cally equivalent to currently circulating highly pathogenic H5N1 viruses, as defined by the surface proteins H5 and N1, as well as an equally host cell–derived virus envelope. With respect to a minor structural difference, that is, the absence of the polybasic cleavage site from the NIBRG-14 hemagglutinin, others have shown that influenza A virus strains that contain such noncleaved hemagglutinins can even be somewhat more resistant to inactivation by, for example, low pH,[17] which would make predictions of product safety versus wild-type viruses based on the data of the current study even more robust. Most importantly though, where the presented experiments have determined virus inactivation on a logarithmic scale, any minor differences between the virus strains will be inconsequential for the general conclusions reached. In contrast to these structural and thus physicochemical similarities, the pathogenicity of the NIBRG-14 virus is significantly different to the currently circulating highly pathogenic H5N1 viruses (see Materials and Methods); that is, it is none. This combination of properties has greatly facilitated performing the laboratory work described, in that for the first time inactivation data could be generated with an H5N1 influenza virus strain without safety concerns for the operators/the environment.

Even before the availability of H5N1 inactivation data, however, several other aspects have argued against the relevance of H5N1 or more generally influenza viruses for the safety of plasma products. First, the occurrence of influenza virus in blood, that is, viremia, has been considered "... uncommon ...,"[7] although several less recent reports have described the very fact[8-11] and even viremia during the preclinical course of influenza virus infection,[8,11] which would represent a setting of utmost relevance for the safety of all blood-derived medicinal products. Importantly though, all this information has been derived from influenza viruses different from the bird influenza virus H5N1.

Second, the virus titers reported during viremia were generally rather lower than those of the viruses established as relevant for transfusion safety, although the notion was challenged by the recently reported approximately 85,000 copies per mL as determined for a serum specimen from a fatal human H5N1 case.[6] Another similar case, however, found a virus titer in plasma of only approximately 3,080 copies per mL.[12] It is emphasized that both of these specimens were obtained from terminally ill patients, that is, under circumstances not applicable for the collection of blood or plasma. Determining the potential viremia levels in asymptomatic individuals remains a research priority, yet expectedly those titers will be lower than those found in individuals in late or even terminal stages of disease.

Third, extensive studies of other lipid-enveloped viruses have indicated that these viruses are easily inactivated and should thus not be considered a concern to the safety of plasma derivatives. The concerns of particularly patient groups whose treatment depends on the safety of plasma-derived products, but also regulators whose remit includes to guarantee the safety of these medications, are nevertheless understandable in view of the history of plasma products.

Based on the data presented the safety margins of plasma products in the event of an H5N1 influenza pandemic can be estimated, following the basic principles set forth in regulatory guidance.[18] With respect to "potential virus input"[18] into the manufacturing process, neither the prevalence of viremic potential blood or plasma donors nor the potential virus load of a donation obtained under such circumstances is known at this time. The level of influenza viremia during preclinical stages of infection, however, can safely be assumed to be lower than those detected in terminally ill individuals, that is, approximately 85,000[6] and 3,080[12] copies per mL, and generally influenza viremia would be less likely in preclinically infected humans who would have qualified as donors. More specific information about the prevalence of viremia in blood or plasma donors as well as peak levels of viremia is necessary to develop more precise assessments and will hopefully become available quickly once a potential influenza pandemic commences.

Regarding the "overall virus inactivation/removal capacity"[18] all the H5N1 virus that could be spiked into experimental downscales to evaluate standard virus inactivation technologies was completely inactivated well before the end of these processes, with virus reduction factors in the range of greater than 4.7 to greater than 7.6 log, that is, well beyond the widely held effectiveness threshold "... of the order of 4 logs or more. . ."[14] Regulations suggest that "... it will be desirable in many cases to incorporate two distinct effective steps ..." into any manufacturing process,[13] which would result in a cumulative reduction of potential virus load by greater than 8 log, that is, by more than 100 million-fold. Given these numbers the safety margins that these dedicated virus reduction techniques would ensure for plasma derivatives become intuitively clear.

Given the central importance of virus reduction for the safety of plasma derivatives, the current investigation thus sought to experimentally confirm the expected behavior for H5N1 influenza virus, in examining the inactivation potential of procedures widely used throughout the plasma products industry against the H5N1 influenza virus itself. Reassuringly, all the inactivation methods tested were shown to completely inactivate all the virus that could be spiked into the respective product intermediates.

Pasteurization was found to be extremely effective in inactivating all the lipid-enveloped viruses tested, that is, HIV, BVDV, PRV, and also H5N1, at both the upper and the lower limits of the specified protein concentration (Table 1).

Vapor heating, a proprietary heat treatment that is used, for example, during the FEIBA manufacturing procedure, was also confirmed to be extremely effective. The viruses tested were completely inactivated before initiation of (BVDV, PRV, H5N1) or early during (HIV) the second heat treatment phase, which thus provides extra margins of safety. Of note, the results obtained would indicate that H5N1 is more stable during lyophilization than is BVDV or PRV (Table 2).

The results obtained for the S/D treatment of IVIG agreed with earlier findings that have established this method as most effective in inactivating lipid enveloped viruses (Table 3). Also, the rather lower pH of the plasma products intermediate tested, that is, pH 5.2, which is equivalent to the intermediate during large scale manufacturing, was realized to contribute to the inactivation of the H5N1 influenza virus (Table 3).

For the low-pH treatment investigated (Table 4), the H5N1 was inactivated particularly effectively. This is not surprising because during the infection cycle of influenza viruses a low pH–induced fusion event is needed for the virus to escape from the late endosome into the cytosol, and if this event occurs outside the susceptible cell, the virus would be rendered noninfectious.[16]

Although not directly investigated in the experiments presented, influenza viruses would, based on their approximate size of 80 to 120 nm,[19] also be expected to be removed by the now widely used nanofilters (virus filters) with nominal pore sizes in the 15- to 75-nm range and typically between 35 and 50 nm.

Together, the data presented should alleviate any H5N1-associated concerns about the safety of plasma derivatives and will hopefully support an evidence-based decision making process in all further dealings with the emergence of influenza viruses. The results will, however, have to stand their test when a possible first blood transfusion transmission of an influenza virus would be documented. Beyond this discussion of the safety of blood and plasma-derived products, the impact of a potential influenza pandemic on the supply of these life-sustaining products needs to be kept in mind. A recently presented model calculation from the US Centers for Disease Control and Prevention (CDC) estimated a donor shortfall of, depending on the specific scenario envisaged, as much as 15 to 20 percent for up to 8 weeks (M. Meltzer, CDC; presented at the PPTA Plasma Forum, June 20, 2006, Washington DC). It is critical, therefore, that all current pandemic influenza preparedness efforts include the provision of adequate supplies of blood and plasma derivatives into their goals.

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研究報告の概要

<背景>
中国は、20世紀前半に梅毒の大きな流行を経た後、1960～80年の20年間、この感染を排除することができた。しかし、中国社会の大きな変化の後、性感染症の流行が再発した。散発的に発行された報告によって梅毒流行の重大性についての警鐘が鳴らされてきたが、計画及び介入のためのデータを得るために、全国サーベイランスが必要とされる。
<方法>
我々は、中国の性感染症サーベイランスシステム及び監視サイトネットワークからの症例報告データを収集し評価した。
<結果>
中国において報告された梅毒の全症例発生率は、1993年には100,000例あたり0.2例であったが、2005年には、第一期及び第二期梅毒だけで100,000例あたり5.7例であった。先天的な梅毒の発生率は、1991年は100,000例の出生児あたり0.01症例であったが、2005年には100.000例の出生児あたり19.68例まで、年平均71.9%の割合で大きく増加した。

使用上の注意記載状況・その他参考事項等

代表として献血ヴェノグロブリン-IH ヨシトミの記載を示す。
2. 重要な基本的注意
(1) 本剤の原材料となる献血者の血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体、抗HTLV-I抗体陰性で、かつALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohnの低温エタノール分画で得た画分からポリエチレングリコール4000処理、DEAEセファデックス処理等により人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びろ過膜処理（ナノフィルトレーション）及びpH3.9～4.4の条件下での液状インキュベーション処理を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見	今後の対応
中国において梅毒患者が急激に増加しているとの報告である。 血漿分画製剤からの梅毒トレポネーマ伝播の事例は報告されていない。梅毒トレポネーマは、低温保管や凍結乾燥、加熱処理により死滅するとされており、またナノフィルトレーションによる除去も容易と考える。そのため、万一原料血漿に梅毒トレポネーマが混入したとしても、製造工程において十分に不活化･除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

Syphilis in China: results of a national surveillance programme

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Summary

Background After a massive syphilis epidemic in the first half of the 20th century, China was able to eliminate this infection for 20 years (1960–80). However, substantial changes in Chinese society have been followed by a resurgent epidemic of sexually transmitted diseases. Sporadic reports have provided clues to the magnitude of the spread of syphilis, but a national surveillance effort is needed to provide data for planning and intervention.

Methods We collected and assessed case report data from China's national sexually transmitted disease surveillance system and sentinel site network.

Findings In 1993, the reported total rate of cases of syphilis in China was 0·2 cases per 100 000, whereas primary and secondary syphilis alone represented 5·7 cases per 100 000 persons in 2005. The rate of congenital syphilis increased greatly with an average yearly rise of 71·9%, from 0·01 cases per 100 000 livebirths in 1991 to 19·68 cases per 100 000 livebirths in 2005.

Interpretation The results suggest that a range of unique biological and social forces are driving the spread of syphilis in China. A national campaign for detection and treatment of syphilis, and a credible prevention strategy, are urgently needed.

Introduction

Syphilis is a very serious infection that causes acute cutaneous manifestations including genital ulcers, chronic severe and debilitating compromise of the cardiovascular and nervous systems, and serious effects on reproductive and neonatal health.[1] During pregnancy, syphilis infection can lead to spontaneous abortion, congenital deformities, and severe neonatal disease.

Syphilis was first recognised in mainland China in 1505.[2] By the time the Communist party assumed power in 1949, the Chinese people were suffering one of the biggest syphilis epidemics in human history. Surveillance studies in the 1950s showed that the infection was present in as many as 84% of prostitutes and 5% of the general population in some large cities, and 2–3% of rural residents.[3,4]

Mao Zedong and his government prioritised health care, and the control of syphilis and other sexually transmitted diseases (STD) was one of their key aims.[4] In 1952, China developed an unprecedented and unique campaign to eliminate STD. The government instituted mass screening, provided free treatment to infected individuals, and closed brothels.[5,6] This programme seemed to be highly effective, and studies by Chinese and international teams verified the virtual eradication of STDs by the 1960s.[7–10]

However, long-term control of STD in China has proved elusive. Economic and social reforms designed to open China to the world have been successful, but also appear to have laid the foundation for the re-emergence of STD. Increased personal wealth, greater geographical mobility, and more relaxed government control[11] set the stage for the spread of STD. The first cases of syphilis in China after the death of Mao were reported in 1979.[12]

These changes led to the establishment of the Chinese National Center for STD Control in 1986, followed by the launch of a national STD surveillance system by the Ministry of Health in 1987. The purpose of this report is to describe the growth and magnitude of the Chinese syphilis epidemic on the basis of Chinese governmental surveillance data.

Methods

Surveillance of STD is done through mandatory case-reporting from government facilities including STD clinics, designated provincial dermatovenereology centres, gynaecology and genitourinary clinics, maternity and children's hospitals, and other health providers in all 31 provinces, municipalities, and autonomous regions of the country. Beginning in 2005, syphilis case-reporting moved from paper reports to electronic online submission.

For each syphilis case, doctors or their assistants filled out a standardised STD reporting card with demographic (age in 10 year intervals, sex, home location, marital status, occupation, and education), clinical (diagnostic evidence, onset of symptoms, stage of syphilis, presence of other STD), and epidemiological information (route of acquisition). According to national guidelines,[13] primary syphilis was defined as a clinically compatible case characterised by one or more chancres and inguinal lymphadenopathy, and laboratory confirmation of *Treponema pallidum* in clinical specimens by dark-field microscopy or reactive non-treponemal rapid plasma reagin, or toluidine red unheated serum test and

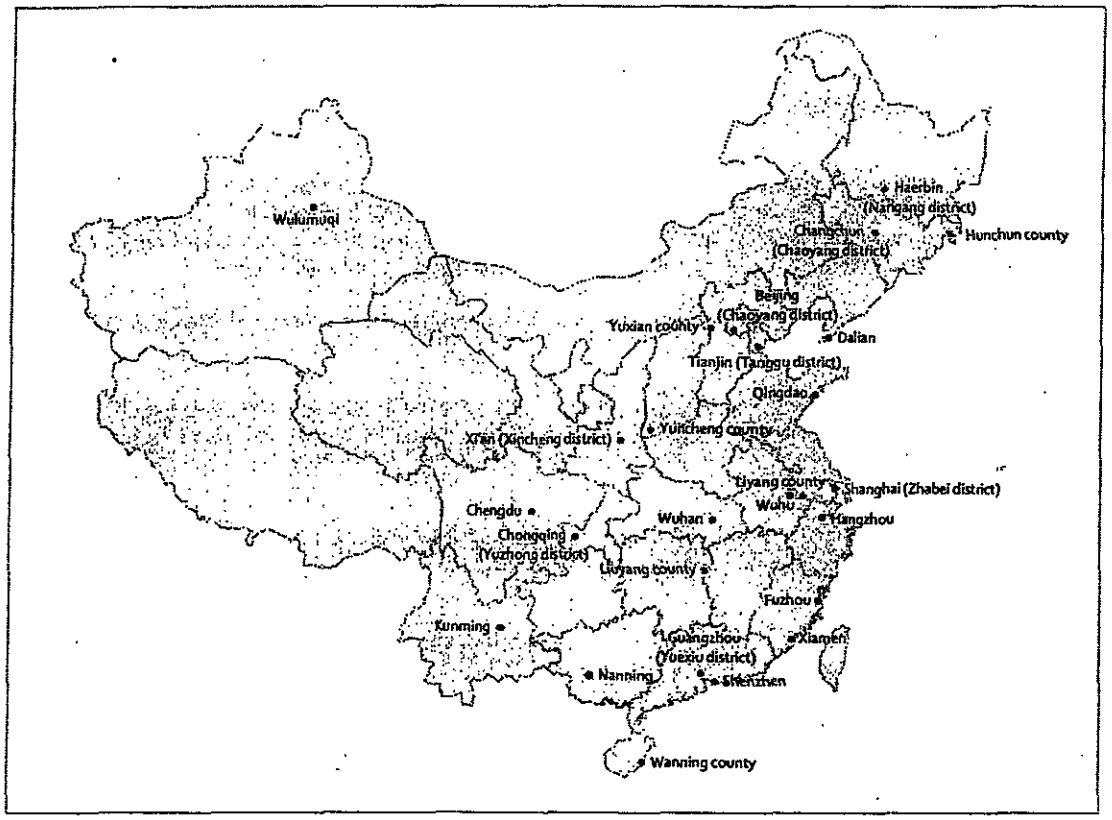

Figure 1: Map of 26 national STD sentinel sites in China

treponemal *T pallidum* haemagglutination, or particle agglutination assay for antibody to *T pallidum*; secondary syphilis was defined as a clinically compatible case characterised by maculopapular rash and, in many cases, lymphadenopathy, and laboratory test confirmation as for primary syphilis; latent syphilis was defined as an asymptomatic case with a possible history of infection supported by two consecutive reactive non-treponemal tests (rapid plasma reagin), a reactive treponemal test (particle agglutination assay), and normal cerebrospinal fluid; and tertiary syphilis was defined as a case with a history of primary, secondary, or latent syphilis with clinical manifestations involving the cardiovascular or central nervous system and laboratory confirmation with reactive non-treponemal tests, or cerebrospinal fluid abnormalities characterised by higher than normal amounts of white blood cells or protein. A case of congenital syphilis was defined as a neonate or child younger than 2 years affected by associated signs and symptoms such as rash, hepatosplenomegaly, and lymphadenopathy, with an infected mother, supported by detection of *T pallidum* in lesions by dark-field microscopy or reactive serological test.[14]

To increase the accuracy with which STD incidence could be assessed, a network of 16 sentinel surveillance sites was established in 1987 in areas with high rates of STD. This network was subsequently expanded in 1993 to 26 sites in various cities throughout China. A map of these sentinel sites is shown in figure 1. Each site has a designated organisational centre from either the dermatovenereology institute or Center for Disease Control hospital networks that coordinates mandated STD reporting from all STD service providers in their jurisdiction, which is in most places a city district or in some an entire city. These sites have strengthened management, standardised diagnosis and treatment protocols, and established laboratory quality assurance measures, for STD surveillance. By comparing the number of STD diagnoses recorded in clinic and laboratory registries at sentinel sites with case reports in the surveillance system, twice-yearly quality control studies indicate that sentinel sites report all but less than 5% of newly diagnosed STD cases.

Information from sentinel and non-sentinel sites is collected at the county level and reported quarterly to the next administrative levels until it reaches the National Center for STD Control, where all compiled surveillance data are stored in an electronic database (figure 2).

EpiInfo (Version 1.1, Centers for Disease Control and Prevention, Atlanta, GA, USA) was used to analyse the results in this study.

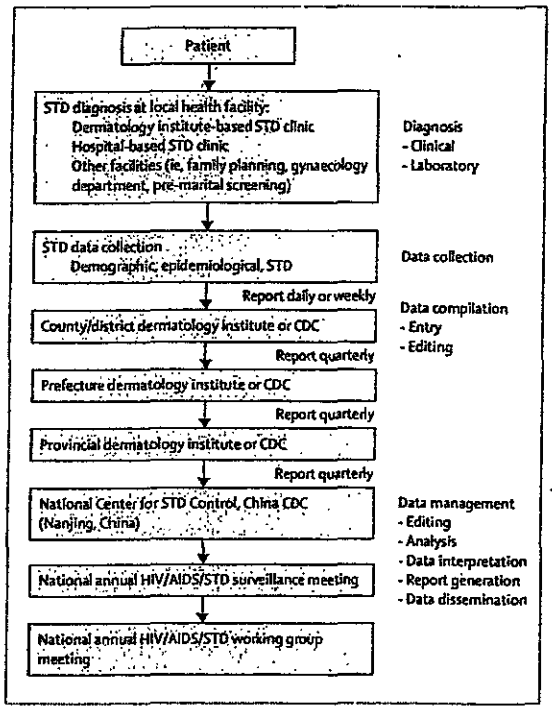

Figure 2: Reporting structure of China's nationwide STD surveillance system

Total syphilis incidence refers to the number of new syphilis cases at any stage per 100000 people per year. Because reports based on classification of syphilis into primary, secondary, latent, and tertiary syphilis were not introduced into surveillance reports until 1996, incidence data before this year refer to total syphilis incidence.

The reported incidence of congenital syphilis was calculated by dividing the number of new congenital syphilis cases by the number of livebirths in a specified year. National population and livebirth data were obtained from the National Bureau of Statistics of China.[15] The average yearly rate of increase in incidence was calculated as a geometric mean by use of the formula: (incidence at time n divided by incidence at time 1)^(1/[n–1])–1, where n is defined by the interval number of years.

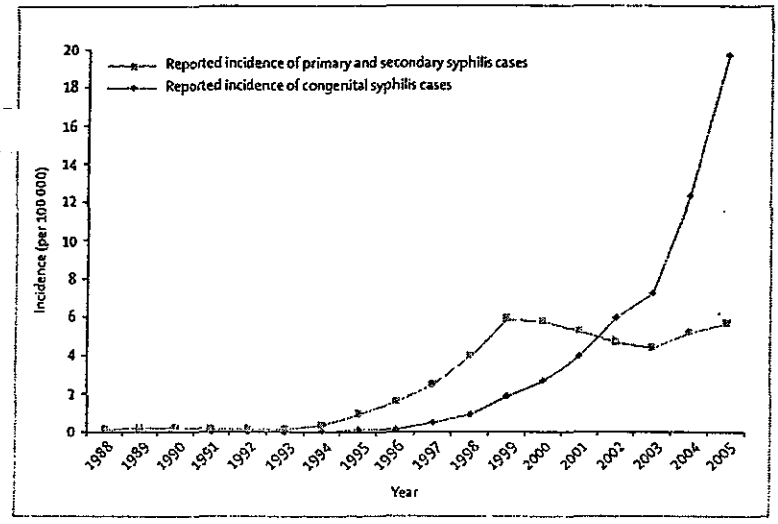

Figure 3: Reported incidence of congenital syphilis and cumulative primary and secondary syphilis in China from 1988 to 2005, nationwide STD surveillance system

*Aside from congenital syphilis, classification into different stages of syphilis was introduced in 1996. Thus, before 1996, data points for primary and secondary syphilis show incidence for total syphilis. However, an ad hoc survey of syphilis reports in 38 cities from 1990 to 1994 suggested that reported cases of primary, secondary, early latent, tertiary, and congenital syphilis accounted for 20·2%, 46·5%, 28·1%, 2·1%, and 0·7% of total cases, respectively.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and the team of co-authors had final responsibility for the decision to submit for publication.

Results

Nationwide surveillance data indicated that after remaining just below 0·2 cases per 100000 people from 1989 to 1993, the total incidence of syphilis increased from 0·17 cases per 100000 in 1993 to 6·5 cases per 100000 in 1999, with incidence of primary and secondary syphilis accounting for 5·85 cases per 100000 (figure 3). After decreasing slightly between 2000 and 2003 (perhaps more a result of administrative changes during that time than a real decline), the incidence of primary and secondary syphilis has increased in the past 2 years to 5·67 cases per 100000 people. The average incidence of primary and secondary syphilis for the years 2000 to 2005 was 5·13 cases per 100000 people per year. Incidence of congenital syphilis had grown at a very rapid rate with an average yearly increase of 71·9%, from 0·01 cases per 100000 livebirths in 1991 to 19·68 cases per 100000 livebirths in 2005 (figure 3). The actual numbers of cases of syphilis classified by the stage of disease are shown in table 1.

More than 70% of reported cases of syphilis in the past 10 years were in people aged 20–49 years. The mean ages were slightly higher in northern and central China than in other regions of the country (table 2). The ratio of male to female individuals with syphilis decreased from 2·0 to 1·0 between 1988 and 2000, and has held steady for the past 5 years.

All China's 2882 counties reported cases of syphilis during the past 5 years. In 2005, the highest rates of total syphilis cases were reported in Shanghai (55·3 cases per 100000 individuals), Zhejiang (35·9 per 100000), and Fujian (26·8 per 100000), which together with Jiangsu (13·0 per 100000) form China's prosperous southeastern seaboard. Beijing municipality had the next highest rate (24·9 per 100000), followed by the southern Zhujiang River Delta (Guangxi, Guangdong, and Hainan provinces), which reported rates of about 14–21 cases per

100 000 individuals. The northeast provinces (Jilin, Liaoning, and Heilongjiang) and the far western provinces of Qinghai and Xinjiang reported rates of 5–12 cases per 100 000 individuals (figure 4).

The 26 sentinel STD sites established in 1993 consistently reported a much higher number of cases than did non-sentinel sites. Incidence of total syphilis cases reported by the enhanced surveillance network rose continuously from 1·4 cases per 100 000 individuals in 1993 to 32·9 per 100 000 in 1999 (figure 5). Incidence fell slightly in 2000 (28·9 cases per 100 000 individuals) was similar in 2001, paralleling the trend reported by the nationwide surveillance system (figure 5). Despite covering a population of only 35–40 million (about 3% of China's population), the 26 sentinel sites reported about 18% of total syphilis cases from 1995 to 2001.

Discussion

Our report provides a comprehensive view of the re-emergence of syphilis in China. These findings are consistent with reports of the exceptional prevalence of syphilis in high-risk groups in China[16–18] and of the spread of other STD in China,[19] including a nationwide cross-sectional survey that showed a high prevalence of chlamydial infection, especially in urban coastal areas.[20] Worldwide, resurgence of syphilis in China corresponds to epidemics reported in several cities in the UK,[21] Ireland,[22] the Russian Federation states,[23] and the USA.[24]

The incidence of primary and secondary syphilis in 2005 (5·67 cases per 100 000) was substantially higher than that in most developed countries; for example, the USA reported 2·7 cases of primary and secondary syphilis per 100 000 individuals in 2004.[24] Furthermore, the number of cases cited might not accurately reflect the true extent of the epidemic. STDs treated at hospitals, family planning centres, gynaecological clinics, pharmacies, and private practitioners go largely unreported,[25,26] although these venues represent important access points for patients with STDs. A study in Shenzhen and Guangzhou[27] showed that 27% of patients with STDs sought initial care at a site other than a government dermatovenereology centre; in Chengdu[28] and Hangzhou,[29] 18–40% of patients sought care from private doctors and pharmacists. In an internal, unpublished quality-control study done in 1999, STD surveillance officials found that in one province, more than 75% of STD cases were not reported. Private practitioners were the least reliable, reporting only 0·2% of cases, followed by district-level hospitals (7·9%), provincial-level hospitals (15·4%), and city-level hospitals (35·5%).

Surveillance reporting might also be limited by the availability of governmental resources. The 26 sentinel sites reported about 18% of the nation's aggregate syphilis cases, although these sites cover only 3% of the population. Such results suggest that non-sentinel sites are probably not reporting the actual scale of the epidemic, and that improved surveillance would yield a higher overall incidence than reported here.

As an alternative approach we did a systematic review of published work,[17] which suggested the following prevalences of syphilis in specified populations: antenatal women 0·45%; premarital testing 0·66%; voluntary blood donors 0·37%; migrant workers 1·4%; remunerated blood donors 2·86%; possible female sex workers 0·83%; incarcerated female sex workers 12·49%; drug users 6·81%; and men who have sex with men 14·6%.[17] In the past 5–10 years, syphilis rates seem to have increased in all these groups, with the greatest increase in drug users (0·96% per year), incarcerated female sex workers (1·41% per year), and men who have sex with men (4·50% per year).[17] Surveillance data and focused reports from throughout China provide compelling evidence of a substantial and worsening

	Primary	Secondary	Tertiary	Congenital	Latent	Primary and secondary	Total
1985	..	..	..	..	..	..	184
1986	..	..	..	..	..	..	337
1987	..	..	..	..	..	..	819
1988	..	..	..	..	..	..	1387
1989	..	..	..	..	..	..	1976
1990	..	..	..	..	..	..	2574
1991	..	..	..	..	..	..	1870
1992	..	..	..	..	..	..	1997
1993	..	..	..	..	..	..	2016
1994	..	..	..	..	..	..	4591
1995	..	..	..	..	..	..	11336
1996	9036	9058	80	35	2548	18094	20757
1997	14134	16085	72	109	3268	30219	33668
1998	23249	25428	143	185	4760	48677	53765
1999	35805	36615	285	359	7342	72420	80406
2000	36075	35424	268	468	7946	71499	80181
2001	32304	33768	199	677	10297	66072	77245
2002	29978	29675	277	971	13428	59653	74329
2003	30080	26415	327	1155	14576	56495	72553
2004	36420	30058	501	2035	19297	66478	88311
2005	40962	33055	933	3182	35556	74017	113688

Table 1: Yearly case reports of syphilis classified by stage, nationwide STD surveillance system

	Mean age (SD), years
North China (Beijing, Tianjin, Hebei, Shanxi, Inner Mongolia)	39·2 (15·6)
Central China (Henan, Hubei, Hunan)	39·6 (15·5)
Northeast China (Liaoning, Heilongjiang, Jilin)	37·5 (13·6)
East China (Shanghai, Zhejiang, Jiangsu, Anhui, Shandong, Jiangxi, Fujian)	37·9 (13·5)
Northwest China (Shaanxi, Gansu, Ningxia, Qinghai, Xinjiang)	36·6 (15·2)
Southwest China (Yunnan, Guizhou, Sichuan, Chongqing, Xizang)	37·3 (13·9)
South China (Guangdong, Guangxi, Hainan)	36·6 (14·4)
Total	37·6 (14·1)

Table 2: Age of people with syphilis in 2005 by region

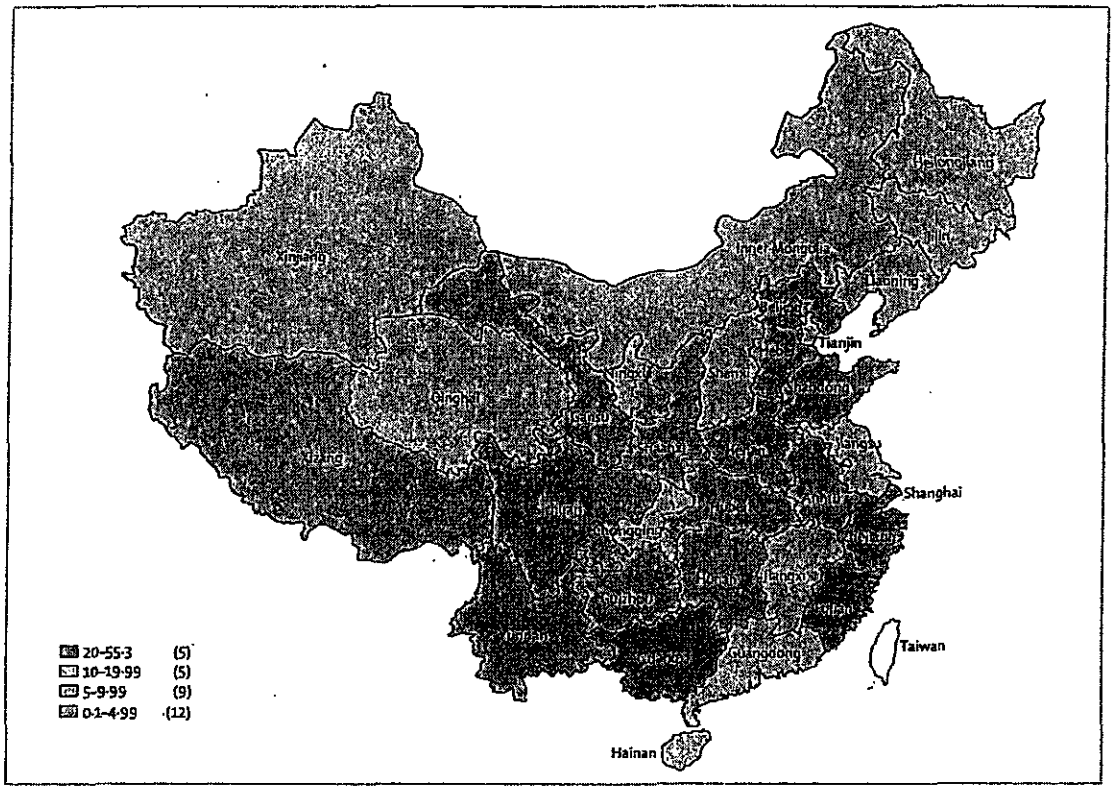

Figure 4: Incidence of total syphilis in 2005 by province, nationwide STD surveillance system
Numbers in parentheses show number of provinces in band.

syphilis epidemic in individuals at high risk, and in the general population.

Syphilis can have devastating health consequences, especially if untreated.[1] The increasing privatisation of health care in China has left many people without resources to seek care, particularly for problems like syphilis that on the surface appear to be self-limiting. In a 2004 survey, half the respondents from three provinces reported foregoing health care in the previous year because of its prohibitive cost.[30] This proportion is probably much higher in rural areas, as shown by results from one study done in a rural county outside Beijing where 80% of women with symptoms of STD did not seek health care because of its high cost and their own lack of knowledge about STD.[31]

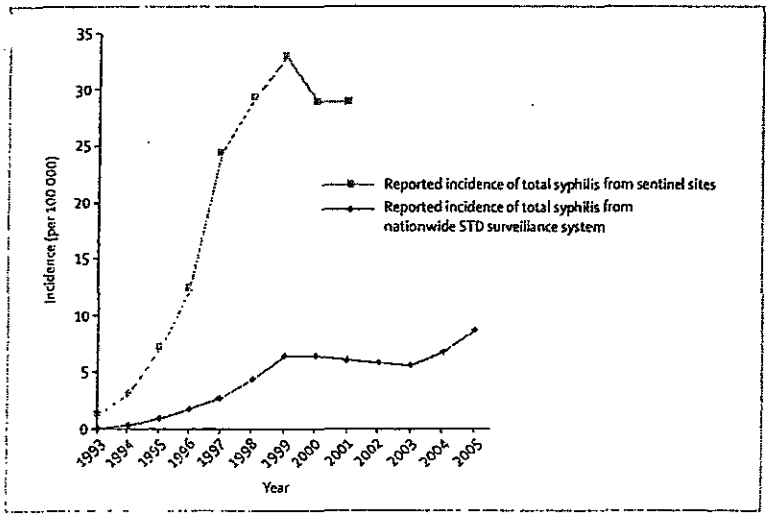

Figure 5: Comparison of incidence of syphilis reported by 26 sentinel sites and nationwide STD surveillance system

Obviously, any defects caused by congenital syphilis would be devastating. Additionally, syphilis can contribute to the spread of HIV infection by raising the viral burden in HIV-infected individuals[32] and by increasing susceptibility to infection.[33] Cotransmission of syphilis and HIV has been reported in Pune, India,[34] and syphilis infection in pregnant women might facilitate the vertical transmission of HIV.[35] Although the gravity of syphilis during pregnancy cannot be overstated, detection and treatment of the disease could be overshadowed by focus on the prevention of vertical HIV transmission.[36]

The rapid spread of syphilis in China is probably attributable to a combination of biological and social forces. Grassly and co-workers[37] have argued that the