Announcements
The 27th China Iodine Deficiency Disorders Day — May 15, 2020

Prevention and Control of Iodine Deficiency Disorders — China, 1995–2020

Recollection
Prevention and Control of Iodine Deficiency Disorders — China, 1995–2020

Preplanned Studies
Hemorrhagic Fever with Renal Syndrome — Liaoning Province, China, 1999–2018


Commentary
Chagas Disease — An Underestimated Global Public Health Challenge
China CDC Weekly

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Iodine deficiency disorders (IDD) are a series of diseases caused by iodine deficiency in the natural environment that include endemic goiter, cretinism, subclinical cretinism, fetal abortion, premature delivery, stillbirth, congenital malformation, etc (1). Since 1993 when the State Council held the “Mobilization meeting of eliminating IDD in China by the year 2000”, the Ministry of Health planned to set up an annual publicity day for the prevention and control of IDD. Through the coordination between the Ministry of Health and other relevant departments, IDD Day was set on May 5 in 1994, and on May 15 since 2002. Since 1994, IDD Day has played an active role in mobilizing all levels leaders of governments and relevant departments as well as the public to support salt iodization in China. After nearly 30 years, the measures have been enriched to include slogans, posters, activities, national workshops, international conferences, and WeChat publicization, webpages, interviews, music videos, etc. IDD knowledge has been successfully spread among Chinese people and therefore ensured the health of masses (2). The national IDD survey shows that China has been in sustainable elimination status of IDD since 2005 (3). The 27th IDD day in China is arriving on May 15, 2020, and the slogans, posters, and music videos have all been prepared well.

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**Prevention and Control of Iodine Deficiency Disorders — China, 1995–2020**

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**Basic Information about Iodine Deficiency Disorders**

Iodine is an essential micronutrient for the human body and an important raw material for the synthesis of thyroid hormones. Thyroid hormones maintain the basic activities of the body and have different effects on almost all systems of the body by promoting growth and development, participating in brain development, regulating metabolism, and impacting most organs and system functions. Thyroid hormones can promote the synthesis and catabolism of protein, fat, and sugar; enhance substance metabolism and energy metabolism by increasing oxygen consumption, generating energy, and influencing basal metabolic rate; and maintain body temperature.

Iodine is rapidly and completely absorbed in the upper segment of stomach and intestine, and after blood iodine is absorbed by the thyroid, iodine is concentrated and thyroid hormone is generated. Iodine in the human body is mainly excreted from urine but can also be excreted through breast milk to supply iodine to infants. Iodine is mainly provided to the human body from various foods and drinking water, and a lack of iodine will cause iodine deficiency disorders (IDD). During a critical period of brain development, the development of the nervous system depends on thyroid hormone, so an iodine deficiency in this period will lead to different degrees of brain development retardation (such as endemic cretinism, etc.), which is irreversible even if iodine or thyroid hormone is supplemented later.

Iodine excess is a state in which iodine intake significantly exceeds the human body’s requirement, and the main cause in China is iodine excesses in sources of water in addition to excesses in food and drugs. Iodine excess can lead to goiter, hypothyroidism, etc., and also can have adverse effects on the health of pregnant women and pregnancy
outcomes. However, there is no definite evidence that excessive iodine intake is related to an increased risk of thyroid cancer.

IDD was once a global problem. The most popular iodine supplement measure is salt iodization, but other measures include eating iodine-rich foods and taking iodine-containing nutrient supplements, oral drugs, or iodine oil pills, etc. However, salt iodization is the safest and most effective measure recommended by the World Health Organization (WHO) to control IDD. Currently, more than 120 countries have implemented salt iodization policies, and at least 97 countries have enacted laws, regulations, or food safety standards to support salt iodization. Beyond salt iodization, some marine products have higher iodine contents, such as kelp, laver, hairtail, dried scallop, etc.; milk has varying levels of iodine depending on brand; and plants, especially fruits and vegetables have the lowest iodine content. When choosing an iodine supplement measure, iodized salt should be considered first, followed by iodine-rich foods, and then iodine-containing nutrient supplements. In areas with serious iodine deficiency issues, iodized oil pills can be given to women at childbearing age, pregnant women, and lactating women when iodized salt prevention measures cannot be effectively implemented (1).

**Progress of Universal Salt Iodization in China**

China previously had a widespread and severe IDD problem. According to an investigation in the 1970s, all provincial-level administrative divisions (PLADs) in China, except Shanghai, have had an incidence of IDD to some degree. Since the 1950s, salt iodization was launched in some endemic areas, which has effectively curbed the IDD epidemic. In 1991, the Chinese Government signed the United Nation’s World Declaration on the Survival, Protection, and Development of Children, and thereafter made a commitment to eliminate IDD by the year 2000. In 1993, China’s State Council convened a “Mobilization Meeting to Achieve the Goal of Eliminating IDD by 2000” and adopted the “China’s Plan for Eliminating IDD by 2000”. The country adopted a series of prevention and control strategies focused on universal salt iodization (USI). Subsequently, it promoted the “Regulations on Eliminating the Harm of IDD by Salt Iodization” and “Regulation on Salt Monopoly”, etc., thus providing a reliable legal guarantee for the prevention and control of IDD. Subsequently, a surveillance system of IDD has been established step by step, which has key roles for making decision during the prevention and control progress (Figure 1). According to the surveillance results, the iodine content in salt was adjusted several times to reach adequate levels of iodine for the population (Figure 2).

**Universal Salt Iodization Achievements in China**

By the year 2000, China has basically achieved the goal of eliminating IDD at the national level. In 2010, 28 PLADs had achieved the goal of eliminating IDD.
while Tibet, Qinghai, and Xinjiang had achieved basic compliance levels for eliminating IDD. By the end of 2015, 94.2% of counties in the country had achieved the goal of eliminating IDD according to the final assessment results of the 12th Five-Year Plan for the Prevention and Control of Endemic Diseases. The 2019 IDD surveillance showed China attained sustainable elimination status of IDD at the national level. The national median urinary iodine of children aged 8–10 years was 207.1 μg/L, which exceeded the standard of being over 100 μg/L. The median urinary iodine of children in 2019 was similar to that of 2016–2018 and lower than that of 1997, 1999, 2002, 2005, and 2011 (Figure 3A). The incidence of goiter in children was 1.5%, which was lower than the 5% requirement and showed a decrease since 2005 (Figure 3B). The median urinary iodine of pregnant women was 169.4 μg/L, which was over the lower adequate limit level of 150 μg/L (median urinary iodine of pregnant women being between 150–249 μg/L is defined as having adequate iodine). The coverage rate of iodized salt was 95.9% and the consumption rate of qualified iodized salt was 90.2%, which indicated a sustained high level since 2005 (Figure 3C). All indicators meet the national standard for IDD elimination. Combined with previous surveillance results, China has been in a state of sustainable IDD elimination since 2005. The implementation of USI has not only eliminated IDD in China but also greatly improved the iodine nutrition of the population (2–12).

**Excessive Iodine in Water Sources and Areas with Related Endemic Diseases in China**

In addition to areas with iodine deficiencies, 110 counties, cities, and districts in 8 PLADs still had excess iodine in water sources. These 110 areas were initially found by the 2005 Excess Iodine Water Sources Survey and were still found to have issues in a resurvey in 2012. China currently implements the strategy of supplying non-iodized salt to areas with excess iodine in water sources and monitors the implementation of these measures every year. The coverage rate of non-iodized salt is sustained at above 90% in iodine excess areas from 2011 to 2017 (Figure 4). In 2017, a nationwide investigation on iodine content in drinking water was organized, and the survey results showed that although China had the largest known range of areas with excess iodine in naturally occurring water sources in the world, it was still a country with widespread iodine deficiency in the natural environment. Some newly found iodine excess areas joined the surveillance system and subsequently decreased the coverage rate of non-iodized salt in 2018 and 2019 (13).

To clarify further, areas with excessive iodine in water sources refer to areas where water iodine exceeds 100 μg/L, and local measures involve the promotion of non-iodized edible salt. Within this classification, areas where the rate of goiter in children aged 8–10 years is greater than 5% are referred to as areas with diseases related to excessive iodine in water sources, and local measures directly target water improvements (14).

**Remaining Challenges**

The general population of China still has a sustained adequate supply of iodine nutrition, but special populations still face the risks of iodine deficiency. China is facing a dual challenge because the prevention and control of IDD is more arduous and complicated than ever before. First, due to the effective implementation of salt iodization measures, serious diseases like cretinism and goiter have become relatively rare, and people are no longer as aware of the harm of iodine deficiency and awareness levels...
gradually decrease. Second, with advancements in the reform of the salt industry system, various salts have been supplied to the market making it easier for residents to buy non-iodized salt. On the other hand, China has the largest known range of areas with high iodine in water sources in the world. Residents living in these areas will be endangered or threatened by iodine excesses that can result in goiter and subclinical hypothyroidism.

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FIGURE 4. The coverage rate of non-iodized salt in water-borne iodine excess areas. The data in 2018 and 2019 included new areas found in a 2017 water iodine investigation.

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Preplanned Studies

Hemorrhagic Fever with Renal Syndrome — Liaoning Province, China, 1999–2018

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Summary

What is already known on this topic?
Hemorrhagic fever with renal syndrome (HFRS) is endemic in Liaoning Province. Both Seoul and Hantaan virus are circulating in rodents, and epidemic outbreaks and sporadic cases have been recorded every year since the disease was recognized.

What is added by this report?
The epidemic trend of HFRS over the past 20 years (1999–2018) in Liaoning was analyzed, which showed both regional complexity and consistence with the epidemic in China. Genetic and antigenic stability of the circulating hantavirus were demonstrated, which suggested the effectiveness of the approved inactivated vaccine currently used in China.

What are the implications for public health practice?
Precise risk-based strategic practices that are integrated and regional are required for further improvement of the prevention and control of HFRS.

Hemorrhagic fever with renal syndrome (HFRS) is an important public health threat in China, and serious epidemic outbreaks and sporadic cases were recorded in the 1980s and 1990s. The incidence and mortality have declined in the past 20 years in China, but the epidemic characteristics of HFRS are highly variable at both the provincial and county levels. Liaoning Province is typically a natural focus of HFRS, and endemic HFRS in Liaoning might reflect the challenges facing China. A total of 39,352 HFRS cases with 285 deaths were reported to the Chinese National Notifiable Disease Surveillance System (NNDSS) from 1999 to 2018, and the incidence and case fatality rate demonstrated region-specific characteristics and spatiotemporal variation of the HFRS epidemic. Hantaviruses circulating in rodents were detected that showed the Seoul virus was the major pathogen causing HFRS in the province. In addition, sub-genotype III is the major genotype, and sub-genotype I and IV of Seoul virus and sub-genotype VI and VII of Hantaan virus were also detected in Liaoning. The dynamic changing of hotspots, the scale of the outbreaks, and sporadic cases required precise risk-based strategies that are integrated and regional precise to target the affected people for further improvement of HFRS prevention and control.

Data for HFRS patients were obtained from the Chinese National Notifiable Disease Surveillance System (NNDSS), and the data were analyzed with Excel (version 2013, Microsoft, USA) and SPSS software (version 16.0, SPSS Inc., USA). Geographic maps were created using ArcGIS Software (ESRI, Redlands, CA, USA).

Rodents were trapped with snap-traps in residential areas and the fields of national HFRS surveillance sites. The rodents’ serum antibodies against hantavirus were detected using double antigen sandwich ELISA (1). The rodents’ lungs were tested for hantavirus antigen with fluorescence labelled monoclonal antibody by direct immunofluorescence assay (2) and for viral genomic RNA by real-time RT-PCR (3). Positive test samples were loaded to Vero E6 cells for virus isolation. The antigenicity of new viral isolates was evaluated with 30 reference sera collected from recovered patients of HFRS using the plaque reduction neutralization test (PRNT) assay. The complete L, M, and S segments of the viral genome were amplified by overlapping PCR and sequenced with the amplification primers using BIG DYE terminator and a capillary sequencer. The hantavirus genomic sequence deposits in GenBank were collected for comparative analysis. All the sequences were aligned with the MAFFT program, version 7 (EMBL-EBI, UK). Comparative analyses of nucleotide sequences and amino acid sequences were operated by DNASTAR (Madison, Wisconsin, USA). Phylogenetic trees were generated using the neighbor-joining (NJ) method implemented in MEGA6.0 (4). Topologies were evaluated by bootstrap analysis of 1000 iterations.

A total of 39,352 HFRS cases with 285 deaths were
reported from 1999 to 2018 in Liaoning. The incidence rate varied from 1.71 to 13.05 per 100,000 persons annually, reaching a peak in 2004, decreasing significantly from 2006, reaching a plateau in 2007, then fluctuating between 1.71–3.0 per 100,000 persons (Figure 1). The national incidence rate, meanwhile, varied from 0.65 to 3.93 per 100,000 persons between 1999 and 2018, started to decrease dramatically since 1999 reaching a plateau in 2007, then fluctuated at a level of 0.65–0.99 per 100,000 (Figure 1).

In Liaoning, reported HFRS cases peak twice annually. The spring peak, occurring between March and May, contributed 35% of cases, and the fall-winter peak, occurring between October and December, contributed 26.5% of cases overall. In most prefecture-level cities, the spring peak was greater than the fall-winter peak, however, the monthly distribution of HFRS varied in different years and places, and the fall/winter peak was greater in Fushun City and Dandong City.

The reported cases involved all the 14 cities in the province, but 7 cities contributed 84% of reported cases. These cities are Huludao (7,114 cases, 18.08%), Jinzhou (5,367 cases, 13.64%), Dandong (5,038 cases, 12.80%), Benxi (4,631 cases, 11.77%), Shenyang (4,194 cases, 10.77%), Anshan (3,524 cases, 8.96%), and Fushun (3,191 cases, 8.11%). The fluctuations in incidence for each city were not synchronous, and the difference was statistically significant (Figure 2).

The ages of the 23,554 HFRS cases reported in 2004–2018, ranging from infancy to 85 years (median: 43 years). The majority of the cases (85.27%) occurred between 15–60 years, while 1.78% were in children <14 years and 12.94% were in persons >60 years. In the past 20 years, the proportion of reported cases in

FIGURE 1. The reported cases and deaths of hemorrhagic fever with renal syndrome (HFRS) from 1999 to 2018 in China (A) and Liaoning Province (B).
the 55–65 years group has increased, while that of the 30–40 years group has decreased significantly (Supplementary Figure S1, available in http://weekly.chinacdc.cn/), which may be related to the fact that the old have replaced the young as the main agricultural production workforce in most rural areas of China. The ratio of male to female patients was 2.88:1. Among female patients, the proportion of cases in the highest age group was higher than that in the male (Supplementary Figure S1). Most patients (62.74%) were farmers, followed by housewives and unemployed (12.94%), and students and non-agriculture workers were the other two occupations at relative high risk of acquiring HFRS (Supplementary Figure S2, available in http://weekly.chinacdc.cn/). There were 285 deaths in total from 1999 to 2018 with an average case fatality rate of 0.72%, which involved all 14 cities. Areas with high mortality were usually areas with low prevalence, such as Fuxin (4.84%, 3/62), Liaoyang (2.31%, 7/303), Dalian (2.01%, 17/847), and Tieling (1.99%, 11/553). To some extent, it showed that the experience and awareness of clinical doctors played an important role in the treatment of HFRS.

Previous laboratory surveillance data of hantavirus were collected and sorted. In 2018, 867 rodents were trapped with 25,336 snap-traps in residential areas and in fields in the cities and counties of Shenyang, Benxi, Dandong, Jinzhou, and Anshan. The predominant rodent species was *Rattus norvegicus* in residential areas and *Apodemus agrarius* in the fields, and the house mouse (*Mus musculus*) was next highest. The captured densities of rodents in residential areas was higher than in fields. In residential areas, the antigen detection rate was about 5.8% (29/500), ranging from 0% (0/50) in Benxi County to 14% (7/50) in Yuhong District and Haicheng City; and the serum antibody detection rate was about 17.2% (86/500), ranging from 2% (1/50) in Benxi county to 50% (25/50) in Fengcheng County and Dandong City. In the fields, the antigen detection rate was about 4.6% (23/500), ranging from 0% (0/50) in Yuhong District to 32% (16/50) in Haicheng City; and the serum antibody detection rate was about 9.2% (46/500), ranging from 0% (1/50) in Yuhong District to 46% (23/50) in Benxi County. Hantavirus-antigen positive rodents were further tested by RT-PCR assay, viral genome RNA were detected from 18 rodents using real-time RT-PCR (3), and the complete genome of L, M and S segments were obtained from 16 *Rattus norvegicus* lung samples directly, including 3 in Fushun, 4 in Shenyang, 2 in Jinzhou, and 7 in Tieling. Two viral isolates were obtained from those lung samples collected at Tieling, named LNTL001 and LNTL003. No significant antigenicity difference was observed between the two new isolates and the reference strain L99 in plaque reduction neutralization tests with blood from 30 recovered patients.

Pair-wise alignment and comparison of complete genome sequences showed that both the nucleotide and amino acid sequences were closely related to each other, with similarity above 95%. The sequences...
obtained in 2018 shared 95.6%–100% of amino acid homology and shared 94%–99.7% of nucleotide homology with sequences obtained previously. No significant recombination was observed among these sequences using recombination detection program version 4 (RDP4) software (5). Phylogenetic analyses showed that the hantavirus in Liaoning could be clustered into the clade of sub-genotype III (S3) and sub-genotype I (S1) of the Seoul virus, and sub-genotype VI of Hantaan virus (H6) (2) (Figure 3). Seoul virus was the predominant pathogen, and S3 was the major genotype currently circulating in the province. S4 and H7 of Hantaan virus were also found in the province (6–7).

**DISCUSSION**

HFRS is endemic in Liaoning, and the incidence peaked twice a year and varied in a cyclic fashion (8). The risk of occasional spillover of hantavirus from rodents to humans showed region-specific characteristics. Areas with high mortality were observed in areas with low prevalence, which suggests that lack of experience and awareness of diagnosis and treatment may cause patients to miss the best period of treatment and increase the patient’s severity and mortality rate, which had been crucial to improving the prevention and treatment of HFRS. In China, the appropriate age for vaccination of current approved HFRS vaccines ranged from 15 to 60 years, while the population out of the protection range of vaccination contributed about 15% of total reported cases, which is another challenge faced by current prevention and control work, especially with an increasing proportion of cases over 60 years old.

Both Seoul and Hantaan virus are circulating in Liaoning. Seoul virus is the main pathogen that cause HFRS, and the major sub-genotype is S3. The highly close relatedness of complete genome sequences

FIGURE 3. Phylogenetic analysis of hantavirus genomic sequences obtained in Liaoning province. (A) phylogenetic tree based on the Gn segment (1383–1630 nt). (B) phylogenetic tree based on the Gc segment (2000–2317 nt). (C) phylogenetic tree based on the S segment (633–991 nt). Sequences in different cities are marked by different colors, and isolates obtained in this study were marked by ▲.
obtained from different places in the province suggested that Liaoning belong to the same natural focus of infection. However, several sub-genotypes detected in rodents revealed the complexity of the natural focus of HFRS in Liaoning. Genetic and antigenic stabilities of the detected hantavirus over a long period of time may suggest the effectiveness of the approved inactivated vaccine currently used in China.

Hantaviruses are enzootic viruses that maintain persistent infections in their rodent hosts, and the spillover of these viruses to humans could occur at any time when contact happens between a susceptible person and an infective virion (9–10). After decades of implementation of comprehensive strategies for HFRS prevention and control, China has brought HFRS from highly common epidemic outbreaks to largely sporadic cases. Further improvement of HFRS prevention and control requires precise risk-based strategic practices that are integrated and regional to target highly-affected people in high-risk areas. These measures could improve public awareness of HFRS transmission, reduce human exposure to infected rodents and their excreta, and increase vaccination among at-risk populations.

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Preplanned Studies


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Summary

What is already known about this topic?
Cervical cancer is one of the most common cancers among HIV-positive women. The World Health Organization (WHO) has recommended a program of cervical cancer screening for HIV-positive women. Prospective follow-up studies and specific recommendations on cervical cancer screening for HIV-positive women in China are not currently being performed.

What is added by this report?
Among HIV-positive women from high HIV-burden areas of China, the detection rate of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) in the baseline survey and the incidence of CIN2+ in the follow-up survey after 18 months was high. High-risk human papillomavirus (hrHPV) infection and early (<18 years old) sexual debut was associated with CIN2+ among HIV-positive women.

What are the implications for public health practice?
HIV-positive women need cervical cancer prevention and regular screening services. These women might benefit from a cervical cancer screening program that combines hrHPV test and cytology and has short intervals between screenings.

Cervical cancer is the fourth most common cancer among women worldwide (1). Due to immunosuppression caused by human immunodeficiency virus (HIV) infection and the prolonged life expectancy associated with antiretroviral treatment (ART), cervical cancer has been one of the most common malignancies among HIV-positive women (2), and the World Health Organization (WHO) has recommended providing HIV-positive women with cervical cancer prevention and screening programs (3). An estimated 158,600 women in China are infected with HIV, but there is a lack of evidence to support the development of strategies for cervical cancer prevention and control that target HIV-positive women in China (4). Using data from a prospective study, we found that the detection rate of cervical intraepithelial neoplasia (CIN) grades 2 or worse (CIN2+) among HIV-positive women was 4.1% at baseline, and the incidence of CIN2+ was 0.1% in our follow-up survey. High-risk human papillomavirus (hrHPV) positive and early (<18 years old) sexual debut was associated with CIN2+ detection. The results draw attention to the need for regular cervical cancer screening among HIV-positive women and provides evidence on which to develop a cervical cancer screening program in China.

The data was derived from a prospective study on the co-infection of human papillomavirus (HPV) among HIV-positive women. The HIV-positive women were offered screening with an HPV test, cytology, and biopsy at baseline in 2015. The follow-up survey followed the same procedure as the baseline survey, which was conducted 1.5 years later on average. HIV-positive women aged 18–49 years were recruited from randomly selected towns in 5 counties of 3 high HIV-burden provincial-level administrative divisions (PLADs) including Yunnan, Guangxi, and Xinjiang. Eligible participants were those with no debilitating illness who had no previous history of cervical neoplasia or uterectomy. All participants provided informed consent to participate in the study. Ethical approval was obtained from the Institutional Review Board of the National Center for Women and Children’s Health, China CDC (No. FY2015–014).

A questionnaire survey was used to collect sociodemographic, reproductive, and sexual behavioral information. The medical records were reviewed to extract data on ART and laboratory results. Trained gynecologists provided gynecological physical examinations and collected cytological specimens. The cytological specimens were sent to a designated
laboratory for cytological examination and HPV DNA test with the Cobas 4800 HPV test [Roche Molecular Diagnostics (Shanghai) Co. Ltd., Shanghai, China] to produce results for HPV16 and HPV18, and a pooled result on the other 12 hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68b). In the baseline survey, another cytological specimen was collected and processed for 14 hrHPV types (16, 18, and the other 12 types).

HIV-positive women with cytology results of atypical squamous cells of undetermined significance (ASCUS) or worse (≥ASCUS) or hrHPV positive received colposcopy. The participants with abnormal colposcopy findings underwent biopsies, and those diagnosed with CIN2+ were referred for proper management. HIV-positive women with negative hrHPV and negative cytology or with negative colposcopy were deemed negative.

The blood samples were collected and tested for syphilis and hepatitis B surface antigen (HBsAg). The results of the CD4 lymphocyte count tests and HIV viral load tests within six months of when the results of the CD4 lymphocyte count tests and HIV were obtained from the clinical records or from laboratory tests at the sites.

The analysis is based on women diagnosed with CIN2+ and those who had negative results from cervical screening in both baseline and follow-up surveys. The data was analyzed using SPSS software (version 23.0, IBM Corp, Armonk, NY, USA). We presented categorized variables as frequencies and proportions and used Pearson’s chi-square test and Fisher’s exact test as appropriate. Factors with a p-value of <0.1 were entered into a binary logistic regression to build the final model. A p-value of <0.05 was considered statistically significant and calculated for adjusted odds ratios (AOR) and 95% confidence intervals (95%CI).

The recruitment, screening, and diagnostic processes are shown in Figure 1. During the baseline survey, 695 HIV-positive women were recruited, and 617 (88.8%) women completed the screening procedure. Of these, 25 women [4.1% (95%CI: 2.5%–5.6%)] of those screened had CIN2+. In the follow-up survey, among the 670 women who followed up, 462 (69.0%) completed the screening procedure, of whom two cases of CIN2+ [0.4% (95%CI: 0.2%–0.7%)] were diagnosed during this study.

0%–1.0%)] were detected. One of the two women (CIN3) was diagnosed with HPV58 infection, ASCUS, and CIN1, and another woman (CIN2) was diagnosed with HPV33/68 infection and negative cytology and colposcopy at the baseline. No cervical cancer was detected. The data of 27 women with CIN2+ and 442 women with negative results in both baseline and follow-up surveys were analyzed.

We present the univariate and multivariate analysis of sociodemographic characteristics, biological indicators of HIV infection, and STI coinfection between CIN2+ and negative women in Table 1. The distributions of age at sexual debut, hrHPV infection, and syphilis differed significantly between those two groups. Compared with women without hrHPV infection, those with single or multiple hrHPV infection or women with HPV16/18 or other hrHPV infection were more likely to have CIN2+ (trend \( \chi^2=81.84, p<0.001 \), trend \( \chi^2=30.69, p<0.001 \), respectively) (Figure 2). After controlling for age, we found hrHPV infection and early (<18 years old) sexual debut were associated with the occurrence of CIN2+ (AOR=49.1, 95% CI: 11.14–216.1, \( p<0.001 \); AOR=3.4, 95% CI: 1.2–10.2, \( p=0.03 \)).

**TABLE 1. Characteristics of HIV-positive women with CIN2+ and with negative result of cervical screening in HIV high-burden areas in China, 2015–2016**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of observations</th>
<th>CIN2+</th>
<th>Normal</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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</thead>
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<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>( \chi^2 )</td>
<td>( p )-value</td>
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<tr>
<td>Total</td>
<td>469 (100)</td>
<td>27 (5.7)</td>
<td>442 (94.3)</td>
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<td>PLAD</td>
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<td>1.68</td>
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<td>Yunnan</td>
<td>196 (41.8)</td>
<td>10 (37.0)</td>
<td>186 (42.1)</td>
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<tr>
<td>Guangxi</td>
<td>149 (31.8)</td>
<td>7 (26.0)</td>
<td>142 (32.1)</td>
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<tr>
<td>Xinjiang</td>
<td>124 (26.4)</td>
<td>10 (37.0)</td>
<td>114 (25.8)</td>
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<td></td>
</tr>
<tr>
<td>Age (years old)</td>
<td></td>
<td></td>
<td></td>
<td>0.19</td>
<td>0.91</td>
</tr>
<tr>
<td>18–29</td>
<td>79 (16.8)</td>
<td>4 (14.8)</td>
<td>75 (17.0)</td>
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</tr>
<tr>
<td>30–39</td>
<td>277 (59.1)</td>
<td>17 (63.0)</td>
<td>260 (58.8)</td>
<td></td>
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</tr>
<tr>
<td>40–49</td>
<td>113 (24.1)</td>
<td>6 (22.2)</td>
<td>107 (24.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
<td></td>
<td>4.11</td>
<td>0.13</td>
</tr>
<tr>
<td>Han and others</td>
<td>210 (44.8)</td>
<td>12 (44.4)</td>
<td>198 (44.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uighur</td>
<td>108 (23.0)</td>
<td>10 (37.1)</td>
<td>98 (22.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jingpo/Dai</td>
<td>151 (32.2)</td>
<td>5 (18.5)</td>
<td>146 (33.0)</td>
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<td></td>
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<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
<td>0.95</td>
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<tr>
<td>Primary school and below</td>
<td>223 (47.5)</td>
<td>13 (48.1)</td>
<td>210 (47.5)</td>
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<tr>
<td>Junior high and above</td>
<td>246 (52.5)</td>
<td>14 (51.9)</td>
<td>232 (52.5)</td>
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<tr>
<td>Current employment</td>
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<td></td>
<td></td>
<td>0.86</td>
<td>0.65</td>
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<tr>
<td>Farmer</td>
<td>216 (46.1)</td>
<td>11 (40.7)</td>
<td>205 (46.4)</td>
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</tr>
<tr>
<td>Housewife</td>
<td>153 (32.6)</td>
<td>11 (40.7)</td>
<td>142 (32.1)</td>
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<td></td>
</tr>
<tr>
<td>Other</td>
<td>100 (21.3)</td>
<td>5 (18.6)</td>
<td>95 (21.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
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<td></td>
<td></td>
<td>0.44</td>
<td>0.51</td>
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<tr>
<td>Married/cohabiting</td>
<td>355 (75.7)</td>
<td>19 (70.4)</td>
<td>336 (76.0)</td>
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<td></td>
</tr>
<tr>
<td>Single/divorced/widowed</td>
<td>114 (24.3)</td>
<td>8 (29.6)</td>
<td>106 (24.0)</td>
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<td></td>
</tr>
<tr>
<td>Annual income (RMB per capita)</td>
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<td></td>
<td></td>
<td>0.10</td>
<td>0.75</td>
</tr>
<tr>
<td>≥5,000</td>
<td>335 (71.4)</td>
<td>20 (74.1)</td>
<td>315 (71.3)</td>
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<td></td>
</tr>
<tr>
<td>&lt;5,000</td>
<td>134 (28.6)</td>
<td>7 (25.9)</td>
<td>127 (28.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residence registration</td>
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<td></td>
<td></td>
<td>1.80</td>
<td>0.18</td>
</tr>
<tr>
<td>Urban</td>
<td>107 (22.8)</td>
<td>9 (33.3)</td>
<td>98 (22.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>362 (77.2)</td>
<td>18 (66.7)</td>
<td>344 (77.8)</td>
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</table>
In this study, we found that the detection rate (4.1%) of CIN2+ among HIV-positive women at baseline was higher than that of general rural women aged 35–64 years (0.1%) in China (5). Previous
research reported an accumulated 6-year risk of CIN2+ was 1.2% among rural women in Shanxi province (6), and the incidence of CIN2+ was 283.79 per 100,000 among women aged between 20 and 65 years old (7). Although newly detected cases were rare and more data is needed for further analysis, our findings show a relatively high incidence rate of CIN2+ among HIV-positive women in a shorter follow-up period compared with previous studies (6). Our results confirmed that HIV-positive women were a high-risk group for cervical precancerous lesions and suggested that the progress of CIN in HIV-positive women was much faster than that among HIV-negative women. The majority of our participants had low educational status and economic status and were from ethnic minority groups and rural areas. Women with those socioeconomic characteristics were significantly less likely to receive cervical cancer screening in China (8). Our findings indicated the needs of cervical cancer screening of HIV-positive women might not be satisfied.

HPV persistent infections are precursors of cervical cancer with 14 types classified as oncogenic (9). The proportion of hrHPV infection (22.6%) among HIV-positive women in this study was much higher than that among the general population of women (16.8%) (10). We confirmed that hrHPV infection among HIV-positive women was highly associated with precancerous lesions, and our findings also demonstrated that there was a higher risk related to multiple hrHPV infections and HPV16/18 infections, which might be due to the cumulative effect of

![FIGURE 2](image-url). The detection of CIN2+ associated with different hrHPV infection groups among HIV-positive women from HIV high-burden area in China, 2015–2016. (A) Chi-square and p-value for trend for multiple hrHPV, single hrHPV, and no hrHPV was trend $\chi^2=81.84$, p<0.001. (B) Chi-square and p-value for trend for HPV16/18, other hrHPV, and no hrHPV was trend $\chi^2=30.69$, p<0.001. Abbreviations: hrHPV=high-risk human papillomavirus; HIV=human immunodeficiency virus; CIN2+=cervical Intraepithelial neoplasia grades 2 or worse; other hrHPV=HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68b.
multiple infections and the strong pathogenic impact of HPV16/18 (11). The Advisory Committee on Immunization Practice (ACIP) has recommended HPV vaccination among HIV-positive women to reduce the risk of cervical cancer in this group (12).

Early sexual debut, multiple sexual partners, smoking, early pregnancy, menopause, and lower educational level were found to be risk factors of cervical cancer in Chinese females (13). For HIV-positive women, lower CD4 lymphocyte count levels might relate to developing cervical cancer (14). However, in our study, except for hrHPV infection, we only found the association between early sexual debut and CIN2+, which might be because such sexual behavior enhanced the probability of exposure to HPV. HIV, HPV, and STIs could all be transmitted through sexual contract and were the main route of infection for women. Though we didn’t find a correlation between syphilis and CIN2+ in multivariate analysis, further research was needed. Our results implied the importance of behavioral change programs for HIV-positive women to promote safe sexual behavior.

This study was subject to a few limitations. The small sample size and the short period of follow-up limited our ability to detect women with cervical cancer. Our study sample also did not allow for generalization of results nation-wide. Future studies are needed to understand the detection and associated factors of cervical cancer among HIV-positive women with a larger sample in both low and high HIV-burden areas in China.

In conclusion, the study found a high detection rate of CIN2+ and the relatively faster progress of CIN among HIV-positive women from high HIV-burden areas of China, which reflected a higher risk of developing cervical cancer of HIV-positive women. Hence, HIV-positive women might benefit from regular cervical cancer screening with a shorter intervals between screenings. As hrHPV infection was associated with the detection of CIN2+, we recommend that cervical cancer screenings apply an approach that combines hrHPV tests and cytology if conditions permit. Our findings that early sexual debut was an associated factor of CIN2+ and points to the need for behavioral change program for HIV-positive women to promote safe sexual behavior.

Conflict of interest: No conflict of interest were reported.

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Chagas Disease — An Underestimated Global Public Health Challenge

Qin Liu¹; Muxin Chen¹; Xiao-nong Zhou²*  

American trypanosomiasis, commonly called Chagas disease (CD), was prevalent once in rural areas of Latin America where poverty is widespread and was considered a silent and poorly visible disease (1). It has become a global neglected tropical disease and a significant public health threat worldwide due to globalization over last century. More recently, it has attracted much more attention, and “April 14” has been designated as “World Chagas Disease Day” by the World Health Assembly of 2019 to raise awareness of the disease as a neglected tropical disease, to improve the rates of early treatment and recovery, and to achieve the ambitious goal to interrupt its transmission (2).

CD was named after the Brazilian physician Carlos Ribeiro Justiniano Chagas, who discovered the first patient on April 14, 1909 (3). The disease is an anthropozoonosis caused by the protozoan parasite Trypanosoma cruzi, which belongs to the order Kinetoplastida, family Trypanosomatidae. It affects about 6–8 million people worldwide and causes approximately 50,000 deaths per year, and nearly 100 million people are living in areas at risk of infection worldwide (1, 4). In the endemic areas of 21 Latin American countries, CD is mainly transmitted by vector triatomine bugs through the bite of the bugs (trypanosome in feces or urine to infect hosts by wound or mucous membrane), but a few other transmission routes are also possible such as oral transmission by food contaminated with triatomine bugs feces or urine (5–6). In recent decades, more cases of CD have been reported in several non-endemic countries such as Canada, the United States, Australia, New Zealand, Spain, Italy, France, United Kingdom, Switzerland, Japan, etc., due to growing population movement (7–9). It has been documented that in non-endemic areas CD is mainly transmitted by blood transfusion, organ transplant, mother and infant congenital transmission, laboratory accidents, and other transmission routes (6).

CD, caused by human infected with T. cruzi, has two successive phases. First, the acute phase is characterized by a high-grade parasitemia after the primary infection, but 95% of cases are asymptomatic. Only 5% of cases are symptomatic with prolonged fever, headache, myalgia, lymphadenitis, hepatomegaly, and splenomegaly manifestations (10). Possibly 60%–70% of infected individuals will never develop signs or symptoms in all life, characterizing the indeterminate form (10). Second, the remaining 30%–40% infections may progress to the chronic phase with Chagas heart disease (CHD) or gastrointestinal tract after 10–30 years, which can only be cured by surgery or organ transplantation, and the drugs for CD, including benznidazole or nifurtimox, are no longer effective in this stage (11). The diagnosis of human CD is difficult because most cases are asymptomatic. Although it is possible to determine the presence of parasites in the peripheral blood by parasitological tests in the acute phase, only 1%–2% of the infected individuals are recognized (1). Furthermore, the chronic phase needs confirmation by at least two serological tests based on different principles in order to detect anti-T. cruzi IgG antibodies (1). Many patients are often diagnosed in late stages of the disease, which causes chronic morbidities, high disabilities and mortalities.

Great efforts have been made in the past decades, and although CD transmission has been controlled effectively both in endemic and non-endemic countries (4), many challenges are still facing including low detection rate in the surveillance, lack of effective drugs, complicated zoonotic characteristics, and diversity of transmission routes (12). Though China is a non-endemic country and no CD cases have been reported yet, we have to improve our capacity in the surveillance of potential risks of the disease transmission, since the vector exists in China. As shown in results from previous surveys, one of the transmission vectors, Triatoma rubrofasciata, has been found in at least five provinces in southern China (13–14). By considering the high mobility between China and the world, CD will be possibly introduced in China. We recommended the following preparedness measures that should be taken by all medical institutions in China including (i)
strengthening information dissemination, communication, and health education on CD control especially for medical workers and common people who will work and travel in endemic countries; (ii) paying much more attention to the disease findings by preparing diagnostic techniques in cooperation with international professionals on CD; (iii) improving our surveillance system on potential imported diseases including CD, such as preparing the fast detection tests for serological screening of high risk population and blood products, setting standard operating procedures for vector reservoir surveillance, etc; and (iv) training more technicians on the diagnosis and surveillance of CD, carrying out relevant scientific research, and preserving relevant technologies. 

On “World Chagas Disease Day”, we would like to call all health workers in China who are working in hospitals or centers for disease control and prevention (CDCs) to monitor CD introduction to non-endemic areas through travelers who come back from the endemic areas and should report to China CDC once suspected cases are found. CD is an underestimated global public health challenge, and we should pay much more attention to the disease’s transmission.

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