*
38 *Obstet Gynecol* 2016; 2016: 4359401.
39
40 20. Rawat A, Diwaker P, Gogoi P, et al. Seroprevalence & changing trends of
41 transfusion-transmitted infections amongst blood donors in a Regional Blood
42 Transfusion Center in north India. *Indian J Med Res* 2017; 146: 642-5.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 21. Chen Y, Liu Z, Zhang Q, et al. Trend in prevalence of syphilis among voluntary blood
4 donors in Xi'an, China from 2006 to 2010. *Int J Infect Dis* 2014; 19: 98-9.
- 5
6
7 22. Li C, Xiao X, Yin H, et al. Prevalence and prevalence trends of transfusion
8 transmissible infections among blood donors at four Chinese regional blood centers
9 between 2000 and 2010. *J Transl Med* 2012; 10: 176.
- 10
11
12 23. National Center for STD Control, Chinese Center for Disease Control and Prevention.
13 Clinical evaluation of syphilis diagnostic reagents in 2016.
14 <http://www.ncstdc.org/show.asp?id=1547> (accessed 7 October 2018).
- 15
16
17 24. Qin JB, Feng TJ, Yang TB, et al. Maternal and paternal factors associated with
18 congenital syphilis in Shenzhen, China: a prospective cohort study. *Eur J Clin*
19 *Microbiol Infect Dis*, 2014, 33(2): 221-32.
- 20
21
22 25. Cao WW, Zhou RR, Qu X, et al. Prevalence of hepatitis B virus, hepatitis C virus,
23 human immunodeficiency virus and *Treponema pallidum* infections in hospitalized
24 patients before transfusion in Xiangya hospital Central South University, China from
25 2011 to 2016. *BMC Infect Dis* 2018; 18: 145.
- 26
27
28 26. Gott CM. Sexual activity and risk-taking in later life. *Health Soc Care Community*
29 2001; 9: 72-8.
- 30
31
32 27. Tillman JL, Mark HD. HIV and STI testing in older adults: an integrative review. *J Clin*
33 *Nurs* 2015; 24: 2074-95.
- 34
35
36 28. Davis T, Teaster PB, Thornton A, et al. Primary care providers' HIV prevention
37 practices among older adults. *J Appl Gerontol* 2016; 35: 1325-42.
- 38
39
40 29. Adekeye OA, Heiman HJ, Onyeabor OS, et al. The new invincibles: HIV screening
41 among older adults in the U.S.. *PLoS One* 2012; 7: e43618.
- 42
43
44 30. Chen YF, Ding JP, Yan HJ, et al. The current status of syphilis prevention and control
45 in Jiangsu province, China: a cross-sectional study. *PLoS One* 2017; 12: e0183409.
- 46
47
48 31. Varghese B, Maher JE, Peterman TA, et al. Reducing the risk of sexual HIV
49 transmission: quantifying the per-act risk for HIV on the basis of choice of partner,
50 sex act, and condom use. *Sex Transm Dis* 2002; 29: 38-43.
- 51
52
53 32. Kim JH. HIV transmissions by stage and sex role in long-term concurrent sexual
54
55
56

1
2
3 partnerships. *Acta Biotheor* 2015; 63: 33-54.

- 4
5 33. Wu XB, Hong FC, Peng DY, et al. Syphilis infection status and the associated factors
6 among partners of married syphilis-infected pregnant women in Shenzhen. *Chin J*
7 *Dis Control Prev* 2016; 20: 1278-81. (in Chinese)
8
9
10 34. National Health Commission of the People's Republic of China. Diagnosis for syphilis.
11 [http://www.nhfpc.gov.cn/zhuz/s9491/201803/5103a5425f9e47d29b91de38434b7f](http://www.nhfpc.gov.cn/zhuz/s9491/201803/5103a5425f9e47d29b91de38434b7f74.shtml)
12 [74.shtml](http://www.nhfpc.gov.cn/zhuz/s9491/201803/5103a5425f9e47d29b91de38434b7f74.shtml) (accessed 7 October 2018).
13
14
15
16 35. Tong ML, Lin LR, Liu GL, et al. Factors associated with serological cure and the
17 serofast state of HIV-negative patients with primary, secondary, latent, and tertiary
18 syphilis. *PLoS One* 2013; 8: e70102.
19
20
21 36. Shi L, Wang J, Liu Z, et al. Blood donor management in China. *Transfus Med*
22 *Hemother* 2014; 41:273-282.
23
24
25 37. Yang AL, Wang SX, Wei TL, et al. *Treponema pallidum* infection and residual risk of
26 blood transmission of syphilis among voluntary blood donors in Shenzhen from
27 2008 to 2012. *J Mod Lab Med* 2013; 28: 122-124. (in Chinese)
28
29
30
31
32
33

34 **FIGURE LEGENDS**

35 Figure 1 Flowchart for syphilis screening and confirmatory testing among blood donors.
36 ELISA: enzyme-linked immunosorbent assay; TPPA: *Treponema pallidum* particle
37 agglutination assay; TRUST: toluidine red unheated serum test.
38
39
40
41
42

43 Figure 2 Prevalence of syphilis infection and active infection in different age groups,
44 2014-2017. (A) Prevalence of syphilis infection and active infection among males. (B)
45 Prevalence of syphilis infection and active infection among females. SI: syphilis infection;
46 AI: active infection.
47
48
49
50

51 Figure 3 Distribution of TRUST titres among active infection donors in different age
52 groups.
53
54
55
56

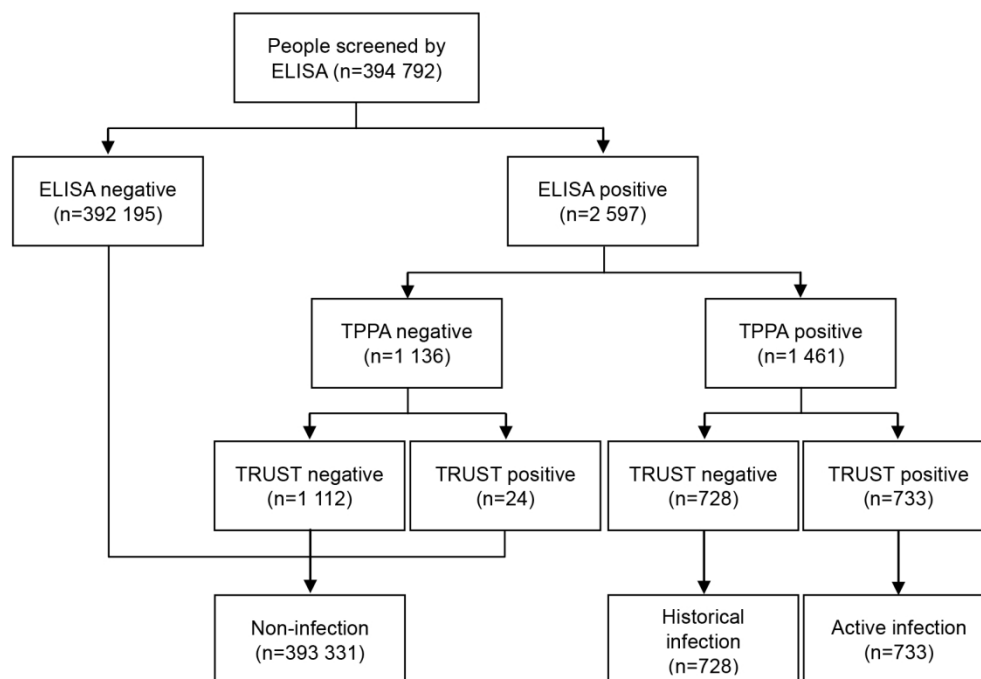


Figure 1 Flowchart for syphilis screening and confirmatory testing among blood donors. ELISA: enzyme-linked immunosorbent assay; TPPA: Treponema pallidum particle agglutination assay; TRUST: toluidine red unheated serum test.

157x116mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

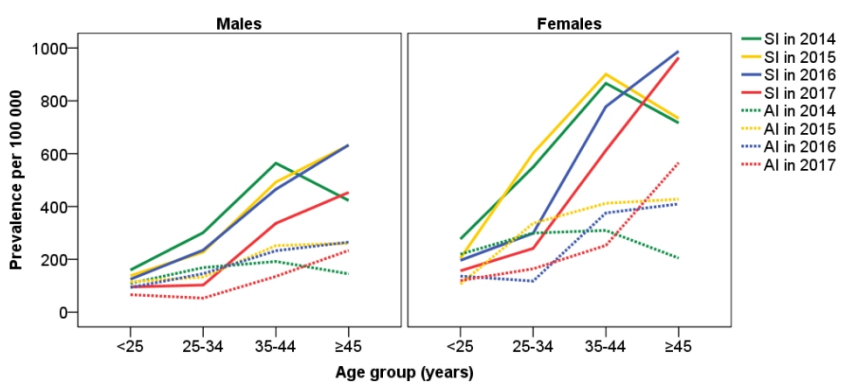


Figure 2 Prevalence of syphilis infection and active infection in different age groups, 2014-2017. (A) Prevalence of syphilis infection and active infection among males. (B) Prevalence of syphilis infection and active infection among females. SI: syphilis infection; AI: active infection.

423x182mm (72 x 72 DPI)

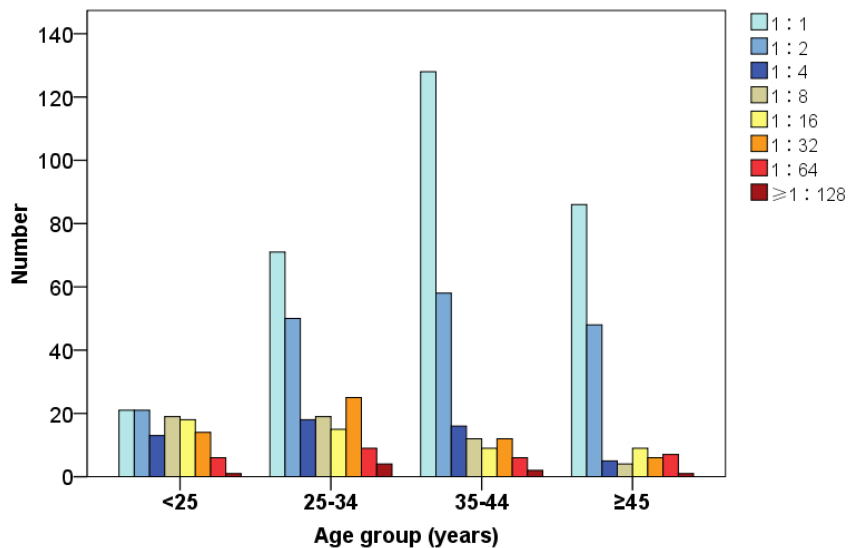


Figure 3 Distribution of TRUST titres among active infection donors in different age groups.

316x182mm (72 x 72 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	P1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P9-10
Objectives	3	State specific objectives, including any prespecified hypotheses	P10
Methods			
Study design	4	Present key elements of study design early in the paper	P10-11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P10-11
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	P10-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P11-12
Bias	9	Describe any efforts to address potential sources of bias	P11
Study size	10	Explain how the study size was arrived at	P10,P13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P12
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	P12
		(b) Describe any methods used to examine subgroups and interactions	P12
		(c) Explain how missing data were addressed	Not applicable
		(d) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	P13

		confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	P24
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P13
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	P13-15
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P13-15
		(b) Report category boundaries when continuous variables were categorized	P13
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	P14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	P15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P17-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	P15-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024393.R2
Article Type:	Original research
Date Submitted by the Author:	22-Feb-2019
Complete List of Authors:	Wu, Xiaobing; Shenzhen Center for Chronic Disease Control Guan, Yang; Shenzhen Center for Chronic Disease Control, Guangdong Ye, Jianbin; Shenzhen Center for Chronic Disease Control Fu, Hanlin; XiangYa School of Public Health, Central South University, Department of Epidemiology and Health Statistics Zhang, Chunlai; Shenzhen Center for Chronic Disease Control Lan, Lina; Shenzhen Center for Chronic Disease Control Wu, Fengxin; School of Public Health, Guangdong Medical University Tang, Fen; Shenzhen Center for Chronic Disease Control Wang, Feng; Shenzhen Center for Chronic Disease Control Cai, Yumao; Shenzhen Center for Chronic Disease Control Yu, Weiye; Shenzhen Center for Chronic Disease Control Feng, Tiejian; Shenzhen Center for Chronic Disease Control, Department of STD control and prevention
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Sexual health, Public health, Epidemiology
Keywords:	Syphilis, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts

Title page

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

Xiaobing Wu,¹ Yang Guan,¹ Jianbin Ye,¹ Hanlin Fu,² Chunlai Zhang,¹ Lina Lan,¹ Fengxin Wu,³ Fen Tang,¹ Feng Wang,¹ Yumao Cai,¹ Weiye Yu,¹ Tiejian Feng¹

Author affiliations

¹Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control, No.2021 Buxin Road, Luohu District, Shenzhen City, Guangdong Province, People's Republic of China

²Xiangya School of Public Health, Central South University, NO. 238 Shang Ma Yuan Ling Xiang, Kaifu District, Changsha City, Hunan Province, People's Republic of China

³School of Public Health, Guangdong Medical University, No.1 Xincheng Boulevard, Songshan Lake, National High Technology Industrial Development Zone, Dongguan City, Guangdong Province, People's Republic of China

Corresponding Author:

Tiejian Feng, MD

Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control

Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong Province, People's Republic of China

E-mail: fengtiej@126.com

Telephone number: +86-755-25618781

First author:

Xiaobing Wu, PhD

Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control

Correspondence to Xiaobing wu; bingfsh@126.com and Tiejian Feng; fengtiej@126.com

1
2
3 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
4 Province, People's Republic of China

5 E-mail: bingfsh@126.com

6
7 Telephone number: +86-755-25106861
8
9

10
11
12 **Co-author:**

13 Yang Guan, MD

14
15 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
16 Chronic Disease Control

17
18 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
19 Province, People's Republic of China

20 E-mail: gygyimi@126.com

21 Telephone number: +86-755-25632714
22
23

24
25
26
27
28 **Co-author:**

29 Jianbin Ye, BSc

30
31 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
32 Chronic Disease Control

33
34 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
35 Province, People's Republic of China

36 E-mail: 842413681@qq.com

37 Telephone number: +86-755-25632714
38
39

40
41
42
43
44 **Co-author:**

45 Hanlin Fu, PhD

46 Xiangya School of Public Health, Central South University

47
48 Postal address: NO. 238 Shang Ma Yuan Ling Xiang, Kaifu District, Changsha City,
49 Hunan Province, People's Republic of China

50 E-mail: 694400861@qq.com

51 Telephone number: +86-15111341391
52
53

54
55
56
57
58
59 **Co-author:**
60

1
2
3 Chunlai Zhang, BSc

4
5 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
6
7 Chronic Disease Control

8
9 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
10
11 Province, People's Republic of China

12
13 E-mail: szzhchl@163.com

14
15 Telephone number: +86-755-25632714

16
17
18 **Co-author:**

19
20 Lina Lan, MPH

21
22 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
23
24 Chronic Disease Control

25
26 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
27
28 Province, People's Republic of China

29
30 E-mail: 8262268@qq.com

31
32 Telephone number: +86-755-25608017

33
34
35 **Co-author:**

36
37 Fengxin Wu, BSc

38
39 School of Public Health, Guangdong Medical University

40
41 Postal address: No.1 Xincheng Boulevard, Songshan Lake, National High Technology
42
43 Industrial Development Zone, Dongguan City, Guangdong Province, People's
44
45 Republic of China

46
47 E-mail: 1162887843@qq.com

48
49 Telephone number: +86-13650232046

50
51
52 **Co-author:**

53
54 Fen Tang, BSc

55
56 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
57
58 Chronic Disease Control

59
60 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
Province, People's Republic of China

1
2
3 E-mail: 791950577@qq.com
4

5 Telephone number: +86-755-25632714
6
7

8
9 **Co-author:**

10 Feng Wang, MSc

11
12 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
13 Chronic Disease Control
14

15
16 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
17 Province, People's Republic of China
18

19 E-mail: biowangfeng@163.com

20 Telephone number: +86-755-25619065
21
22

23
24
25 **Co-author:**

26 Yumao Cai, MPH

27
28 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
29 Chronic Disease Control
30

31
32 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
33 Province, People's Republic of China
34

35 E-mail: 64165469@qq.com

36 Telephone number: +86-755-25632714
37
38

39
40
41 **Co-author:**

42 Weiye Yu, MD

43
44 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
45 Chronic Disease Control
46

47
48 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
49 Province, People's Republic of China
50

51 E-mail: ywy2002@126.com

52 Telephone number: +86-755-25531338
53
54

55
56
57
58 **Word Counts:** 298 words (abstract); 3009 words (text);

59 **Tables:** 3 tables;
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figures: 3 figures.

For peer review only

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 Program for Syphilis Prevention and Control in 2014-2017. Blood samples were screened using the enzyme-linked immunosorbent assay (ELISA), 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% confidence interval (CI), 351.1-389.0 per 100 000]; the prevalence of active infection was 185.7 per 100 000 (95% CI, 172.2-199.1 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 ($\chi^2_{\text{trend}} = 311.9$, $p_{\text{trend}} < 0.001$) and active infection ($\chi^2_{\text{trend}} = 72.1$, $p_{\text{trend}} < 0.001$) increased significantly with age. After stratification by gender and year of donation, the increasing trend of prevalence with age remained ($p_{\text{trend}} < 0.05$), 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 $\geq 1:8$, 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 enzyme-linked immunosorbent assay (ELISA) as a screening test and then using *Treponema pallidum* particle agglutination assay (TPPA) and toluidine red unheated serum test (TRUST) 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.

MAIN TEXT

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 human immunodeficiency virus (HIV) and syphilis, was shown from recent surveillance data.³⁻⁵ This large disease burden among older people calls for improvements in the healthcare system and more investments and programs 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, death, etc., 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 (SARS) outbreak.⁹ The reported incidence was slightly higher among females than males (ratio, 1.00 to 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

1
2
3 of >10 million, is one of the cities that most affected by syphilis. The reported
4 incidence of syphilis was over 60 per 100 000 in last 10 years, which was much higher
5 than the national incidence.^{5,10} Consistent with the aforementioned characteristics
6 of varied age groups, a rapid increase in syphilis incidence among older adults was
7 observed in Shenzhen.¹¹ Studies usually considered blood donors as a representative
8 of the general population and used the prevalence data of blood donors for
9 real-time surveillance and identification of high-risk groups.¹² Whether the syphilis
10 seroprevalence among blood donors agrees with reported incidence characteristics
11 remains to be studied. Shenzhen launched a comprehensive program, the Shenzhen
12 Program for Syphilis Prevention and Control (SPSPC), in November 2013 to enhance
13 syphilis screening among blood donors and five other subgroups (HIV voluntary
14 counsellors, methadone maintenance treatment users, female sex workers, men
15 who have sex with men, and women of childbearing age), as well as case
16 management, including diagnosis, treatment, and follow-up, for syphilis-infected
17 adults.¹³ Based on the data from the SPSPC, this study aimed to examine differences
18 in syphilis seroprevalence among blood donors and describe the distribution of
19 serological titres among syphilis-infected donors with respect to age groups, to
20 confirm the syphilis epidemic characteristics in southern China and support the
21 design of effective interventions for older adults.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39

40 **METHODS**

41 **Subjects and blood donation process**

42 Blood donors were recruited by the Shenzhen Blood Center between 2014 and 2017.
43 About 10 blood mobiles, with the Shenzhen Blood Center logo and the words
44 'non-remunerated blood donation', were dispatched around the city to increase the
45 accessibility of blood donation. Volunteers could either go to the mobiles or to the
46 blood centre directly.
47
48
49
50
51
52
53

54 Before donation, all potential donors needed to complete a health history
55 questionnaire, sign a donation registration form, and undergo rapid testing and a
56 brief physical examination. The health history questionnaire contained a total of 27
57 medical conditions that would permanently or temporarily prevent the donors from
58
59
60

1
2
3 donation, including a series of chronic diseases and infectious diseases (e.g., HIV,
4 syphilis), transplant, high-risk behaviours (e.g., homosexual behaviours, drug use),
5 surgery, delivery, breastfeeding, etc. Pre-donation repaid testing included blood type,
6 haemoglobin, hepatitis B surface antigen, and alanine transaminase. Weight, blood
7 pressure, heart rate and body temperature were measured. Clinical examination of
8 the skin and limbs was conducted. People who conformed to the Whole Blood and
9 Component Donor Selection Requirements (GB 18467-2001) could proceed to
10 donate blood. All blood donors were non-remunerated. Light refreshment, a blood
11 donation certification, and a blood credit allowing free transfusion for donors or
12 their direct relatives were provided as incentives. The donation process and blood
13 management were fully in accordance with the *Blood Donation Law of the People's*
14 *Republic of China* and the *Blood Donation Regulation of the Shenzhen Special*
15 *Economic Zone*.

26 27 28 29 **Serological testing**

30 After donation, the blood samples were transferred to the Shenzhen Blood Center
31 and underwent a series of laboratory testing. The enzyme-linked immunosorbent
32 assay (ELISA; Zhuhai Lizhu Bio-engineering Co. Ltd., Zhuhai, China) was performed on
33 all blood samples for syphilis screening. Syphilis-positive samples, with a form listing
34 the donors' name, age, and gender, were then transferred to the Shenzhen Center
35 for Chronic Disease Control [SZCCC, a city-level prevention and control centre for
36 sexually transmitted diseases (STDs)] under SPSPC guidelines. A treponemal test of
37 *Treponema pallidum* particle agglutination (TPPA; Fujirebio Inc., Tokyo, Japan) and a
38 non-treponemal test of toluidine red unheated serum test (TRUST; Shanghai
39 Rongsheng BioTech Co. Ltd., Shanghai, China) were used at the SZCCC to confirm the
40 infection status. TRUST-positive samples further underwent quantitative titre testing
41 to monitor response to treatment. TPPA and TRUST results were sent back to the
42 Shenzhen Blood Center within 2 days after the samples were received.

43 44 45 46 47 48 49 50 51 52 53 54 55 56 **Definition of syphilis infection**

57 Based on serological test results, syphilis seropositivity was divided into historical
58 infection and active infection, which was consistent with the classification from
59
60

1
2
3 previous studies.¹² Historical infection was defined as TPPA positive but TRUST
4 negative and active infection as both TPPA and TRUST positive.¹⁴ Syphilis
5 seropositivity was defined as TPPA positive, including both TRUST negative and
6 TRUST positive. Moreover, high-titre was defined as a quantitative titre of $\geq 1 : 8$ in
7 patients with active infection. For the purpose of this study, syphilis seropositivity
8 which represented the overall infection status among the target population, and
9 active infection and high-titre status which were correlated with disease activity,
10 were analysed.
11
12
13
14
15
16
17
18
19

20 **Statistical analysis**

21 Primary outcomes of interest were the prevalence of syphilis seropositivity and
22 active infection among all blood donors in different age groups. There were four age
23 groups, <25 years, 25-34 years, 35-44 years, and ≥ 45 years, fully considering the age
24 coverage of blood donors and age classification in previous studies.^{15,16} We
25 calculated the crude prevalence and its 95% confidence interval (CI). The chi-squared
26 (χ^2) test for trend was used to assess the difference in prevalence among age groups.
27 Odds ratios (ORs) and their 95% CIs were calculated when comparing the risk of
28 syphilis seropositivity and active infection between the ≥ 45 years age group and
29 other age groups. Line graphs were used to describe the changes in prevalence for
30 both syphilis seropositivity and active infection among the age groups after
31 stratification by gender and year of donation. Furthermore, we described the
32 distribution of TRUST titres among the age groups and compared the difference
33 using the χ^2 test for trend. Data were analysed using SPSS 17.0 for Windows (IBM
34 Corp., Armonk, USA); $p < 0.05$ was considered statistically significant in the χ^2 test.
35
36
37
38
39
40
41
42
43
44
45
46
47
48

49 **Patient and public involvement statement**

50 Patients and the public were not involved in developing the hypothesis or research
51 questions, nor were they involved in developing plans for the design or
52 implementation of this study. The staff of the Shenzhen Blood Center were
53 responsible for telling syphilis-positive participants about the test results and
54 providing referral services related to syphilis treatment and management by phone.
55
56
57
58
59
60

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 ($\chi^2 = 11249.0$, $p < 0.001$) and among years of donation ($\chi^2 = 1182.0$, $p < 0.001$). People aged 25-34 years accounted for the largest proportion of donors (**Table 1**).

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

Variables	Aged <25 years (n=95736)	Aged 25-34 years (n=137447)	Aged 35-44 years (n=102422)	Aged \geq 45 years (n=59187)	χ^2	<i>p</i> value
Gender					11249.0	<0.001
Male	51409(19.3%)	96237(36.2%)	74445(28.0%)	44061(16.6%)		
Female	44327(34.5%)	41210(32.0%)	27977(21.7%)	15126(11.8%)		
Year of donation					1182.0	<0.001
2014	22389(25.3%)	31929(36.0%)	23131(26.1%)	11210(12.6%)		
2015	24330(25.7%)	33096(35.0%)	24011(25.4%)	13241(14.0%)		
2016	24560(24.0%)	35736(34.9%)	26362(25.7%)	15843(15.5%)		
2017	24457(22.4%)	36686(33.7%)	28918(26.5%)	18893(17.3%)		

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, 351.1-389.0 per 100 000), and the prevalence of active infection was 185.7 per 100 000 (95% CI, 172.2-199.1 per 100 000). The prevalence of syphilis seropositivity and active infection was higher among females than males (syphilis seropositivity: $\chi^2 = 60.4$, $p < 0.001$; active infection: $\chi^2 = 36.1$, $p < 0.001$) and showed a decreasing trend from 2014 to 2017 (syphilis seropositivity: $\chi^2_{\text{trend}} = 27.1$, $p_{\text{trend}} < 0.001$; active infection: $\chi^2_{\text{trend}} = 7.8$, $p_{\text{trend}} = 0.005$). People aged \geq 45 years reported the highest prevalence of both syphilis seropositivity and active infection, which was 3.8 times (OR = 3.8; 95% CI, 3.1-4.6) and 2.4 times (OR = 2.4; 95% CI, 1.9-3.0) higher than that among people

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

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

Age group	Number of screened	Syphilis seropositivity				Active infection			
		Number	Prevalence per 100 000 (95%CI)	χ^2_{trend}	p_{trend} value	Number	Prevalence per 100 000 (95%CI)	χ^2_{trend}	p_{trend} value
Aged <25 years	95736	158	165.0(139.3-190.8)	311.9	<0.001	113	118.0(96.3-139.8)	72.1	<0.001
Aged 25-34 years	137447	376	273.6(245.9-301.2)			211	153.5(132.8-174.2)		
Aged 35-44 years	102422	559	545.8(500.7-590.9)			243	237.3(207.5-267.0)		
Aged ≥45 years	59187	368	621.8(558.4-685.1)			166	280.5(237.9-323.1)		

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 ($\chi^2_{\text{trend}} = 53.6$, $p_{\text{trend}} < 0.001$) (Table 3).

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%)

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 United States (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 (i.e., 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 >98% 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 if without timely and adequate treatment. The higher the serological titre, the more the risk of transmission (e.g., 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

1
2
3 patients was similar to that reported in the United States.¹²
4
5

6
7 This study found that syphilis prevalence significantly increased with age. Older
8 adults aged ≥ 45 years displayed the highest prevalence of both syphilis seropositivity
9 and active infection. More importantly, from the national surveillance data, people
10 aged ≥ 60 years had a remarkably higher increase in reported incidence compared
11 with those aged 45-60 years.⁵ Hospitalised patients aged ≥ 70 years showed the
12 highest syphilis prevalence (4.8%), followed by patients aged 61-70 years (3.9%) and
13 those aged 51-60 years (3.2%), which was much different from that for HIV infection
14 for which patients aged 31-40 years recorded the highest prevalence.²⁵ Based on the
15 results of this study and previous studies, health awareness and syphilis prevention
16 focusing on older adults are needed.
17
18
19
20
21
22
23
24
25

26
27 The higher prevalence among older adults might be due to several reasons. First,
28 many older people are sexually active,²⁶ and their sexual health and behaviour affect
29 syphilis transmission. Low self-perception of risk and misconceptions or limited
30 knowledge about syphilis and other STDs were frequently reported as reasons for
31 condomless sex among older adults.^{5,27} Second, older adults have been largely
32 neglected by healthcare providers due to age-related stigma.²⁸ Sexual health services
33 for HIV or STDs rarely focus on older adults, leaving this group behind in both testing
34 and prevention. Third, presenting with a late diagnosis has been significantly
35 associated with older age. Older people were more likely to be aware of their
36 serostatus when in hospital or had an active offer for testing.²⁹ In this study, analysis
37 of the TRUST results suggests that $> 90\%$ of syphilis-infected people aged ≥ 45 years
38 with TRUST negative or with low titres had a previous infection. However, late
39 presentation is particularly worrying among older people because it further increases
40 the risk of cardiovascular syphilis, neurosyphilis, paresis, etc. As syphilis is a great
41 imitator, doctors often ignore syphilis infection when diagnosing the elderly, leading
42 to omission of syphilis testing and misdiagnosis of the disease.
43
44
45
46
47
48
49
50
51
52
53
54
55
56

57
58 Evidence suggests that the most significant factor affecting testing patterns in older
59 adults is the active provision of the screening test.²⁹ Since the initiation of China's
60

1
2
3 national syphilis control plan, syphilis screening has been widely integrated into HIV
4 voluntary counselling and testing (VCT) services. More than 95% of people who
5 received HIV testing services have undergone free syphilis testing.³⁰ Referral,
6 treatment, and follow-up services would be provided to those diagnosed with
7 syphilis. In Shenzhen, more than half of VCT sites are set in community health service
8 centres, where a separate room is arranged for counselling and testing service.
9
10 However, due to the low awareness of self-testing, older adults rarely positively seek
11 the services. Meanwhile, most health staff are unwilling to provide the service
12 actively because of limited experience, lack of time, discomfort in discussing sexual
13 behaviours and STDs with older adults, stigma, ageism, etc.²⁸ Hence, enhanced
14 training of healthcare providers and education of older adults are necessary.
15
16
17
18
19
20
21
22
23
24

25 Consistent with the results of some previous studies, the prevalence of both syphilis
26 seropositivity and active infection were higher among females than males.^{21,22} It may
27 stem partly from the different physiology and anatomy of the genital organs
28 between both sexes, leading to females being more likely to contract STDs in
29 receptive vaginal sex behaviours.³¹ Some studies have proved that the
30 male-to-female transmission rate is higher than the female-to-male rate in certain
31 STDs, such as HIV.^{31,32} Besides, a proportion of females have multiple sex partners
32 during their lifetime. A previous study has found that the syphilis prevalence among
33 husbands of 2261 syphilis-infected pregnant women was < 30%.³³ Premarital or
34 extramarital sexual partners may greatly increase the risk of syphilis infection among
35 females. Additionally, serological response differs between males and females.³⁴
36 Females are more likely to be serofast [defined as remaining positive in a
37 non-treponemal test and keeping the titre at a certain level (mostly 1:8 or below)
38 after recommended therapy and follow-up 1 to 3 years according to syphilis stage]
39 when comparing with males,³⁵ leading to more females staying in the state of active
40 infection. The exact mechanism underlying this difference is unclear, but it may be
41 partly associated with the varied immune system between both sexes.³⁴
42 Furthermore, men who have sex with men are considered a major high-risk
43 subgroup for syphilis infection and are permanently deferred from blood donation in
44 China.³⁶ In this study, males were excluded if they reported they had ever engaged in
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 homosexual behaviour in the health history questionnaire, which may be one of the
4 reasons for the low syphilis prevalence among males.
5
6
7

8 **Limitations**

9
10 Our study has several limitations. First, limited financial and human resources
11 restricted us in using a population-based design, which is considered as the gold
12 standard in evaluating disease epidemics.¹² The choice of blood donors as population
13 samples may result in potential bias, such as selection bias for age coverage and
14 self-identified health conditions. Second, the syphilis seroprevalence among
15 first-time donors was significantly higher than that among repeat donors.^{12,15} This
16 study did not collect the information of first-time donors and repeat donors, which
17 may lead to underestimation of syphilis seroprevalence. Third, false-negative results
18 attributable to the window period of syphilis infection may result in an
19 underestimation of syphilis seroprevalence. However, the residual risk of syphilis
20 infection is very low according to a residual risk analysis conducted in Shenzhen.³⁷
21
22
23
24
25
26
27
28
29
30
31

32 **Conclusions**

33 This study provides an in-depth analysis of the association between syphilis
34 seroprevalence and age. Older adults showed a high prevalence of both syphilis
35 seropositivity and active infection but a small proportion of high titres, which point
36 towards the compelling need to heighten awareness among healthcare providers
37 and deliver more targeted prevention interventions for older adults to promote early
38 testing.
39
40
41
42
43
44
45
46
47
48

49 **Acknowledgements** The authors would like to thank Qiong Yu and Xi Chen from the
50 Shenzhen Blood Center for their support in data collection, and Qianqiu Wang and
51 Yueping Yin from the Chinese Academy of Medical Sciences in revising the
52 manuscript. The authors also give thanks to all the blood donors for taking part in
53 this study.
54
55
56
57
58
59

60 **Contributors** XW and TF contributed to designing the study, coordinating data

1
2
3 collection and drafting the article. YG, JY, CZ and FT contributed to data collection,
4 patient treatment and disease management. HF, LL and FW contributed to data
5 collection and data analysis. FW contributed to syphilis testing and laboratory quality
6 control. YC and WY contributed to making important comments of the manuscript.
7
8 All authors read and approved the final draft of the manuscript.
9
10
11
12
13

14 **Funding** This work was supported by the Science, Technology and Innovation
15 Commission of Shenzhen Municipality (grant number JCYJ20160428145537703) and
16 the Sanming Project of Medicine in Shenzhen (No. SZSM201611077).
17
18

19
20
21 **Competing interests** The authors declare no competing interest.
22
23

24
25 **Patient consent** Not applicable.
26
27

28
29 **Ethics approval** Ethics approval was obtained from the Ethics Committee of
30 Shenzhen Center for Chronic Disease Control (No. 20180212).
31
32

33
34 **Provenance and peer review** Not commissioned; externally peer reviewed.
35
36

37
38 **Data sharing statement** Data are available by emailing XW(bingfsh@126.com).
39
40
41
42

43 REFERENCES

- 44
45 1. Department of Economic and Social Affairs, Population Division, United Nations.
46 *World Population Ageing: 1950-2050*.
47 <http://www.un.org/esa/population/publications/worldageing19502050/>
48 (accessed 7 October 2018)
49
- 50
51 2. Prince MJ, Wu F, Guo Y, et al. The burden of disease in older people and
52 implications for health policy and practice. *Lancet* 2015; 385: 549-62.
53
- 54
55 3. Tavoschi L, Gomes Dias J, Pharris A, et al. New HIV diagnoses among adults aged
56 50 years or older in 31 European countries, 2001-15: an analysis of surveillance
57 data. *Lancet HIV* 2017; 4: e514-21.
58
59
60

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
4. Mahy M, Autenrieth CS, Stanecki K, et al. Increasing trends in HIV prevalence among people aged 50 years and older: evidence from estimates and survey data. *AIDS* 2014; 28: S453-9.
 5. Gong X, Yue X, Teng F, et al. Syphilis in China from 2000 to 2013: epidemiological trends and characteristics. *Chin J Dermatol* 2014; 47: 310-5. (in Chinese)
 6. Workowski KA and Bolan GA. Sexually transmitted disease treatment guidelines, 2015. *MMWR Recomm Rep* 2015; 64: 34-49.
 7. Kotsafti O, Pappas V, Kourkounti S, et al. Early syphilis affects markers of HIV infection. *Int J STD AIDS* 2016; 27: 739-45.
 8. Newman L, Rowley J, Vander Hoorn S, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One* 2015; 10: e0143304.
 9. Yang S, Wu J, Ding C, et al. Epidemiological features of and changes in incidence of infectious disease in China in the first decade after the SARS outbreak: an observational trend study. *Lancet Infect Dis* 2017; 17: 716-25.
 10. Wu X, Hong F, Lan L, et al. Poor awareness of syphilis prevention and treatment knowledge among six different populations in south China. *BMC Public Health* 2016; 16: 287.
 11. Lan LN, Wu XB, Zhang CL, et al. Epidemiological analysis of syphilis in Shenzhen from 2004 to 2013. *China Tropical Medicine* 2015; 15: 700-3. (in Chinese)
 12. Kane MA, Bloch EM, Bruhn R, et al. Demographic determinants of syphilis seroprevalence among U.S. blood donors, 2011-2012. *BMC Infect Dis* 2015; 15: 63.
 13. Wu XB, Zhang CL, Lan LN, et al. Syphilis infection among five different groups of people and analysis of treatment situation in Shenzhen. *China Tropical Medicine* 2015; 15: 830-2. (in Chinese)
 14. Chen YY, Qiu XH, Zhang YF, et al. A better definition of active syphilis infection. *Clin Chim Acta* 2015; 444: 1-2.
 15. Liu J, Huang Y, Wang J, et al. The increasing prevalence of serologic markers for syphilis among Chinese blood donors in 2008 through 2010 during a syphilis epidemic. *Transfusion* 2012; 52: 1741-9.
 16. Vera L, Milka D, Nurith SL, et al. Prevalence and incidence of syphilis among

- 1
2
3 volunteer blood donors in Israel. *J Blood Transfus* 2014; 2014: 154048.
4
5 17. Baiao AM, Kupek E, Petry A. Syphilis seroprevalence estimates of Santa Catarina
6 blood donors in 2010. *Rev Soc Bras Med Trop* 2014; 47: 179-85.
7
8 18. Abate M, Wolde T. Seroprevalence of Human Immunodeficiency Virus, Hepatitis
9 B Virus, Hepatitis C Virus, and Syphilis among Blood Donors at Jigjiga Blood Bank,
10 Eastern Ethiopia. *Ethiop J Health Sci* 2016; 26: 153-60.
11
12 19. Dionne-Odom J, Mbah R, Rembert NJ, et al. Hepatitis B, HIV, and Syphilis
13 seroprevalence in pregnant women and blood donors in Cameroon. *Infect Dis*
14 *Obstet Gynecol* 2016; 2016: 4359401.
15
16 20. Rawat A, Diwaker P, Gogoi P, et al. Seroprevalence & changing trends of
17 transfusion-transmitted infections amongst blood donors in a Regional Blood
18 Transfusion Center in north India. *Indian J Med Res* 2017; 146: 642-5.
19
20 21. Chen Y, Liu Z, Zhang Q, et al. Trend in prevalence of syphilis among voluntary
21 blood donors in Xi'an, China from 2006 to 2010. *Int J Infect Dis* 2014; 19: 98-9.
22
23 22. Li C, Xiao X, Yin H, et al. Prevalence and prevalence trends of transfusion
24 transmissible infections among blood donors at four Chinese regional blood
25 centers between 2000 and 2010. *J Transl Med* 2012; 10: 176.
26
27 23. National Center for STD Control, Chinese Center for Disease Control and
28 Prevention. Clinical evaluation of syphilis diagnostic reagents in 2016.
29 <http://www.ncstdc.org/show.asp?id=1547> (accessed 7 October 2018).
30
31 24. Qin JB, Feng TJ, Yang TB, et al. Maternal and paternal factors associated with
32 congenital syphilis in Shenzhen, China: a prospective cohort study. *Eur J Clin*
33 *Microbiol Infect Dis*, 2014, 33(2): 221-32.
34
35 25. Cao WW, Zhou RR, Qu X, et al. Prevalence of hepatitis B virus, hepatitis C virus,
36 human immunodeficiency virus and *Treponema pallidum* infections in
37 hospitalized patients before transfusion in Xiangya hospital Central South
38 University, China from 2011 to 2016. *BMC Infect Dis* 2018; 18: 145.
39
40 26. Gott CM. Sexual activity and risk-taking in later life. *Health Soc Care Community*
41 2001; 9: 72-8.
42
43 27. Tillman JL, Mark HD. HIV and STI testing in older adults: an integrative review. *J*
44 *Clin Nurs* 2015; 24: 2074-95.
45
46 28. Davis T, Teaster PB, Thornton A, et al. Primary care providers' HIV prevention
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- practices among older adults. *J Appl Gerontol* 2016; 35: 1325-42.
29. Adekeye OA, Heiman HJ, Onyeabor OS, et al. The new invincibles: HIV screening among older adults in the U.S.. *PLoS One* 2012; 7: e43618.
30. Chen YF, Ding JP, Yan HJ, et al. The current status of syphilis prevention and control in Jiangsu province, China: a cross-sectional study. *PLoS One* 2017; 12: e0183409.
31. Varghese B, Maher JE, Peterman TA, et al. Reducing the risk of sexual HIV transmission: quantifying the per-act risk for HIV on the basis of choice of partner, sex act, and condom use. *Sex Transm Dis* 2002; 29: 38-43.
32. Kim JH. HIV transmissions by stage and sex role in long-term concurrent sexual partnerships. *Acta Biotheor* 2015; 63: 33-54.
33. Wu XB, Hong FC, Peng DY, et al. Syphilis infection status and the associated factors among partners of married syphilis-infected pregnant women in Shenzhen. *Chin J Dis Control Prev* 2016; 20: 1278-81. (in Chinese)
34. Tong ML, Lin LR, Liu GL, et al. Factors associated with serological cure and the serofast state of HIV-negative patients with primary, secondary, latent, and tertiary syphilis. *PLoS One* 2013; 8: e70102.
35. National Health Commission of the People's Republic of China. Diagnosis for syphilis.
<http://www.nhc.gov.cn/wjw/s9491/201803/5103a5425f9e47d29b91de38434b7f74.shtml> (accessed 18 February 2019).
36. Shi L, Wang J, Liu Z, et al. Blood donor management in China. *Transfus Med Hemother* 2014; 41:273-282.
37. Yang AL, Wang SX, Wei TL, et al. *Treponema pallidum* infection and residual risk of blood transmission of syphilis among voluntary blood donors in Shenzhen from 2008 to 2012. *J Mod Lab Med* 2013; 28: 122-124. (in Chinese)

FIGURE LEGENDS

Figure 1 Flowchart for syphilis screening and confirmatory testing among blood donors. ELISA, enzyme-linked immunosorbent assay; TPPA, *Treponema pallidum* particle agglutination assay; TRUST, toluidine red unheated serum test.

1
2
3
4
5 Figure 2 Prevalence of syphilis seropositivity and active infection in different age
6 groups, 2014-2017. (A) Prevalence of syphilis seropositivity and active infection
7 among males. (B) Prevalence of syphilis seropositivity and active infection among
8 females. SS, syphilis seropositivity; AI, active infection.
9
10
11
12
13

14 Figure 3 Distribution of TRUST titres among active infection donors in different age
15 groups.
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

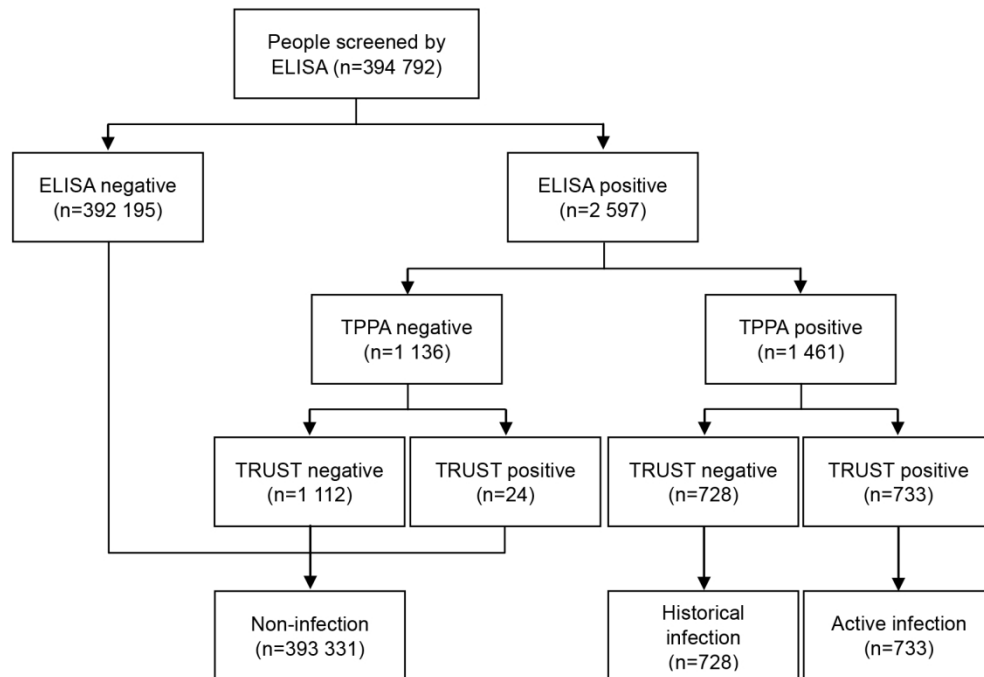


Figure 1 Flowchart for syphilis screening and confirmatory testing among blood donors. ELISA, enzyme-linked immunosorbent assay; TPPA, Treponema pallidum particle agglutination assay; TRUST, toluidine red unheated serum test.

157x116mm (300 x 300 DPI)

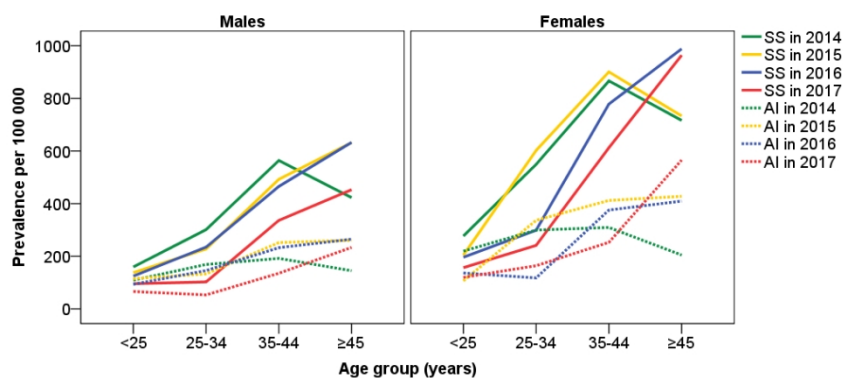


Figure 2 Prevalence of syphilis seropositivity and active infection in different age groups, 2014-2017. (A) Prevalence of syphilis seropositivity and active infection among males. (B) Prevalence of syphilis seropositivity and active infection among females. SS, syphilis seropositivity; AI, active infection.

424x182mm (72 x 72 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

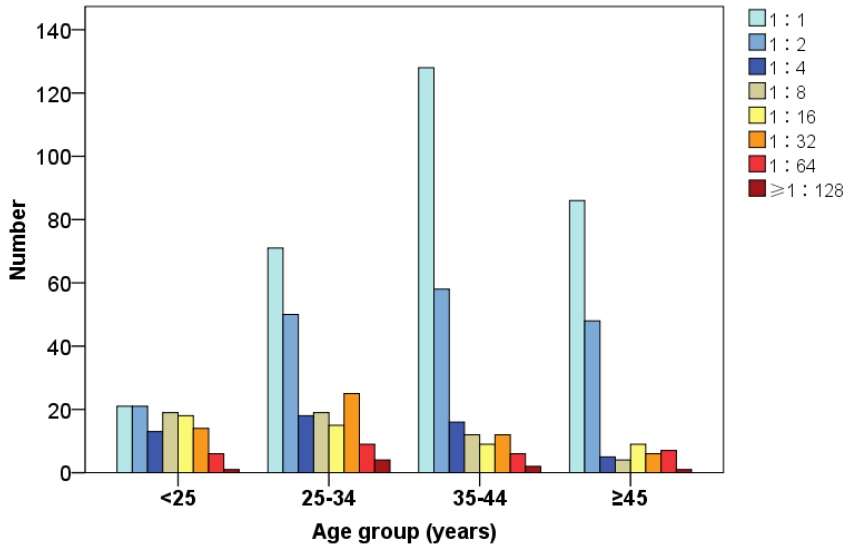


Figure 3 Distribution of TRUST titres among active infection donors in different age groups.

316x182mm (72 x 72 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	P1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P8-9
Objectives	3	State specific objectives, including any prespecified hypotheses	P9
Methods			
Study design	4	Present key elements of study design early in the paper	P9-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P9-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	P9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P10-11
Bias	9	Describe any efforts to address potential sources of bias	P9-10
Study size	10	Explain how the study size was arrived at	P9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	P11
		(b) Describe any methods used to examine subgroups and interactions	P11
		(c) Explain how missing data were addressed	Not applicable
		(d) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P12
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	P23
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P12
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	P12-14
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P12-14
		(b) Report category boundaries when continuous variables were categorized	P11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	P12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	P14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	P17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024393.R3
Article Type:	Original research
Date Submitted by the Author:	17-Jul-2019
Complete List of Authors:	Wu, Xiaobing; Shenzhen Center for Chronic Disease Control Guan, Yang; Shenzhen Center for Chronic Disease Control, Guangdong Ye, Jianbin; Shenzhen Center for Chronic Disease Control Fu, Hanlin; XiangYa School of Public Health, Central South University, Department of Epidemiology and Health Statistics Zhang, Chunlai; Shenzhen Center for Chronic Disease Control Lan, Lina; Shenzhen Center for Chronic Disease Control Wu, Fengxin; School of Public Health, Guangdong Medical University Tang, Fen; Shenzhen Center for Chronic Disease Control Wang, Feng; Shenzhen Center for Chronic Disease Control Cai, Yumao; Shenzhen Center for Chronic Disease Control Yu, Weiye; Shenzhen Center for Chronic Disease Control Feng, Tiejian; Shenzhen Center for Chronic Disease Control, Department of STD control and prevention
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Sexual health, Public health, Epidemiology
Keywords:	Syphilis, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts

Title page

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

Xiaobing Wu,¹ Yang Guan,¹ Jianbin Ye,¹ Hanlin Fu,² Chunlai Zhang,¹ Lina Lan,¹ Fengxin Wu,³ Fen Tang,¹ Feng Wang,¹ Yumao Cai,¹ Weiye Yu,¹ Tiejian Feng¹

Author affiliations

¹Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control, No.2021 Buxin Road, Luohu District, Shenzhen City, Guangdong Province, People's Republic of China

²Xiangya School of Public Health, Central South University, NO. 238 Shang Ma Yuan Ling Xiang, Kaifu District, Changsha City, Hunan Province, People's Republic of China

³School of Public Health, Guangdong Medical University, No.1 Xincheng Boulevard, Songshan Lake, National High Technology Industrial Development Zone, Dongguan City, Guangdong Province, People's Republic of China

First author and corresponding author:

Xiaobing Wu, PhD

Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control

Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong Province, People's Republic of China

E-mail: bingfsh@126.com

Telephone number: +86-755-25106861

Co-author:

Yang Guan, MD

Institute of Dermatology and STD Prevention and Control, Shenzhen Center for Chronic Disease Control

Correspondence to Xiaobing wu; bingfsh@126.com

1
2
3 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
4 Province, People's Republic of China

5 E-mail: gygyimi@126.com

6
7 Telephone number: +86-755-25632714
8
9

10
11
12 **Co-author:**

13 Jianbin Ye, BSc

14
15 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
16 Chronic Disease Control

17
18 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
19 Province, People's Republic of China

20 E-mail: 842413681@qq.com

21 Telephone number: +86-755-25632714
22
23

24
25
26
27
28 **Co-author:**

29 Hanlin Fu, PhD

30 Xiangya School of Public Health, Central South University

31
32 Postal address: NO. 238 Shang Ma Yuan Ling Xiang, Kaifu District, Changsha City,
33 Hunan Province, People's Republic of China

34 E-mail: 694400861@qq.com

35 Telephone number: +86-15111341391
36
37

38
39
40
41
42
43 **Co-author:**

44 Chunlai Zhang, BSc

45
46 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
47 Chronic Disease Control

48
49 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
50 Province, People's Republic of China

51 E-mail: szzhchl@163.com

52 Telephone number: +86-755-25632714
53
54

55
56
57
58
59 **Co-author:**
60

1
2
3 Lina Lan, MPH

4
5 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
6
7 Chronic Disease Control

8
9 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
10
11 Province, People's Republic of China

12
13 E-mail: 8262268@qq.com

14
15 Telephone number: +86-755-25608017

16
17
18 **Co-author:**

19
20 Fengxin Wu, BSc

21
22 School of Public Health, Guangdong Medical University

23
24 Postal address: No.1 Xincheng Boulevard, Songshan Lake, National High Technology
25
26 Industrial Development Zone, Dongguan City, Guangdong Province, People's

27
28 Republic of China

29
30 E-mail: 1162887843@qq.com

31
32 Telephone number: +86-13650232046

33
34
35 **Co-author:**

36
37 Fen Tang, BSc

38
39 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
40
41 Chronic Disease Control

42
43 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
44
45 Province, People's Republic of China

46
47 E-mail: 791950577@qq.com

48
49 Telephone number: +86-755-25632714

50
51
52 **Co-author:**

53
54 Feng Wang, MSc

55
56 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
57
58 Chronic Disease Control

59
60 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
Province, People's Republic of China

1
2
3 E-mail: biowangfeng@163.com
4

5 Telephone number: +86-755-25619065
6
7

8
9 **Co-author:**

10 Yumao Cai, MPH

11
12 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
13 Chronic Disease Control
14

15
16 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
17 Province, People's Republic of China
18

19 E-mail: 64165469@qq.com

20 Telephone number: +86-755-25632714
21
22

23
24
25 **Co-author:**

26 Weiye Yu, MD

27
28 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
29 Chronic Disease Control
30

31
32 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
33 Province, People's Republic of China
34

35 E-mail: ywy2002@126.com

36 Telephone number: +86-755-25531338
37
38

39
40
41 **Co-author:**

42 Tiejian Feng, MD

43
44 Institute of Dermatology and STD Prevention and Control, Shenzhen Center for
45 Chronic Disease Control
46

47
48 Postal address: No. 2021, Buxin Road, Luohu District, Shenzhen City, Guangdong
49 Province, People's Republic of China
50

51 E-mail: fengtiej@126.com

52 Telephone number: +86-755-25618781
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Word Counts: 298 words (abstract); 3200 words (text);

Tables: 3 tables;

Figures: 3 figures.

For peer review only

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 Program for Syphilis Prevention and Control in 2014-2017. Blood samples were screened using the enzyme-linked immunosorbent assays (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% confidence interval (CI), 351.1-389.0 per 100 000]; the prevalence of active infection was 185.7 per 100 000 (95% CI, 172.2-199.1 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 ($\chi^2_{\text{trend}} = 311.9$, $p_{\text{trend}} < 0.001$) and active infection ($\chi^2_{\text{trend}} = 72.1$, $p_{\text{trend}} < 0.001$) increased significantly with age. After stratification by gender and year of donation, the increasing trend of prevalence with age remained ($p_{\text{trend}} < 0.05$), 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 $\geq 1:8$, 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 enzyme-linked immunosorbent assays (ELISAs) as a screening test and then using *Treponema pallidum* particle agglutination assay (TPPA) and toluidine red unheated serum test (TRUST) 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.

MAIN TEXT

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 human immunodeficiency virus (HIV) and syphilis, was shown from recent surveillance data.³⁻⁵ This large disease burden among older people calls for improvements in the healthcare system and more investments and programs 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, death, etc., 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 (SARS) outbreak.⁹ The reported incidence was slightly higher among females than males (ratio, 1.00 to 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

1
2
3 of >10 million, is one of the cities that most affected by syphilis. The reported
4 incidence of syphilis was over 60 per 100 000 in last 10 years, which was much higher
5 than the national incidence.^{5,10} Consistent with the aforementioned characteristics
6 of varied age groups, a rapid increase in syphilis incidence among older adults was
7 observed in Shenzhen.¹¹ Studies usually considered blood donors as a representative
8 of the general population and used the prevalence data of blood donors for
9 real-time surveillance and identification of high-risk groups.¹² Whether the syphilis
10 seroprevalence among blood donors agrees with reported incidence characteristics
11 remains to be studied. Shenzhen launched a comprehensive program, the Shenzhen
12 Program for Syphilis Prevention and Control (SPSPC), in November 2013 to enhance
13 syphilis screening among blood donors and five other subgroups (HIV voluntary
14 counsellors, methadone maintenance treatment users, female sex workers, men
15 who have sex with men, and women of childbearing age), as well as case
16 management, including diagnosis, treatment, and follow-up, for syphilis-infected
17 adults.¹³ Based on the data from the SPSPC, this study aimed to examine differences
18 in syphilis seroprevalence among blood donors and describe the distribution of
19 serological titres among syphilis-infected donors with respect to age groups, to
20 confirm the syphilis epidemic characteristics in southern China and support the
21 design of effective interventions for older adults.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39

40 **METHODS**

41 **Subjects and blood donation process**

42 Blood donors were recruited by the Shenzhen Blood Center between 2014 and 2017.
43 About 10 blood mobiles, with the Shenzhen Blood Center logo and the words
44 'non-remunerated blood donation', were dispatched around the city to increase the
45 accessibility of blood donation. Volunteers could either go to the mobiles or to the
46 blood centre directly.
47
48
49
50
51
52
53

54 Before donation, all potential donors needed to sign a donation registration form,
55 complete a health history questionnaire, and undergo rapid testing and a brief
56 physical examination. A concise introduction of blood use, donation procedure,
57 laboratory testing, and legal and regulatory requirements was shown at the front of
58
59
60

1
2
3 the registration form. Inform consent was obtained from the donors for the
4 laboratory testing and use of the blood, the academic use of the data and the
5 publication of the report. The health history questionnaire contained a total of 27
6 medical conditions that would permanently or temporarily prevent the donors from
7 donation, including a series of chronic diseases and infectious diseases (e.g., HIV,
8 syphilis), transplant, high-risk behaviours (e.g., homosexual behaviours, drug use),
9 surgery, delivery, breastfeeding, etc. Pre-donation repaid testing included blood type,
10 haemoglobin, hepatitis B surface antigen, and alanine transaminase. Weight, blood
11 pressure, heart rate and body temperature were measured. Clinical examination of
12 the skin and limbs was conducted. People who conformed to the *Whole Blood and*
13 *Component Donor Selection Requirements (GB 18467-2001)* could proceed to donate
14 blood. All blood donors were non-remunerated. Light refreshment, a blood donation
15 certification, and a blood credit allowing free transfusion for donors or their direct
16 relatives were provided as incentives. The donation process and blood management
17 were fully in accordance with the *Blood Donation Law of the People's Republic of*
18 *China* and the *Blood Donation Regulation of the Shenzhen Special Economic Zone*.

34 Serological testing

35
36 After donation, the blood samples were transferred to the Shenzhen Blood Center
37 and underwent a series of laboratory testing. The enzyme-linked immunosorbent
38 assays (ELISAs) with two different reagents (Zhuhai Lizhu Bio-engineering Co. Ltd.,
39 Zhuhai, China; DiaSorin S.p.A. UK Branch, UK) were performed simultaneously on all
40 blood samples for syphilis screening. Syphilis-positive samples of one or both
41 screening assays, with a form listing the donors' name, age, and gender, were then
42 transferred to the Shenzhen Center for Chronic Disease Control [SZCCC, a city-level
43 prevention and control centre for sexually transmitted diseases (STDs)] under SPSPC
44 guidelines. A treponemal test of *Treponema pallidum* particle agglutination (TPPA;
45 Fujirebio Inc., Tokyo, Japan) and a non-treponemal test of toluidine red unheated
46 serum test (TRUST; Shanghai Rongsheng BioTech Co. Ltd., Shanghai, China) were
47 used at the SZCCC to confirm the infection status. TRUST-positive samples further
48 underwent quantitative titre testing to monitor response to treatment. TPPA and
49 TRUST results were sent back to the Shenzhen Blood Center within 2 days after the
50
51
52
53
54
55
56
57
58
59
60

1
2
3 samples were received.
4
5
6

7 **Definition of syphilis infection**

8
9 Based on serological test results, syphilis seropositivity was divided into historical
10 infection and active infection, which was consistent with the classification from
11 previous studies.¹² Historical infection was defined as TPPA positive but TRUST
12 negative and active infection as both TPPA and TRUST positive.¹⁴ Syphilis
13 seropositivity was defined as TPPA positive, including both TRUST negative and
14 TRUST positive. Moreover, high-titre was defined as a quantitative titre of $\geq 1 : 8$ in
15 patients with active infection. For the purpose of this study, syphilis seropositivity
16 which represented the overall infection status among the target population, and
17 active infection and high-titre status which were correlated with disease activity,
18 were analysed.
19
20
21
22
23
24
25
26
27
28

29 **Statistical analysis**

30
31 Data of donors' number among different subgroups (age, gender and year of
32 donation) and syphilis testing results were sourced from the Shenzhen Blood Center
33 and the SZCCC, respectively. Primary outcomes of interest were the prevalence of
34 syphilis seropositivity and active infection among all blood donors in different age
35 groups. There were four age groups, <25 years, 25-34 years, 35-44 years, and ≥ 45
36 years, fully considering the age coverage of blood donors and age classification in
37 previous studies.^{15,16} We calculated the crude prevalence and its 95% confidence
38 interval (CI). The chi-squared (χ^2) test for trend was used to assess the difference in
39 prevalence among age groups. Odds ratios (ORs) and their 95% CIs were calculated
40 when comparing the risk of syphilis seropositivity and active infection between the \geq
41 45 years age group and other age groups. Line graphs were used to describe the
42 changes in prevalence for both syphilis seropositivity and active infection among the
43 age groups after stratification by gender and year of donation. Furthermore, we
44 described the distribution of TRUST titres among the age groups and compared the
45 difference using the χ^2 test for trend. Data were analysed using SPSS 17.0 for
46 Windows (IBM Corp., Armonk, USA); $p < 0.05$ was considered statistically significant
47 in the χ^2 test.
48
49
50
51
52
53
54
55
56
57
58
59
60

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 ($\chi^2 = 11249.0$, $p < 0.001$) and among years of donation ($\chi^2 = 1182.0$, $p < 0.001$). People aged 25-34 years accounted for the largest proportion of donors (**Table 1**).

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

Variables	Aged <25 years (n=95736)	Aged 25-34 years (n=137447)	Aged 35-44 years (n=102422)	Aged ≥45 years (n=59187)	χ^2	<i>p</i> value
Gender					11249.0	<0.001
Male	51409(19.3%)	96237(36.2%)	74445(28.0%)	44061(16.6%)		
Female	44327(34.5%)	41210(32.0%)	27977(21.7%)	15126(11.8%)		
Year of donation					1182.0	<0.001
2014	22389(25.3%)	31929(36.0%)	23131(26.1%)	11210(12.6%)		
2015	24330(25.7%)	33096(35.0%)	24011(25.4%)	13241(14.0%)		
2016	24560(24.0%)	35736(34.9%)	26362(25.7%)	15843(15.5%)		
2017	24457(22.4%)	36686(33.7%)	28918(26.5%)	18893(17.3%)		

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,

351.1-389.0 per 100 000), and the prevalence of active infection was 185.7 per 100 000 (95% CI, 172.2-199.1 per 100 000). The prevalence of syphilis seropositivity and active infection was higher among females than males (syphilis seropositivity: $\chi^2 = 60.4$, $p < 0.001$; active infection: $\chi^2 = 36.1$, $p < 0.001$) and showed a decreasing trend from 2014 to 2017 (syphilis seropositivity: $\chi^2_{\text{trend}} = 27.1$, $p_{\text{trend}} < 0.001$; active infection: $\chi^2_{\text{trend}} = 7.8$, $p_{\text{trend}} = 0.005$). 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, 3.1-4.6) and 2.4 times (OR = 2.4; 95% CI, 1.9-3.0) higher than that among people aged < 25 years, and 2.3 times (OR = 2.3; 95% CI, 2.0-2.6) and 1.8 times (OR = 1.8; 95% CI, 1.5-2.2) higher than that among people aged 25-34 years, respectively. Trend analysis showed that the prevalence of syphilis seropositivity ($\chi^2_{\text{trend}} = 311.9$, $p_{\text{trend}} < 0.001$) and active infection ($\chi^2_{\text{trend}} = 72.1$, $p_{\text{trend}} < 0.001$) increased significantly with age (Table 2). After stratification by gender and year of donation, the increasing trend of prevalence with age remained ($p_{\text{trend}} < 0.05$), except for the prevalence of active infection among males ($\chi^2_{\text{trend}} = 0.923$, $p_{\text{trend}} = 0.337$) and females ($\chi^2_{\text{trend}} = 0.224$, $p_{\text{trend}} = 0.636$) in 2014 (Figure 2).

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

Age group	Number of screened	Syphilis seropositivity				Active infection			
		Number	Prevalence per 100 000 (95%CI)	χ^2_{trend}	p_{trend} value	Number	Prevalence per 100 000 (95%CI)	χ^2_{trend}	p_{trend} value
Aged < 25 years	95736	158	165.0(139.3-190.8)	311.9	< 0.001	113	118.0(96.3-139.8)	72.1	< 0.001
Aged 25-34 years	137447	376	273.6(245.9-301.2)			211	153.5(132.8-174.2)		
Aged 35-44 years	102422	559	545.8(500.7-590.9)			243	237.3(207.5-267.0)		
Aged ≥ 45 years	59187	368	621.8(558.4-685.1)			166	280.5(237.9-323.1)		

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 $\geq 1:8$. 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 ($\chi^2_{\text{trend}} = 53.6$, $p_{\text{trend}} < 0.001$) (Table 3).

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

Age group	TRUST titre < 1 : 8	TRUST titre \geq 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 \geq 45 years	139 (83.7%)	27 (16.3%)		

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 United States (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 (i.e., 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.

1
2
3 To our knowledge, this study is the first in-depth study focusing on active infection
4 and serological titre distribution of syphilis among blood donors in mainland China.
5 Active infection is different from historical infection as the former indicates more
6 transmission and late syphilis if without timely and adequate treatment. The higher
7 the serological titre, the more the risk of transmission (e.g., mother-to-child
8 transmission) and adverse outcomes.²⁴ This study documented that 50.2% (733/1461)
9 of syphilis seropositive donors had active infection, and 13.6% (198/1461) had a
10 TRUST titre of $\geq 1:8$. Here, the proportion of high titres among syphilis seropositive
11 patients was similar to that reported in the United States.¹²

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

41 The higher prevalence among older adults might be due to several reasons. First,
42 many older people are sexually active,²⁶ and their sexual health and behaviour affect
43 syphilis transmission. Low self-perception of risk and misconceptions or limited
44 knowledge about syphilis and other STDs were frequently reported as reasons for
45 condomless sex among older adults.^{5,27} Second, older adults have been largely
46 neglected by healthcare providers due to age-related stigma.²⁸ Sexual health services
47 for HIV or STDs rarely focus on older adults, leaving this group behind in both testing
48 and prevention. Third, presenting with a late diagnosis has been significantly
49 associated with older age. Older people were more likely to be aware of their
50 serostatus when in hospital or had an active offer for testing.²⁹ In this study, analysis
51 of the TRUST results suggests that $> 90\%$ of syphilis-infected people aged ≥ 45 years

1
2
3 with TRUST negative or with low titres had a previous infection. However, late
4 presentation is particularly worrying among older people because it further increases
5 the risk of cardiovascular syphilis, neurosyphilis, paresis, etc. As syphilis is a great
6 imitator, doctors often ignore syphilis infection when diagnosing the elderly, leading
7 to omission of syphilis testing and misdiagnosis of the disease.
8
9
10
11

12
13
14 Evidence suggests that the most significant factor affecting testing patterns in older
15 adults is the active provision of the screening test.²⁹ Since the initiation of China's
16 national syphilis control plan, syphilis screening has been widely integrated into HIV
17 voluntary counselling and testing (VCT) services. More than 95% of people who
18 received HIV testing services have undergone free syphilis testing.³⁰ Referral,
19 treatment, and follow-up services would be provided to those diagnosed with
20 syphilis. In Shenzhen, more than half of VCT sites are set in community health service
21 centres, where a separate room is arranged for counselling and testing service.
22 However, due to the low awareness of self-testing, older adults rarely positively seek
23 the services. Meanwhile, most health staff are unwilling to provide the service
24 actively because of limited experience, lack of time, discomfort in discussing sexual
25 behaviours and STDs with older adults, stigma, ageism, etc.²⁸ Hence, enhanced
26 training of healthcare providers and education of older adults are necessary.
27
28
29
30
31
32
33
34
35
36
37
38
39

40 Consistent with the results of some previous studies, the prevalence of both syphilis
41 seropositivity and active infection were higher among females than males.^{21,22} It may
42 stem partly from the different physiology and anatomy of the genital organs
43 between both sexes, leading to females being more likely to contract STDs in
44 receptive vaginal sex behaviours.³¹ Some studies have proved that the
45 male-to-female transmission rate is higher than the female-to-male rate in certain
46 STDs, such as HIV.^{31,32} Besides, a proportion of females have multiple sex partners
47 during their lifetime. A previous study has found that the syphilis prevalence among
48 husbands of 2261 syphilis-infected pregnant women was < 30%.³³ Premarital or
49 extramarital sexual partners may greatly increase the risk of syphilis infection among
50 females. Additionally, serological response differs between males and females.³⁴
51 Females are more likely to be serofast [defined as remaining positive in a
52
53
54
55
56
57
58
59
60

1
2
3 non-treponemal test and keeping the titre at a certain level (mostly 1:8 or below)
4 after recommended therapy and follow-up 1 to 3 years according to syphilis stage]
5 when comparing with males,³⁵ leading to more females staying in the state of active
6 infection. The exact mechanism underlying this difference is unclear, but it may be
7 partly associated with the varied immune system between both sexes.³⁴
8
9 Furthermore, men who have sex with men are considered a major high-risk
10 subgroup for syphilis infection and are permanently deferred from blood donation in
11 China.³⁶ In this study, males were excluded if they reported they had ever engaged in
12 homosexual behaviour in the health history questionnaire, which may be one of the
13 reasons for the low syphilis prevalence among males.
14
15
16
17
18
19
20
21
22

23 Limitations

24
25 Our study has several limitations. First, limited financial and human resources
26 restricted us in using a population-based design, which is considered as the gold
27 standard in evaluating disease epidemics.¹² The choice of blood donors as population
28 samples may result in potential bias, such as selection bias for age coverage and
29 self-identified health conditions. Second, the syphilis seroprevalence among
30 first-time donors was significantly higher than that among repeat donors.^{12,15} This
31 study did not collect the information of first-time donors and repeat donors, which
32 may lead to underestimation of syphilis seroprevalence. Third, false-negative results
33 attributable to the window period of syphilis infection may result in an
34 underestimation of syphilis seroprevalence. However, the residual risk of syphilis
35 infection is very low according to a residual risk analysis conducted in Shenzhen.³⁷
36
37 Fourth, this study used two reagents in syphilis screening. Samples with one positive
38 result or both positive results would be considered as problematic samples. This
39 parallel testing method was strict and suitable for blood donors. However, we did
40 not collect the data of each reagent and the positive predictive value cannot be
41 calculated respectively.
42
43
44
45
46
47
48
49
50
51
52
53
54
55

56 Conclusions

57
58 This study provides an in-depth analysis of the association between syphilis
59 seroprevalence and age. Older adults showed a high prevalence of both syphilis
60

1
2
3 seropositivity and active infection but a small proportion of high titres, which point
4 towards the compelling need to heighten awareness among healthcare providers
5 and deliver more targeted prevention interventions for older adults to promote early
6 testing.
7
8
9

10
11
12
13
14 **Acknowledgements** The authors would like to thank Qiong Yu and Xi Chen from the
15 Shenzhen Blood Center for their support in data collection, and Qianqiu Wang and
16 Yueping Yin from the Chinese Academy of Medical Sciences in revising the
17 manuscript. The authors also give thanks to all the blood donors for taking part in
18 this study.
19
20
21
22

23
24
25 **Contributors** XW and TF contributed to designing the study, coordinating data
26 collection and drafting the article. YG, JY, CZ and FT contributed to data collection,
27 patient treatment and disease management. HF, LL and FW contributed to data
28 collection and data analysis. FW contributed to syphilis testing and laboratory quality
29 control. YC and WY contributed to making important comments of the manuscript.
30 All authors read and approved the final draft of the manuscript.
31
32
33
34
35
36
37

38 **Funding** This work was supported by the National Natural Science Foundation of
39 China (grant number 81903379), the Science, Technology and Innovation
40 Commission of Shenzhen Municipality (grant number JCYJ20160428145537703) and
41 the Sanming Project of Medicine in Shenzhen (No. SZSM201611077).
42
43
44
45
46

47 **Competing interests** The authors declare no competing interest.
48
49

50 **Patient consent** Not applicable.
51
52

53
54 **Ethics approval** Ethics approval was obtained from the Ethics Committee of
55 Shenzhen Center for Chronic Disease Control (No. 20180212).
56
57
58

59 **Provenance and peer review** Not commissioned; externally peer reviewed.
60

Data sharing statement Data are available by emailing XW(bingfsh@126.com).

REFERENCES

1. Department of Economic and Social Affairs, Population Division, United Nations. *World Population Ageing 2017*.
https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Report.pdf (accessed 15 July 2019)
2. Prince MJ, Wu F, Guo Y, et al. The burden of disease in older people and implications for health policy and practice. *Lancet* 2015; 385: 549-62.
3. Tavoschi L, Gomes Dias J, Pharris A, et al. New HIV diagnoses among adults aged 50 years or older in 31 European countries, 2001-15: an analysis of surveillance data. *Lancet HIV* 2017; 4: e514-21.
4. Mahy M, Autenrieth CS, Stanecki K, et al. Increasing trends in HIV prevalence among people aged 50 years and older: evidence from estimates and survey data. *AIDS* 2014; 28: S453-9.
5. Gong X, Yue X, Teng F, et al. Syphilis in China from 2000 to 2013: epidemiological trends and characteristics. *Chin J Dermatol* 2014; 47: 310-5. (in Chinese)
6. Workowski KA and Bolan GA. Sexually transmitted disease treatment guidelines, 2015. *MMWR Recomm Rep* 2015; 64: 34-49.
7. Kotsafti O, Pappas V, Kourkounti S, et al. Early syphilis affects markers of HIV infection. *Int J STD AIDS* 2016; 27: 739-45.
8. Newman L, Rowley J, Vander Hoorn S, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One* 2015; 10: e0143304.
9. Yang S, Wu J, Ding C, et al. Epidemiological features of and changes in incidence of infectious disease in China in the first decade after the SARS outbreak: an observational trend study. *Lancet Infect Dis* 2017; 17: 716-25.
10. Wu X, Hong F, Lan L, et al. Poor awareness of syphilis prevention and treatment knowledge among six different populations in south China. *BMC Public Health* 2016; 16: 287.

11. Lan LN, Wu XB, Zhang CL, et al. Epidemiological analysis of syphilis in Shenzhen from 2004 to 2013. *China Tropical Medicine* 2015; 15: 700-3. (in Chinese)
12. Kane MA, Bloch EM, Bruhn R, et al. Demographic determinants of syphilis seroprevalence among U.S. blood donors, 2011-2012. *BMC Infect Dis* 2015; 15: 63.
13. Wu XB, Zhang CL, Lan LN, et al. Syphilis infection among five different groups of people and analysis of treatment situation in Shenzhen. *China Tropical Medicine* 2015; 15: 830-2. (in Chinese)
14. Chen YY, Qiu XH, Zhang YF, et al. A better definition of active syphilis infection. *Clin Chim Acta* 2015; 444: 1-2.
15. Liu J, Huang Y, Wang J, et al. The increasing prevalence of serologic markers for syphilis among Chinese blood donors in 2008 through 2010 during a syphilis epidemic. *Transfusion* 2012; 52: 1741-9.
16. Vera L, Milka D, Nurith SL, et al. Prevalence and incidence of syphilis among volunteer blood donors in Israel. *J Blood Transfus* 2014; 2014: 154048.
17. Baiao AM, Kupek E, Petry A. Syphilis seroprevalence estimates of Santa Catarina blood donors in 2010. *Rev Soc Bras Med Trop* 2014; 47: 179-85.
18. Abate M, Wolde T. Seroprevalence of Human Immunodeficiency Virus, Hepatitis B Virus, Hepatitis C Virus, and Syphilis among Blood Donors at Jigjiga Blood Bank, Eastern Ethiopia. *Ethiop J Health Sci* 2016; 26: 153-60.
19. Dionne-Odom J, Mbah R, Rembert NJ, et al. Hepatitis B, HIV, and Syphilis seroprevalence in pregnant women and blood donors in Cameroon. *Infect Dis Obstet Gynecol* 2016; 2016: 4359401.
20. Rawat A, Diwaker P, Gogoi P, et al. Seroprevalence & changing trends of transfusion-transmitted infections amongst blood donors in a Regional Blood Transfusion Center in north India. *Indian J Med Res* 2017; 146: 642-5.
21. Chen Y, Liu Z, Zhang Q, et al. Trend in prevalence of syphilis among voluntary blood donors in Xi'an, China from 2006 to 2010. *Int J Infect Dis* 2014; 19: 98-9.
22. Li C, Xiao X, Yin H, et al. Prevalence and prevalence trends of transfusion transmissible infections among blood donors at four Chinese regional blood centers between 2000 and 2010. *J Transl Med* 2012; 10: 176.
23. National Center for STD Control, Chinese Center for Disease Control and

- 1
2
3 Prevention. Clinical evaluation of syphilis diagnostic reagents in 2018.
4 <http://www.ncstdc.cn/upfiles/201905/20190528094607204.pdf> (accessed 15
5 July 2019).
6
7
8
9 24. Qin JB, Feng TJ, Yang TB, et al. Maternal and paternal factors associated with
10 congenital syphilis in Shenzhen, China: a prospective cohort study. *Eur J Clin*
11 *Microbiol Infect Dis*, 2014, 33(2): 221-32.
12
13 25. Cao WW, Zhou RR, Qu X, et al. Prevalence of hepatitis B virus, hepatitis C virus,
14 human immunodeficiency virus and *Treponema pallidum* infections in
15 hospitalized patients before transfusion in Xiangya hospital Central South
16 University, China from 2011 to 2016. *BMC Infect Dis* 2018; 18: 145.
17
18 26. Gott CM. Sexual activity and risk-taking in later life. *Health Soc Care Community*
19 2001; 9: 72-8.
20
21 27. Tillman JL, Mark HD. HIV and STI testing in older adults: an integrative review. *J*
22 *Clin Nurs* 2015; 24: 2074-95.
23
24 28. Davis T, Teaster PB, Thornton A, et al. Primary care providers' HIV prevention
25 practices among older adults. *J Appl Gerontol* 2016; 35: 1325-42.
26
27 29. Adekeye OA, Heiman HJ, Onyeabor OS, et al. The new invincibles: HIV screening
28 among older adults in the U.S.. *PLoS One* 2012; 7: e43618.
29
30 30. Chen YF, Ding JP, Yan HJ, et al. The current status of syphilis prevention and
31 control in Jiangsu province, China: a cross-sectional study. *PLoS One* 2017; 12:
32 e0183409.
33
34 31. Varghese B, Maher JE, Peterman TA, et al. Reducing the risk of sexual HIV
35 transmission: quantifying the per-act risk for HIV on the basis of choice of
36 partner, sex act, and condom use. *Sex Transm Dis* 2002; 29: 38-43.
37
38 32. Kim JH. HIV transmissions by stage and sex role in long-term concurrent sexual
39 partnerships. *Acta Biotheor* 2015; 63: 33-54.
40
41 33. Wu XB, Hong FC, Peng DY, et al. Syphilis infection status and the associated
42 factors among partners of married syphilis-infected pregnant women in
43 Shenzhen. *Chin J Dis Control Prev* 2016; 20: 1278-81. (in Chinese)
44
45 34. Tong ML, Lin LR, Liu GL, et al. Factors associated with serological cure and the
46 serofast state of HIV-negative patients with primary, secondary, latent, and
47 tertiary syphilis. *PLoS One* 2013; 8: e70102.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 35. National Health Commission of the People's Republic of China. Diagnosis for
4 syphilis.
5
6
7 <http://www.nhc.gov.cn/wjw/s9491/201803/5103a5425f9e47d29b91de38434b7>
8 [f74.shtml](http://www.nhc.gov.cn/wjw/s9491/201803/5103a5425f9e47d29b91de38434b7) (accessed 18 February 2019).
9
10 36. Shi L, Wang J, Liu Z, et al. Blood donor management in China. *Transfus Med*
11 *Hemother* 2014; 41:273-282.
12
13 37. Yang AL, Wang SX, Wei TL, et al. *Treponema pallidum* infection and residual risk
14 of blood transmission of syphilis among voluntary blood donors in Shenzhen
15 from 2008 to 2012. *J Mod Lab Med* 2013; 28: 122-124. (in Chinese)
16
17
18
19
20
21
22

23 FIGURE LEGENDS

24 Figure 1 Flowchart for syphilis screening and confirmatory testing among blood
25 donors. ELISA, enzyme-linked immunosorbent assay; TPPA, *Treponema pallidum*
26 particle agglutination assay; TRUST, toluidine red unheated serum test.
27
28
29

30
31
32 Figure 2 Prevalence of syphilis seropositivity and active infection in different age
33 groups, 2014-2017. (A) Prevalence of syphilis seropositivity and active infection
34 among males. (B) Prevalence of syphilis seropositivity and active infection among
35 females. SS, syphilis seropositivity; AI, active infection.
36
37
38

39
40
41 Figure 3 Distribution of TRUST titres among active infection donors in different age
42 groups.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

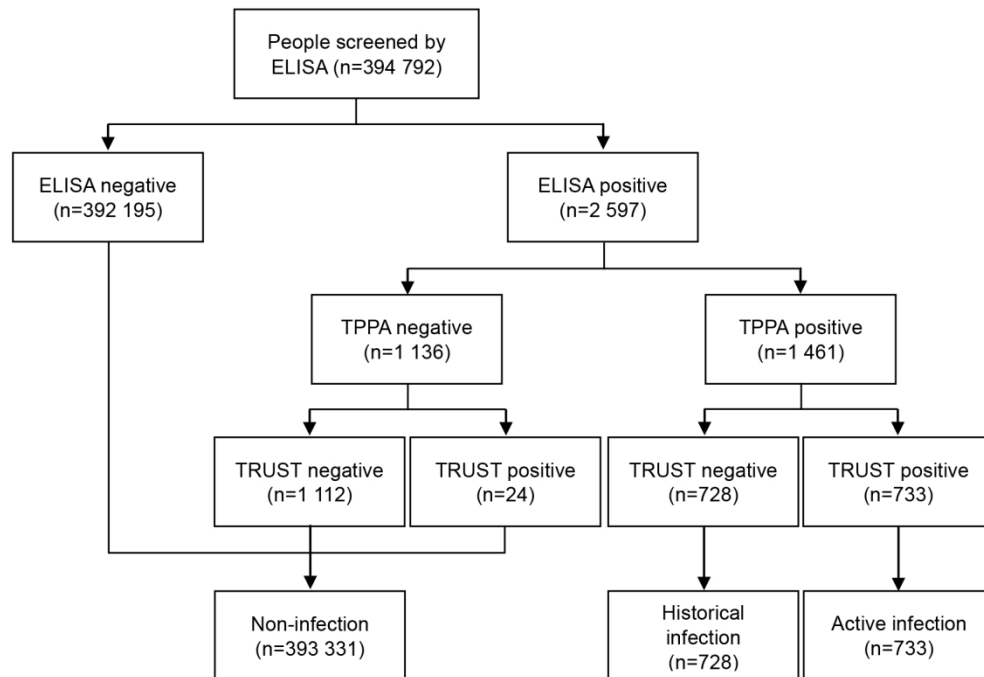


Figure 1 Flowchart for syphilis screening and confirmatory testing among blood donors. ELISA, enzyme-linked immunosorbent assay; TPPA, Treponema pallidum particle agglutination assay; TRUST, toluidine red unheated serum test.

157x116mm (300 x 300 DPI)

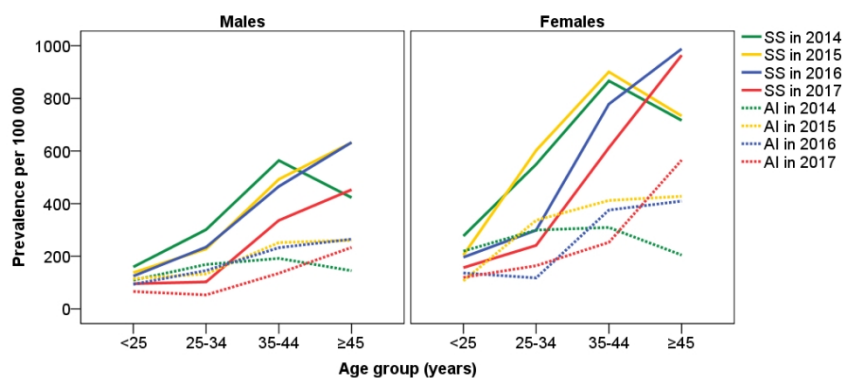


Figure 2 Prevalence of syphilis seropositivity and active infection in different age groups, 2014-2017. (A) Prevalence of syphilis seropositivity and active infection among males. (B) Prevalence of syphilis seropositivity and active infection among females. SS, syphilis seropositivity; AI, active infection.

424x182mm (72 x 72 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

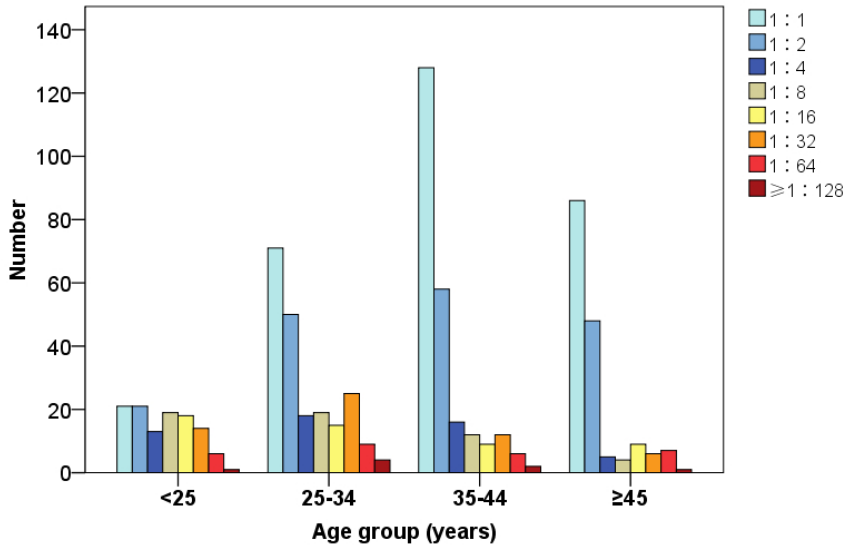


Figure 3 Distribution of TRUST titres among active infection donors in different age groups.

316x182mm (72 x 72 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	P1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P8-9
Objectives	3	State specific objectives, including any prespecified hypotheses	P9
Methods			
Study design	4	Present key elements of study design early in the paper	P9-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P9-10
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	P9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P10-11
Bias	9	Describe any efforts to address potential sources of bias	P9-10
Study size	10	Explain how the study size was arrived at	P9-10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	P11
		(b) Describe any methods used to examine subgroups and interactions	P11
		(c) Explain how missing data were addressed	Not applicable
		(d) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P12
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	P23
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P12
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	P12-14
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P12-14
		(b) Report category boundaries when continuous variables were categorized	P11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	P12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	P14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	P17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.