Impact factor 5.49

Eurosurveillance

Europe's journal on infectious disease epidemiology, prevention and control

Vol. 18 | Weekly issue 47 | 21 November 2013

Surveillance and outbreak reports

Research articles

News

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Trends of hepatitis B notification rates in Turkey, 1990 to 2012

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Citation style for this article:
Ay P, Torunoglu MA, Com S, Çipil Z, Mollahaliloğlu S, Erkoç Y, Dilmen U. Trends of hepatitis B notification rates in Turkey, 1990 to 2012. Euro Surveill. 2013;18(47):pii=20636. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20636

Article submitted on 17 November 2012 / published on 21 November 2013

Turkey is a country with intermediate endemicity for hepatitis B, and approximately 4% of the population are HBsAg-positive. A number of measures have been implemented to prevent hepatitis B infection. In 1998, hepatitis B antigen was included in the national immunisation programme, and infants have since been vaccinated with three doses. Catch-up strategies, vaccination for high risk groups and screening measures were also adopted. The aim of this study was to evaluate the impact of the prevention and control strategies on hepatitis B notification rates in Turkey in the period from 1990 to 2012, using data from the national surveillance system. Secular trends revealed that rates showed an initial increasing trend, followed by a steady decline from 2005. The most dramatic decline occurred among children younger than 15 years, highlighting the benefits of vaccination and catch-up strategies. However, vaccination cannot fully explain the decrease in this age group. Socioeconomic development, through interrupting the horizontal transmission may also have contributed. After 2005, a steady decline was achieved also among those 15 years and older. The rates in adults were higher, which indicates that stronger prevention measures are needed to target this group, particularly men.

Introduction

It is estimated that approximately 2 billion people in the world have been infected with hepatitis B virus (HBV) [1,2]. Among those, 360 million are chronic carriers and have a 15% to 25% risk of premature death from consequences such as liver cirrhosis and hepatocellular cancer [1,3]. The burden of hepatitis B differs worldwide. Countries in eastern and southern Europe have a moderate prevalence of chronic hepatitis, and Turkey is classified as a country of intermediate endemicity with approximately 4% of the population HBsAg-positive [2,4]. In a meta-analysis, evaluating seroprevalence studies published between 1999 and 2009, it was determined that the overall HBsAg positivity in Turkey was 4.6% [5].

Rates of HBsAg positivity vary within Turkey. Seroepidemiological studies show a decreasing trend from south-east to west in all age groups [5-12]. In a meta-analysis evaluating studies published between 1999 and 2009, Toy et al. estimated that the prevalence rates of HBsAg positivity in the west, middle and eastern regions were 3.5%, 4.9% and 6.8%, respectively. In the same study, the authors concluded that the lowest prevalence was in children who were younger than 15 years (2.8%) and the highest prevalence was among 25-34 year-olds (6.4%) [5].

In Turkey, hepatitis B vaccine has been on the market since the late 1980s, yet a systematic vaccination policy was not adopted at that time [13]. Since 1998, when hepatitis B antigen was included in the national immunisation programme, infants have been vaccinated with three consecutive doses. Although there have been some changes regarding vaccination schedules, infants have since 2003 received the antigen within the first 72 h after birth, followed by two additional doses at the end of the first and the sixth month of age. Catch-up strategies targeting older age groups are also used as a supplement to routine infant vaccination because studies among children six to 17 years of age, carried out in different parts of the country, indicate a gradual increase in the seroprevalence with rising age [4,10-12,14]. This finding suggests that horizontal transmission, through close contact with infected family members, is the main mode of transmission among children [4,10,14-16]. Vaccination activities were therefore carried out in primary schools during the period 2005 to 2009. In Turkey, eight years of primary schooling is mandatory and children start school at the age of six years. Target age groups which were included in catch-up vaccinations are presented in the Table. In

Table

Target age groups for catch-up vaccinations by school year, Turkey, 2005–2009

School year	Target group
2005–06	Primary school students at the eighth grade (13 years-old)
2006–07	Primary school students at the sixth, seventh and eighth grades (11, 12 and 13 years-old)
2007–08	Primary school students at the third, fourth, fifth, and sixth grades (8, 9, 10 and 11 years-old)
2008–09	High school students at the fourth grade (17 years-old)

Turkey, vaccination policies are adopted at the national level and are the same in all geographic regions.

Also high-risk groups for contracting hepatitis B have been vaccinated free-of-charge since 1998, namely healthcare workers, people who inject drugs, persons with high-risk sexual behaviour, persons who frequently require blood or blood products, haemodialysis patients, close contacts of HBsAg-positive persons, persons residing in orphanages, detention centres and prisons.

Strategies for screening were also adapted. In Turkey, it has been mandatory since 1993 to screen all voluntary blood donations for HBV. All registered sex workers are tested for hepatitis B every three months. Since sex workers are categorised as a high-risk group, vaccinations are offered free of charge. Screening is also carried out when an unregistered sex worker is arrested by the police. Since 2002, couples who appeal for marriage are asked whether they have hepatitis B infection, and counselling is provided, but laboratory analysis is carried out only among the ones who meet the definition of high risk as presented above. Vaccinations are offered to people testing negative. Antenatal screening for HBsAg among pregnant women is not mandatory. Condom use is promoted as a preventive strategy. In Turkey, condoms are freely available at the primary level of care. Advertisements on visual and written media are used for raising awareness about prevention measures.

The aim of this study was to evaluate the impact of the above prevention and control strategies on acute hepatitis B notification rates in Turkey. The main goal was to assess the trend in acute hepatitis B notifications from 1990 to 2012, in order to address future prevention and control activities.

Methods

In this study, data obtained from the National Surveillance System (NSS) were used for evaluating acute hepatitis B notification rates. In Turkey, acute hepatitis B has been notifiable since 1990, and data were collected on a monthly basis by sex, age and province. However, a national guideline encompassing standard case definitions was not in use at that time. In 2004, the Turkish Ministry of Health updated the NSS and introduced standard case definitions for each notifiable disease. According to the newly launched definitions, patients compatible with the clinical picture and positive for anti-HBc IgM and/or HBsAg, were identified as acute hepatitis B cases [17]. Notification was restricted to acute cases. Practically, the newly launched case definition for acute hepatitis B did not differ from the criteria used for acute infections before 2004 in clinical practice. But this was the first time a standard case definition was adopted and circulated to all healthcare institutions throughout the country. Training programmes for physicians were implemented, introducing the case definitions and also emphasising the importance of surveillance.

Notification rates were calculated per 100,000 population. Age groups were defined as 0, 1–4, 5–9, 10–14 and ≥15 years. For calculating regional rates, the Nomenclature of Territorial Units for Statistics (NUTS) was used and provinces were categorised in 12 territorial units [18].

In Turkey, healthcare providers report the number of vaccinated children on a monthly basis to the Ministry of Health through the district and provincial health authorities. Reporting has been carried out electronically since 2011. Hepatitis B vaccination coverage refers to the percentage of fully vaccinated children reaching their first birthday. An infant that has received three doses of hepatitis B vaccine is defined as fully vaccinated. In this study, vaccine coverage data were obtained from the Ministry of Health.

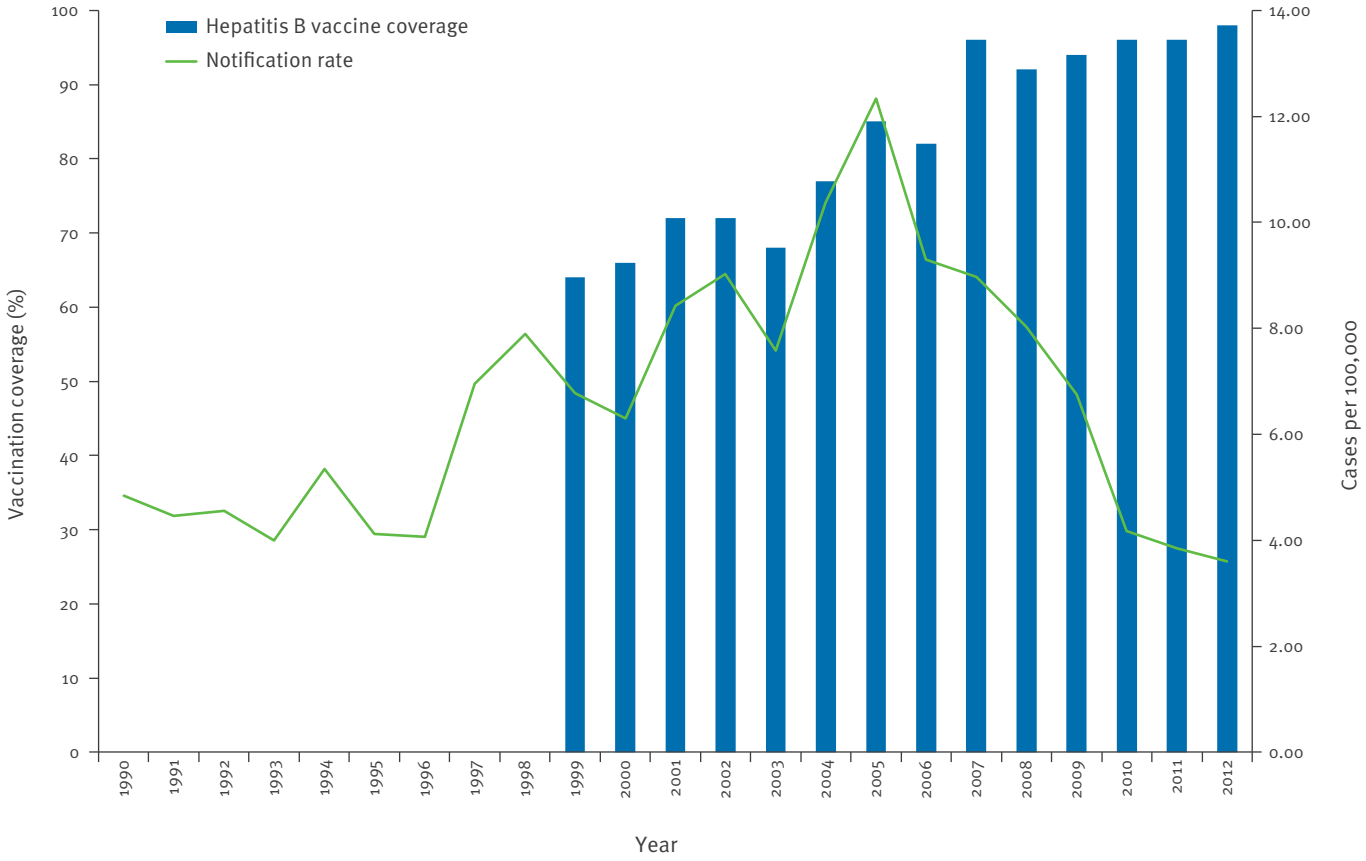
Results

Acute hepatitis B notification rates between 1990 and 2012 are presented in Figure 1. In 1990, the notification rate was 4.8 per 100,000 population. Rates showed an increasing trend and reached 12.3 per 100,000 in 2005. After 2005, there was a steady decline, and the rates in 2011 and 2012 dropped to 3.9 and 3.6 per 100,000, respectively (Figure 1). Vaccine coverage rates between 1999 and 2012 are also presented in Figure 1. In 1999, 64% of infants had been vaccinated with three doses of hepatitis B antigen. Coverage showed an increasing trend and rates above 90% were maintained after 2006 (Figure 1).

Notification rates by age groups are presented in Figure 2. Notification rates in 1997 for children aged <1 year, 1–4 years, 5–9 years and 10–14 years were 8.19, 5.21, 9.54 and 8.74 per 100,000, respectively. Rates for children under the age of 15 years showed a decreasing trend until 2004. In 2001 and 2005 there were small peaks among those younger than 15 years. However, after 2005 a steady decline was observed in all age groups younger than 15 years. The notification rates

Figure 1

Notification rates for acute hepatitis B (1990–2012) and percentage of infants vaccinated with three doses of hepatitis B virus antigen (1999–2012), Turkey*



in 2012 for the 1–4, 5–9 and 10–14 year-olds were 1.8, 0.2, 0.5 and 0.9 per 100,000, respectively.

Since infant vaccination started in 1998, notification rates for the under five years-old in 2002 and 2003 represent the first results for age groups that received vaccination.

The notification rate for those 15 years and older was 6.45 per 100,000 in 1997. Unlike the younger population, rates for this age group showed an increasing trend until 2005 and declined thereafter. The rates in 2005 and 2012 were 15.32 and 4.6 per 100,000, respectively.

Notification rates by age and sex for 2012 are presented in Figure 3. Notification rates for males and females in 2012 were 4.6 and 3.6 per 100,000, respectively. The rates were higher among male than among female infants for 2012, data from previous years showed similar rates (data not shown). Rates were slightly higher among boys during childhood after the first year. Men older than 19 years had higher rates than women. The highest rate difference between men and women was observed in the age group of 30–44 year-olds. Among this age group, the rate difference was 3.3 per 100,000 in 2012.

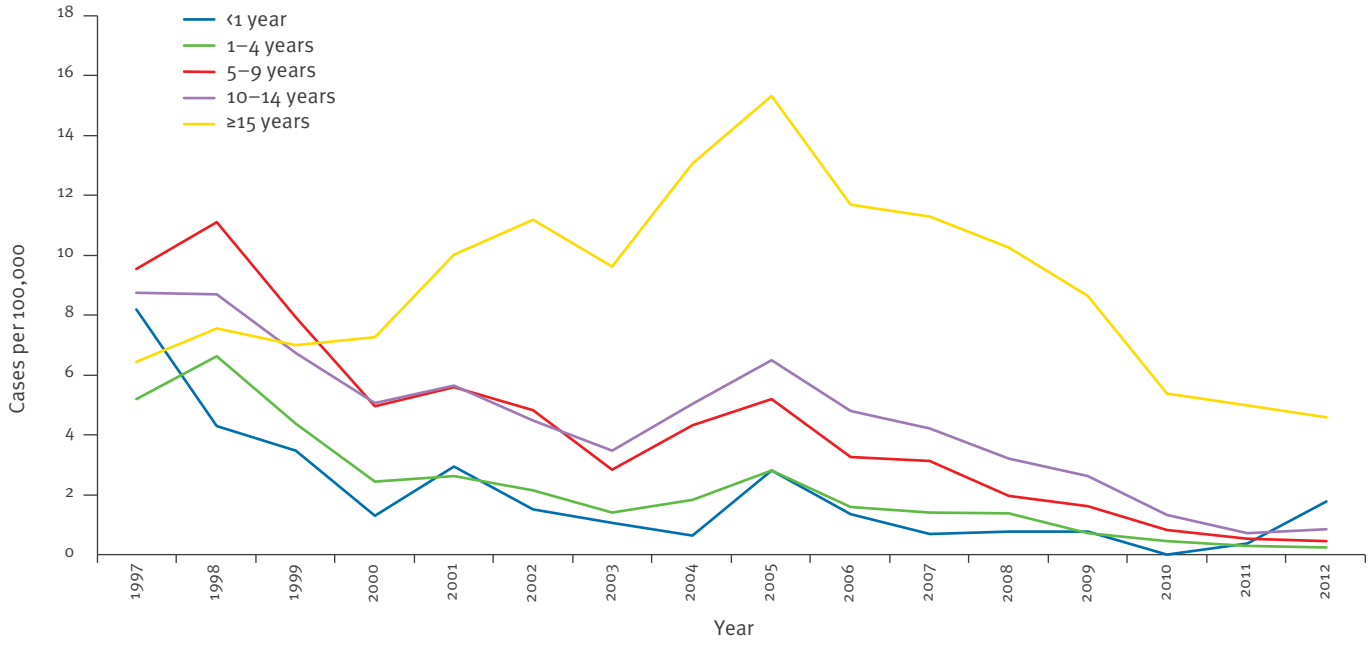
Notification rates are also analysed by geographical region (Figure 4). Highest rates were observed in Istanbul, west Marmara, northern regions and middle Anatolia. Southern regions had lower rates. Eastern Anatolia showed exceptionally low notification rates. Vaccination rates were similar throughout the country, but lowest rates were observed in the eastern regions.

Discussion

Notification rates of acute hepatitis B showed a decreasing trend among those younger than 15 years between 1997 and 2004. The most dramatic decline was observed among children under the age of five years, highlighting the benefits of vaccination which had been introduced in 1998. However, in 2001 and 2005, the downward trend changed and notification rates peaked among children under 15 years of age. The trend change in 2005 could be related to the introduction of the new notification system. In 2004 with the change of the Communicable Disease Notification System, a standard case definition was adopted for acute hepatitis B infection [19,20]. Although the newly launched criteria were not different from those used in daily practice before, revisions may have created awareness among health personnel and led to an increase in notification rates. After 2005 and until

Figure 2

Notification rates for acute hepatitis B by age group, Turkey, 1997–2012



2012, the rates have been declining steadily among all age groups under 15 years.

The first infant cohort was vaccinated in 1998 as part of the national immunisation programme. This group reached the age of five in 2003 explaining the decrease in the rates for 5–9 year-olds after 2003. Children younger than 15 years had been vaccinated by 2007 through catch-up activities, therefore the decrease after 2007 for children aged 10–15 years was also expected. However, not all the decline can be explained by vaccination activities. Epidemiological studies in Turkey show that HBsAg positivity is more prevalent among socioeconomically disadvantaged groups, and that horizontal transmission is the main route of transmission [4,9,10,12,14-16,21]. In a study carried out in one of the hospitals in Turkey during 2001–05, it was determined that HBsAg carrier rate was higher among fathers than among mothers. However, in the present study, it was determined that the children of mother index cases had higher rates of HBsAg compared with the children of father index cases. So in intra-familiar transmission, mother-to-child has been suggested as the main route. Since mothers mostly are not working and spend longer time with their children, their risk of transmitting the virus is higher compared to fathers. [16]. Socioeconomic development, leading to improved living conditions, less crowded families, improved sanitation and hygiene practices could have interrupted intra-familiar transmission and contributed to the decreasing trends [22-25]. A study in Italy showed that the decrease in acute hepatitis B was more apparent before the introduction of the mass immunisation. The authors concluded that the improved socioeconomic

Figure 3

Notification rates for acute hepatitis B by sex and age group, Turkey, 2012

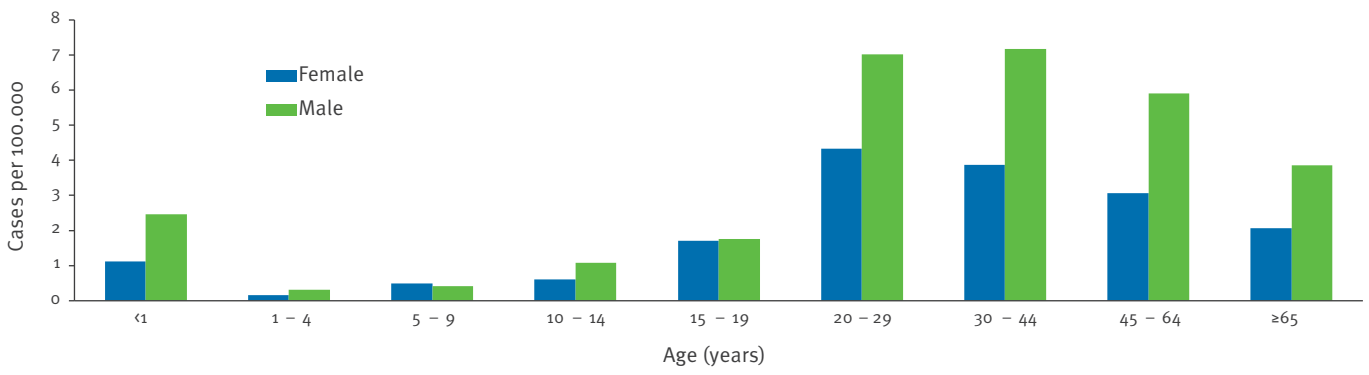
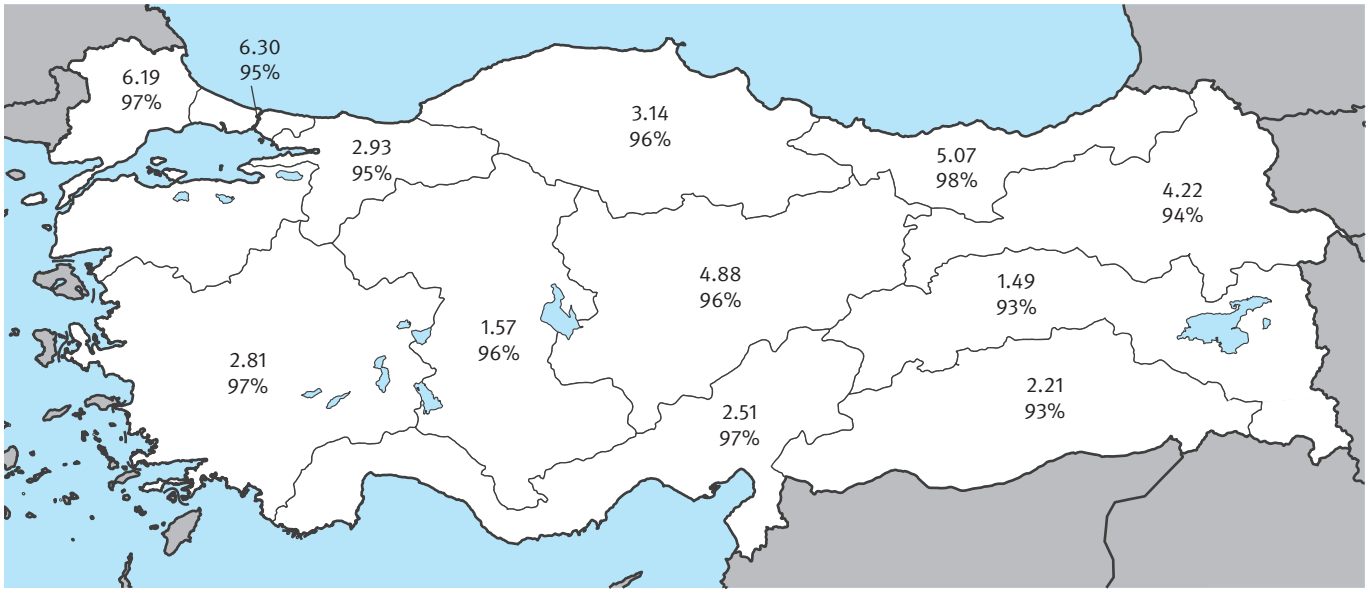


Figure 4

Notification rates for acute hepatitis B cases per 100,000 and percentage of infants vaccinated with three doses of hepatitis B virus antigen, by region, Turkey, 2012



Source: Kartenwerkstatt; http://commons.wikimedia.org

and sanitary conditions in the country had resulted in declining rates [22].

The notification rates for those 15 years and older followed an upward trend until 2005 and a decrease thereafter. Introduction of standard case definitions in 2004 and prevention activities among adults may have had an impact, but are not sufficient to explain the trend change after 2005. There is not any information on the uptake of vaccination outside the national immunisation programme. Still, the continuing downward trend after 2005 suggests that there is a true reduction in hepatitis B infections also among this age group.

Adults still had relatively higher rates of hepatitis B seroprevalence compared with children, highlighting the need to strengthen vaccination services targeting adults. In Turkey, hepatitis B vaccines are provided free of charge to individuals at high-risk for contracting the virus. It is therefore important to assess individuals at every opportunity at consultations in primary care and to offer vaccination for high-risk groups. It is important to remember that both patients and healthcare providers can be reluctant to report high-risk sexual practices, particularly in traditional societies. Information should therefore be provided about the risk factors for contracting hepatitis B infection and benefits of vaccination [26].

Data stratified by sex indicated that notification rates were comparable until adulthood. From the age of 20 years, however, rate differences between men and women increased. In the age group 30–44 years, the rate difference was 3.3 per 100,000. Seroepidemiological studies carried out in different parts of Turkey among adults also show higher rates of HBsAg positivity among men [5,9,21,27,28]. Sex differences suggest a higher rate of exposure to risk factors among men. Unfortunately in Turkey, routes of transmission are not reported for notified cases, but we can consider several reasons for men to predominantly contract the infection. High-risk behaviours such as having multiple sexual partners, male homosexual contact, using intravenous drugs, or sharing contaminated blades in barber shops may be more prevalent among men [6,29]. High-risk groups, particularly males, should be asked about potential exposure and offered vaccination at every opportunity.

Notification rates differed by geographical region, with the highest rates identified in Istanbul, western Marmara, the Black Sea and middle Anatolia. We need to be cautious in comparing these rates because access to healthcare, diagnostic capacity and notification rates may vary widely. Seroepidemiological studies show that residents of eastern, particularly south-eastern, Anatolia have higher rates of HBsAg positivity compared to the other regions [6,10,11]. Also the meta-analysis carried out by Toy et al. which evaluated studies published between 1999 and 2009, identified the highest rates in the eastern parts of Turkey [5]. Our results for south-eastern Anatolia could therefore be an underestimation and may be related to low access to healthcare, underdiagnosis and/or notification practices. Eastern parts are the least developed regions in Turkey. So we expect there a higher rate of underestimation than in the other regions. Efforts

should be made to understand the regional differences and eliminate their causes.

In 2008 and 2012, notification rates for acute hepatitis B in Turkey were 8.0 and 3.6 per 100,000, respectively. In Europe (among 27 European Union Member States and three European Economic Area countries), the notification rate of acute hepatitis B was 0.8 per 100,000 in 2010 [30]. Among the countries reporting acute cases, the Czech Republic (2.3 per 100,000), Romania (2.3 per 100,000) and Lithuania (2.1 per 100,000) had the highest notification rates [30]. The rates notified from Turkey were higher than in other European countries, although direct comparison between countries is not possible, due to differences in surveillance systems. It is hard to predict the level of underestimation and project the actual rates. However, a study conducted in one Turkish city in 2003 provides a clue on the rate of underestimation: Durusoy and Karababa compared data obtained from serology laboratories with the notifications received by the Provincial Health Directorate in order to understand the completeness of acute hepatitis B notifications in 2003 in Izmir, the third largest city in Turkey located in the west near the Aegean coast. At that time, the notification rate of acute hepatitis B in Izmir was 6.4 per 100,000. Yet by capture–recapture analyses, the authors calculated the notification rate as 52.2 per 100,000 (95% confidence interval: 39.9–64.5 per 100,000) [31].

The reported rates therefore suggest an underestimation. However, secular trends indicate that the rates are declining. With the available data, it is not possible to determine the quantitative impact of each preventive measure on notification rates. Although it is possible to assume that all measures had interacted synergistically, the trend among the younger age groups highlighted in particular the importance of universal vaccination and catch-up strategies. The impact of infant and school vaccination on acute hepatitis B notification rates had been demonstrated in a number of studies [23,32-34]. Still, vaccination can only partly explain the decline in hepatitis B infections among children. Since horizontal transmission is an important route particularly among groups with low socioeconomic status, improved living conditions, interrupting the horizontal transmission, may have contributed to the downward trend.

Conclusion

Secular trends reveal that the notification of acute hepatitis B is decreasing in all age groups in Turkey. High vaccination coverage and catch-up strategies had a positive impact among young age groups. Although a decreasing trend was achieved for adults after 2005, these rates remain high and demand strengthened prevention measures targeting adults, particularly men.

*Erratum:

The correct illustration for Figure 1 was uploaded on 25 November 2013.

References

1. World Health Organization (WHO). Hepatitis B. Fact Sheet 204. Geneva: WHO; 2000. Available from: http://who.int/inf-fs/en/fact204.html
2. Hepatitis B vaccines. Wkly Epidemiol Rec. 2004;79(28):255-63. PMid:15344666.
3. The Global Alliance for Vaccines and Immunizations (GAVI). Hepatitis B Fact Sheet. Geneva: GAVI; 2005.
4. Değertekin H, Güneş G. Horizontal transmission of hepatitis B virus in Turkey. Public Health. 2008;122(12):1315-7. http://dx.doi.org/10.1016/j.puhe.2008.04.010 PMid:18752817
5. Toy M, Önder FO, Wörmann T, Bozdayi AM, Schalm SW, Borsboom GJ, et al. Age- and region-specific hepatitis B prevalence in Turkey estimated using generalized linear mixed models: a systematic review. BMC Infect Dis. 2011;11:337. http://dx.doi.org/10.1186/1471-2334-11-337 PMid:22151620 PMCid:PMC3262158
6. Mehmet D, Meliksah E, Serif Y, Gunay S, Tuncer O, Zeynep S. Prevalence of hepatitis B infection in the southeastern region of Turkey: comparison of risk factors for HBV infection in rural and urban areas. Jpn J Infect Dis. 2005;58(1):15-9. PMid:15728984
7. Yildirim B, Barut S, Bulut Y, Yenişehirli G, Ozdemir M, Cetin I, et al. Seroprevalence of hepatitis B and C viruses in the province of Tokat in the Black Sea region of Turkey: A population-based study. Turk J Gastroenterol. 2009;20(1):27-30. PMid:19330732
8. Karabay O, Serin E, Tamer A, Gökdoğan F, Alpteker H, Ozcan A, et al. Hepatitis B carriage and Brucella seroprevalence in urban and rural areas of Bolu province of Turkey: a prospective epidemiologic study. Turk J Gastroenterol. 2004;15(1):11-3. PMid:15264115
9. Akcam FZ, Uskun E, Avsar K, Songur Y. Hepatitis B virus and hepatitis C virus seroprevalence in rural areas of the southwestern region of Turkey. Int J Infect Dis. 2009;13(2):274-84. http://dx.doi.org/10.1016/j.ijid.2008.07.005 PMid:18945630
10. Değertekin H, Tuzcu A, Yalçin K. Horizontal transmission of HBV infection among students in Turkey. Public Health. 2000;114(5):411-2. PMid:11035467
11. Kanra G, Tezcan S, Badur S, Turkish National Study Team. Hepatitis B and measles seroprevalence among Turkish children. Turk J Pediatr. 2005;47(2):105-10. PMid:16052847
12. Otkun M, Erdogan MS, Tatman-Otkun M, Akata F. Exposure time to hepatitis B virus and associated risk factors among children in Edirne, Turkey. Epidemiol Infect. 2005;133(3):509-16. http://dx.doi.org/10.1017/S0950268805003675 PMid:15962558 PMCid:PMC2870275
13. Badur S. Hepatit B infeksiyonları: Epidemiyoloji ve Aşı [Hepatitis B Infections: Epidemiology and Vaccine]. Klinik Gelişim. 2005;18(3):32-43.Turkish.
14. Ertekin V, Selimoğlu MA, Altinkaynak S. Sero-epidemiology of hepatitis B infection in an urban paediatric population in Turkey. Public Health. 2003;117(1):49-53. http://dx.doi.org/10.1016/S0033-3506(02)00018-5
15. Doganci T, Uysal G, Kir T, Bakirtas A, Kuyucu N, Doganci L. Horizontal transmission of hepatitis B virus in children with chronic hepatitis B. World J Gastroenterol. 2005;11(3):418-20. PMid:15637758
16. Ucmak H, Kokoglu OF, Celik M, Ergun UGO. Intra-familial spread of hepatitis B virus infection in eastern Turkey. Epidemiol Infect. 2007;135(8):1338–43. http://dx.doi.org/10.1017/S0950268807008011 PMid:17313693 PMCid:PMC2870700
17. General Directorate for Primary Health Care. Bulaşıcı Hastalıkların İhbarı ve Bildirim Sistemi: Standart Tanı, Sürveyans ve Bildirim Sistemi. [Standard Diagnosis, Surveillance and Laboratory Guideline for Communicable Diseases' Notification and Reporting System]. Ankara: Turkish Ministry of Health; 2004. Turkish.
18. Classification Sever. Ankara: TUIK Turkish Statistical Institute. [Accessed: 1 Sep 2012] Available from: http://

tuikapp.tuik.gov.tr/DIESS/SiniflamaSurumDetayAction.do?surumId=164&turId=7&turAdi= 5. Geographical Classifications

19. Bulaşıcı Hastalıkların Bildirim Sistemi Yönergesi. 24.02.2004 tarih ve 1534 sayılı [Communicable disease notification system directive. No. 1534]. Ankara: Ministry of Health; 24 Feb 2004. Turkish. Available from: http://www.saglik.gov.tr/TR/belge/1-4005/bulasici-hastaliklarin-ihbari-ve-bildirim-sistemi-yoner-.html
20. Bulaşıcı Hastalıkların İhbarı ve Bildirim Sistemi Genelgesi 22.10.2004 tarih ve 129 sayılı [Communicable Disease Notification System Circular. No. 129]. Ankara: Ministry of Health; 22 Oct 2004. Turkish. Available from: https://www.google.com.tr/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CCsQFjAA&url=http%3A%2F%2Fwww.saglik.gov.tr%2FASHGM%2Fdosya%2F1-12244%2Fh%2Fbulasicihbargenelge.doc&ei=kbmIUqmtE8_Kswb454DQCg&usg=AFQjCNE3WzQXP5QY9WK6g_4OBwZTboBWjg
21. Erden S, Büyüköztürk S, Calangu S, Yilmaz G, Palanduz S, Badur S. A study of serological markers of hepatitis B and C viruses in Istanbul, Turkey. Med Princ Pract. 2003;12(3):184-8. http://dx.doi.org/10.1159/000070757 PMid:12766338
22. Stroffolini T, Mele A, Tosti ME, Gallo G, Balocchini E, Ragni P, et al. The impact of the hepatitis B mass immunisation campaign on the notification and risk factors of acute hepatitis B in Italy. J Hepatol. 2000;33(6):980-5. http://dx.doi.org/10.1016/S0168-8278(00)80132-4
23. Mele A, Tosti ME, Mariano A, Pizzuti R, Ferro A, Borrini B, et al. Acute hepatitis B 14 years after the implementation of universal vaccination in Italy: areas of improvement and emerging challenges. Clin Infect Dis. 2008;46(6):868-75. http://dx.doi.org/10.1086/528687 PMid:18269332
24. La Torre G, Nicolotti N, de Waure C, Chiaradia G, Specchia ML, Mannocci A, et al. An assessment of the effect of hepatitis B vaccine in decreasing the amount of hepatitis B disease in Italy. Virol J. 2008;5:84. http://dx.doi.org/10.1186/1743-422X-5-84 PMid:18652653 PMCid:PMC2517063
25. D'Argenio P, Esposito D, Mele A, Ortolani G, Adamo B, Rapicetta M, et al. Decline in the exposure to hepatitis A and B infections in children in Naples, Italy. Public Health. 1989;103(5):385-9. http://dx.doi.org/10.1016/S0033-3506(89)80009-5
26. Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep. 2006;55(RR-16):1-33. PMid:17159833
27. Demirtürk N, Demirdal T, Toprak D, Altindis M, Aktepe OC. Hepatitis B and C virus in West-Central Turkey: seroprevalence in healthy individuals admitted to a university hospital for routine health checks. Turk J Gastroenterol. 2006;17(4):267-72. PMid:17205404
28. Emiroglu HH, Altunay H, Oguz S. Prevalence of hepatitis B virus carriers among soldiers and civilians in Turkey. J Clin Gastroenterol. 2004;38(7):614-5. http://dx.doi.org/10.1097/00004836-200408000-00018 PMid:15232371
29. Khan F, Shams S, Qureshi ID, Israr M, Khan H, Sarwar MT, et al. Hepatitis B virus infection among different sex and age groups in Pakistani Punjab. Virol J. 2011;8:225 http://dx.doi.org/10.1186/1743-422X-8-225 PMid:21569532 PMCid:PMC3118204
30. European Centre for Disease Prevention and Control (ECDC). Annual Epidemiological Report 2012. Reporting on 2010 surveillance data and 2011 epidemic intelligence data. Stockholm: ECDC; 2013. Available from: http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?ID=753&List=4f55ad51-4aed-4d32-b960-af70113dbb90
31. Durusoy R, Karababa AO. Completeness of hepatitis, brucellosis, syphilis, measles and HIV/AIDS surveillance in Izmir, Turkey. BMC Public Health. 2010;10:71. http://dx.doi.org/10.1186/1471-2458-10-71 PMid:20158922 PMCid:PMC2834629
32. Pitigoi D, Rafila A, Pistol A, Arama V, Molagic V, Streinu-Cercel A. Trends in hepatitis B notification in Romania, 1989-2005. Euro Surveill. 2008;13(2):pii=8012. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=8012. PMid:18445385
33. Salleras L, Dominguez A, Bruguera M, Carde-osa N, Batalla J, Carmona G, et al. Dramatic decline in acute hepatitis B infection and disease notification rates among adolescents and young people after 12 years of a mass hepatitis B vaccination programme of pre-adolescents in the schools of Catalonia (Spain). Vaccine. 2005;23(17-18):2181-4. http://dx.doi.org/10.1016/j.vaccine.2005.01.068 PMid:15755591
34. Hong Z, Smart G, Zaniewski G, Wu H, Wu J, Goedhuis N, et al. Epidemiological study of hepatitis B virus infection in Manitoba, Canada, 1992-2003. Eur J ClinMicrobiol Infect Dis. 2005;24(7):464-70. http://dx.doi.org/10.1007/s10096-005-1350-6 PMid:15959814

Hepatitis B prevalence in Denmark – an estimate based on nationwide registers and a national screening programme, as on 31 December 2007

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Citation style for this article:
Hansen N, Hay G, Cowan S, Jepsen P, Bygum Krarup H, Obel N, Weis N, Brehm Christensen P. Hepatitis B prevalence in Denmark – an estimate based on nationwide registers and a national screening programme, as on 31 December 2007. Euro Surveill. 2013;18(47):pii=20637. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20637

Article submitted on 20 October 2012 / published on 21 November 2013

The prevalence of chronic hepatitis B virus (HBV) infection in Denmark is not clear. The primary aim of this study was to estimate the prevalence of chronic HBV infection in Denmark. The capture–recapture method was used to estimate the total population diagnosed with chronic HBV infection in Denmark using four nationwide registers. The population with undiagnosed chronic HBV infection was estimated by incorporating data from a two-year nationwide HBsAg screening programme in pregnant women. We identified 4,466 individuals with chronic HBV infection in the four registers until the end of 2007, and the capture–recapture estimate of the total population diagnosed with chronic hepatitis B was 7,112 (95% confidence interval (CI): 6,953–10,747). Only 17% of the identified patients attended recommended clinical care according to national guidelines. Including undiagnosed patients, the current population alive with HBV infection was 10,668 (95% CI: 10,224–16,164), corresponding to a prevalence of 0.24% (95% CI: 0.23–0.37%) in the Danish population older than 15 years. The estimated prevalence of chronic HBV infection among adults in Denmark was lower than reported from other northern European countries. Only half of the infected population had been diagnosed, and a minority attended specialised clinical care.

Background

Hepatitis B virus (HBV) infection is a major global health problem. More than 350 million people are chronically infected with HBV, causing 500,000 to 1,200,000 deaths annually [1,2]. The reported incidence of acute hepatitis B in Denmark has been declining for the last two decades to 0.4 per 100,000 per year; in contrast, the incidence of diagnosed chronic hepatitis B has increased to 5.2 per 100,000 per year [3]. Universal childhood vaccination is not a part of the Danish hepatitis B prevention programme, as this is targeted at high prevalence groups. However, since November 2005, all pregnant women have been screened for HBV. People who inject drugs (PWID) are offered a HBV test and vaccination free of charge, and programmes for this have been implemented in prisons and drug treatment centres. Other high prevalence groups (migrants from HBV-endemic countries, men who have sex with men (MSM) etc.) are recommended for HBV testing and vaccination, but the coverage of this intervention is unknown [4,5].

The exact number of persons with chronic infection in Denmark is unknown as a national seroprevalence survey has never been performed. Notification of chronic HBV infection to the national register of notifiable diseases has been mandatory since 2000, but reporting rates are low [6]. The National Board of Health estimated the prevalence of chronic hepatitis B in Denmark at 0.28% (15,000 patients) in 2002 [7]. Based on the national screening of pregnant women for hepatitis B from 2005 to 2007, the prevalence of hepatitis B was estimated at 0.2 to 0.3% (13,500 persons) in 2007 [8].

The primary aim of this study was to estimate the prevalence of chronic hepatitis B (both diagnosed and undiagnosed) in Denmark. A secondary aim was to estimate the coverage of diagnosed patients by national registers.

Methods

All persons with permanent residence in Denmark are assigned a 10-digit personal identification number.

This number was used to identify patients with a diagnosis of chronic HBV infection in the four different nationwide registers. Persons without a valid personal identification number were excluded from the analysis (mean: 1% in source registers).

Registers

Laboratory register (DANVIR)

This is a research database that includes patients tested for hepatitis B and C in 14 of the 17 Danish laboratories performing HBV and hepatitis C virus (HCV) testing [9]. This database included data on 280,643 persons tested for hepatitis B as of 31 December 2007. Samples reactive for HBsAg were retested with a confirmatory HBsAg assay, and only confirmed positives were included in this analysis. All tests were commercial kits approved by the health authorities, but each laboratory chose its own supplier and thus the test kit used varied between laboratories and over time in the individual laboratories.

National patient register

This national register was established in 1977 and records all discharge diagnoses from hospitals in Denmark according to ICD-8 and, from 1994, ICD-10 codes. Since 1995, the register has also included diagnoses from hospital outpatient visits. From this register we extracted all individuals registered with chronic HBV infection with or without delta agent (ICD-10 diagnosis codes DB18.0 and DB18.1).

The Danish database for chronic hepatitis B and C (DANHEP)

This nationwide clinical database was established in 2002. It includes patients older than 15 years with chronic viral hepatitis attending medical care in one of the 14 specialised medical units treating patients with viral hepatitis in Denmark. From this database we included all patients registered with chronic HBV infection.

Communicable diseases register

This national register of notifiable diseases has been recording acute hepatitis B since 1980 and chronic hepatitis B since 2000. Although reporting is mandatory for any clinician diagnosing a patient with hepatitis B infection, reporting rates are low [6,10]. We included all patients reported with chronic HBV infection. The register has been estimated to cover 35–40% of all diagnosed individuals [6,10].

The civil register

This register was established in 1968 and stores information on vital status and residency as well as immigration and emigration for all Danish residents. From this register we extracted vital status and residency data.

Definition of chronic HBV infection

Classically, chronic hepatitis B infection is defined as two positive HBsAg tests measured at least six months apart. Anti-HBc IgM is positive in the early state of infection and becomes negative after months of infection [11]. Thus patients who are HBsAg-positive and anti-HBc IgM negative are likely to be chronically infected.

For DANHEP, the national patient register, and the register for communicable diseases, the case definition was two positive HBsAg tests six month apart, as specified by the National Board of Health [7]. This definition could not be used for the laboratory register, as many patients had not been tested twice. In addition, many HBsAg-positive patients with only one test had not been tested for anti-HBc IgM. As the vast majority of patients reported with acute hepatitis B are native Danes, we included place of origin as a criterion in the case definitions used for the laboratory register:

1. Definite chronic hepatitis B: two samples at least six months apart positive for HBsAg;
2. Definite or likely chronic hepatitis B: As in 1., or one sample positive for HBsAg and negative for anti-HBc IgM;
3. Definite or possible chronic hepatitis B: As in 1. or 2., or one sample positive for HBsAg, anti-HBc IgM not done, and the patient born in a country of high endemicity.

Estimates were calculated with all three case definitions, but detailed results are only presented for the estimates based on definition 3.

Study population

We included all cases identified with chronic HBV infection diagnosed before 31 December 2007 in any of the registers described above. As the laboratory register had three definitions, three different study populations were extracted. We linked these populations with data from the civil register, extracting vital status, residency, immigration and emigration information. We excluded patients who were younger than 16 years, had no assigned address, or were reported dead, missing or emigrated by 31 December 2007.

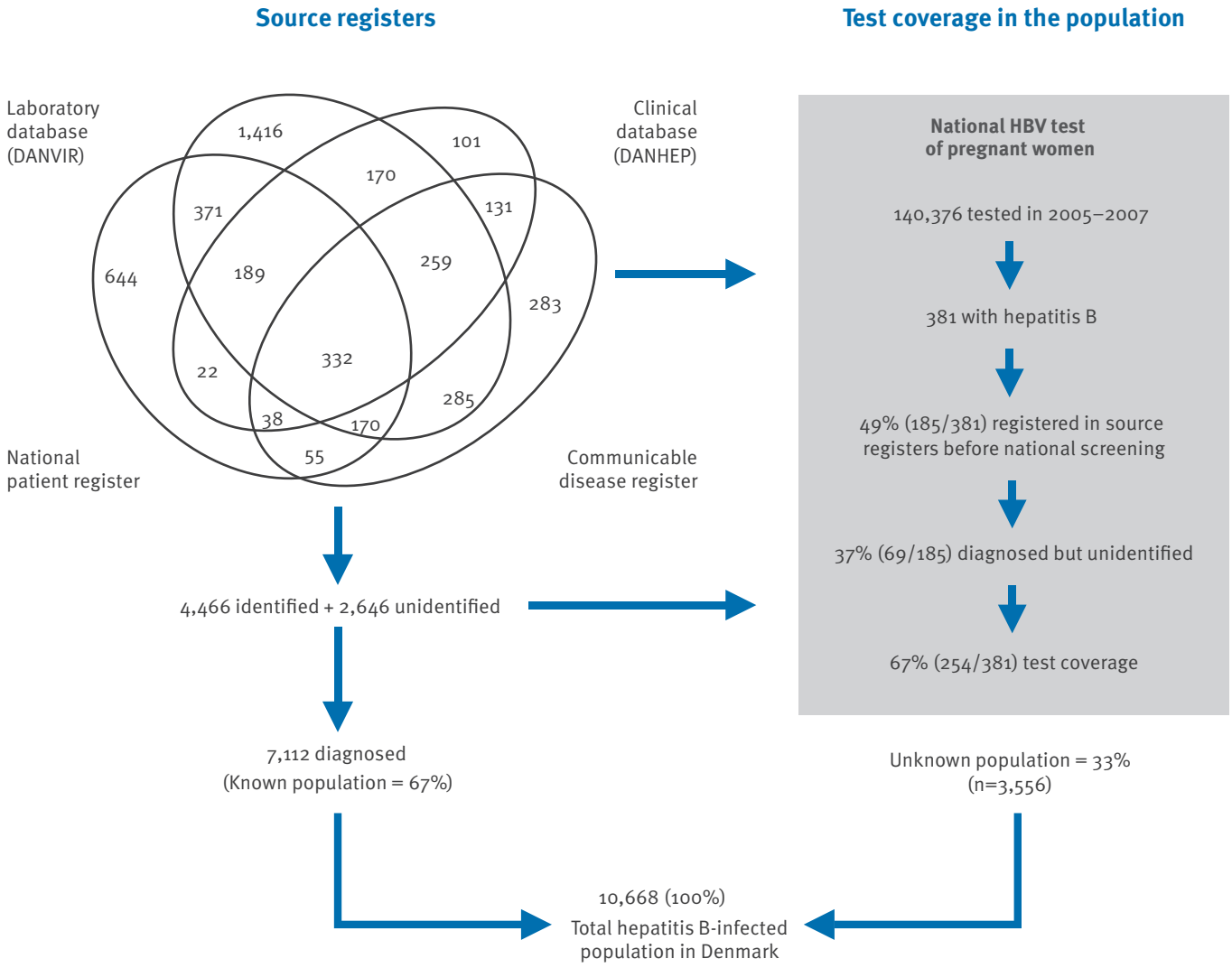
Statistical analysis

We estimated the prevalence of chronic HBV infection in the Danish population in the following two steps:

Firstly, the population with diagnosed chronic hepatitis B was calculated by capture–recapture analysis of an overlap table of the four source registers stratified by age (three groups), sex, geographical region (five) and calendar time (first diagnosis before versus after year 2000) [12,13]. The calculation was based on log-linear modelling using the statistical programme GLIM 4 [14,15]. The model contained 60 strata, and in total 113 different models, including all possible two-way and three-way interactions, were fitted to the overlap data for each individual stratum. The Akaike

Figure

Capture–recapture estimate of patients diagnosed with hepatitis B and total population estimate end 2007 based on hepatitis B virus test among pregnant women 2005–2007, Denmark (n=10,668)



HBV: hepatitis B virus.

information criterion was used to find the best fitting model, but we also calculated a weighted estimate for each overlap pattern. This weighted estimate was averaged across all fitted models using the Schwartz criterion as a weight. Some of the 113 models produced unrealistically high estimates; therefore, if an estimate was more than five times the observed number, then a weight of zero was attached to that estimate in order to decrease the influence of what we considered to be unrealistic estimates. If the best model suggested by the Akaike information criterion resulted in an estimate that differed markedly from the weighted estimate, we used the Schwartz criterion to obtain the best fitting model. When the choice between the Akaike and Schwartz criterion was not clear, we chose the model that gave an estimate closest to the ratio of known to estimated number of infected patients found in other strata. The 95% confidence intervals (CI) for the total estimate were calculated by bootstrap analysis of 1,000 samples [13,15].

Secondly, the proportion of patients with chronic hepatitis B who had not been diagnosed (never tested) was calculated from a complete two-year national screening programme for HBsAg among pregnant women performed from 2005 to 2007 [8]. We identified the overlap between the four source registers and women identified in the screening programme. The proportion of all HBsAg-positive women identified in the screening programme who were present in one or more of the source registers, gave a direct estimate of the diagnosed fraction of the population with hepatitis B (as well as a direct estimate of the prevalence of hepatitis B among pregnant women). We used the national

estimate of the 'hidden proportion' (e.g. diagnosed with hepatitis B but not present in any of the four source registers) to calculate the total number of pregnant women diagnosed with hepatitis B. Assuming the same proportion of diagnosed HBV infection outside the national screening programme (e.g. among drug users, MSM etc.) we calculated the total prevalence of HBV in Denmark (Figure). A further bootstrap analysis, which also included a binomial distribution to account for the coverage rate, was used to obtain a 95% CI of the total prevalence.

Statistical analysis was performed using SPSS version 19 and GLIM 4. The study was approved by the Danish Data Protection Agency (J. 2008-41-2402).

Results

The four source registers identified 5,547 patients with chronic hepatitis B of whom 1,081 (19.5%) were excluded due to death, emigration, unknown address or age under 16 years. A total of 4,466 patients were included in the study. The 4,466 were identified as cases of possible chronic HBV infection in one or more of the four registers using definition 3 in the laboratory database ("definite or possible HBV infection") (Table 1).

Of the identified population, 72% (n=3,192) were registered in DANVIR, whereas the other registers identified 28–41% (1,242–1,821) (Table 1). Women accounted for around 50% of the population in all four registers. Three quarters (n=3,345) of those who were registered with HBV infection were younger than 40 years when first registered in any of the registers, and 69% (n=3,095) of cases were registered after the year 2000.

The estimated total population diagnosed with chronic HBV infection was 7,112 (95% CI: 6,953–10,747), corresponding to a prevalence of 0.16% (95% CI: 0.16%–0.24%) among Danish adults [16] (Table 2). This included a 'hidden' population of 2,646 (37%) individuals diagnosed with chronic HBV infection but not registered in any of the registers. The prevalence was a little higher among men than women and in most of the regions the prevalence was lowest in the group aged 16 to 25 years. Copenhagen represented 42% (n=2,996) of all diagnosed cases, and only 4% (n=313) came from the North Denmark region, corresponding to, respectively, 0.23% and 0.07% of the adult population. This is consistent with the regional distribution of immigrants in Denmark: in 2008, 48% of immigrants lived in the Copenhagen region and 6% in the North

Table 1

Persons identified with chronic hepatitis B according to four nationwide registers on 31 December 2007 (n=4,466)

	Laboratory database (DANVIR) register	Communicable diseases register	National patient register	Hepatitis database (DANHEP)	Total
Number	3,192	1,553	1,821	1,242	4,466
% of total	71.5	34.8	40.8	27.8	100.0
Male (%)	48.3	46.0	52.1	48.7	49.8
Age (%)					
<25 years	36.8	48.5	31.6	39.7	35.2
25–40 years	40.8	36.0	39.2	38.7	39.7
≥40 years	22.4	15.5	29.2	21.6	25.1
Region (%)					
North	5.7	3.7	5.1	10.3	5.6
Central	20.8	18.3	21.3	18.2	19.7
South	23.2	17.4	18.1	17.6	21.9
Zealand	6.5	10.2	8.5	6.3	8.2
Copenhagen	43.7	50.4	47.0	47.6	44.5
Year of inclusion (%)					
2000 or earlier	30.4	24.3	39.5	24.2	30.7
After 2000	69.6	75.7	60.5	75.8	69.3

Table 2

Capture–recapture estimate of patients with chronic hepatitis B alive on 31 December 2007, Denmark (n=7,112)

	North	Central	South	Zealand	Copenhagen	Total	Population prevalence %
Proportion of estimate for Denmark (%)	4	18	24	11	42	100	
Prevalence (%)	0.07	0.13	0.18	0.12	0.23	0.16	
Population of Denmark >15 years (x1,000)	465	993	959	658	1,321	4,396	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Age							
<25 years	88 (28)	386 (29)	495 (29)	206 (27)	841 (28)	2,016 (28)	0.35
25–40 years	147 (47)	440 (34)	658 (38)	304 (40)	1,230 (41)	2,779 (39)	0.25
≥40 years	78 (25)	486 (37)	581 (33)	247 (33)	925 (31)	2,317 (33)	0.08
Sex							
Male	154 (49)	781 (60)	978 (56)	373 (49)	1,626 (54)	3,912 (55)	0.18
Female	159 (51)	531 (40)	756 (44)	384 (51)	1,370 (46)	3,200 (45)	0.14
Entrance in register							
2000 or earlier	93 (30)	330 (25)	656 (38)	134 (18)	877 (29)	2,090 (29)	NA
After 2000	220 (70)	982 (75)	1,078 (62)	623 (82)	2,119 (71)	5,022 (71)	NA
Total	**313 (100)**	**1,312 (100)**	**1,734 (100)**	**757 (100)**	**2,996 (100)**	**7,112 (100)**	**0.16**

NA: not applicable.

Denmark region [17]. Among the 7,112 individuals with chronic HBV infection, 50% were registered in the laboratory register, 26% in the National patient register, 22% in the register of communicable diseases and 17% in the clinical register (DANHEP).

By the stricter case definitions we identified 3,675 patients diagnosed with definite chronic HBV infection (two HBsAg tests positive six months apart), and 4,003 patients diagnosed with definite or likely chronic HBV infection (one sample HBsAg positive and anti-HBc IgM negative). The corresponding estimates were respectively 6,121, and 6,815 diagnosed patients.

Estimation of the undiagnosed population with chronic hepatitis B infection

Of 140,376 pregnant women tested for HBsAg in Denmark in the years 2005 to 2007, 381 were identified with chronic hepatitis B, and of these, 185 were registered in one or more of the registers described above. Adjusting for 37% diagnosed but not present in the source registers, this corresponded to 66.6% (254/381) (95% CI: 62–71%) [12]. Assuming the same diagnostic coverage among patients with chronic HBV infection in the general population as in this group of pregnant women, the total national estimate was 10,668 (95% CI: 10,224–16,164), corresponding to a prevalence of 0.24% (95% CI: 0.23–0.37%) in the Danish population older than 15 years.

Discussion

In this large register-based study we estimated the adult population alive and diagnosed with chronic hepatitis B infection to be 0.16% in Denmark. Including undiagnosed cases, the estimated prevalence of chronic hepatitis B infection for persons aged 16 years or older on 31 December 2007 was 0.24%.

The majority of patients were diagnosed after the year 2000, and unexpectedly, we did not find an increasing prevalence with age. This probably reflects an increase in immigration, and an increased focus on the disease, as indicated by the fact that reporting of chronic HBV infection to the register of communicable diseases became mandatory in 2000, and antenatal screening was implemented in 2005. Most patients were younger than 40 years when first diagnosed with HBV infection. Studies performed 10 to 30 years ago have found that the population with chronic hepatitis B in Denmark primarily consists of immigrants from high endemic countries infected by vertical transmission, and immigrants are younger than the general Danish population [6,18]. The population of foreign origin has increased from 3% to 10% of the total Danish population during the last 30 years [17]. This also explains why the overall prevalence of HBV infection among pregnant women overall has increased from 0.11% in 1971 to 0.26% in 2007, while in the same period, the prevalence among pregnant native Danes fell from 0.11% to 0.01% [8,18]. In accordance with this, a Norwegian study found that chronic HBV infection was more likely to be diagnosed

among immigrants than native Norwegians, and more likely among 20 to 29 year-olds than among 50 to 59 year-olds [19].

It was disappointing to us that only 28% of the observed population (corresponding to 17% of the estimated population with the diagnosis) had attended an outpatient clinic that specialised in viral hepatitis (registered in the clinical register, DANHEP). In accordance with this, only one third of the observed cases were reported to the public health register, as previously reported [6,10]. This suggest that increased efforts will be necessary to assure that chronic hepatitis B patients receive the appropriate clinical care - as specified in current Danish guidelines [5]. This is important, as the treatment possibilities for hepatitis B have greatly improved in the last decade [20].

Our study has several limitations: capture–recapture analysis requires a closed population and the same case definition in each register used in the analysis [21]. Ideally there should be independency between the different registers, although any dependencies to some degree can be explained and accounted for using log-linear modelling. The case definition was assumed to be the same in the three clinical registers but expanded in the laboratory register, as 18% of HBsAg positives did not have a follow-up test registered to fulfil the classical definition of chronic hepatitis B. Patients who tested positive for anti-HBc IgM were excluded to avoid inclusion of patients with acute hepatitis B of whom more than 90% eventually clear the infection [11]. However, it is well known that patients with chronic hepatitis B may be intermittently anti-HBc IgM-positive [11]. In contrast, using the geographical definition (patients with only one HBsAg-positive sample and not tested for anti-HBc IgM) we would include patients of foreign origin with acute hepatitis B. This would underestimate the true number of infected individuals. In a sensitivity analysis among patients with definite chronic hepatitis B (two HBsAg six months apart), we found that 92% (1,225/1,337) of those tested were anti-HBc IgM-negative and 90% (1,874/2,083) were immigrants (for 1,592 patients no country of origin was registered). Among the pregnant women identified in the national screening programme 96% (341/355) were immigrants (for 26 of 381, country of origin was not available). By excluding patients with chronic HBV infection who were anti-HBc IgM-positive and chronically infected Danes with only one HBsAg positive sample, our capture–recapture estimate would become too large.

The issue of independency between the registers may only have been partially resolved. A patient from the clinical registers was more likely to be represented also in the laboratory register because being tested for hepatitis B is a prerequisite for entering any of the other three registers. Those registered in the clinical database (DANHEP) attended a specialised clinical unit that should report to the register for communicable diseases (mandatory since 2000), and those patients should also have a diagnosis of chronic hepatitis B in the national patient register. It is obvious in Table 1 that this was not always the case. We did adjust for interactions between the registers in the statistical model, but as appearance in one register increased the likelihood of appearing in another register, the estimate of the hidden population might still be too small. In addition, as our model did not produce stable estimates for several of the cells in the final table, we truncated these cell estimates at five times the observed number. The truncation due to instability of the model may have underestimated the true number of infected patients.

From the capture–recapture model, we were only able to estimate the diagnosed number of patients with chronic HBV infection, thereby missing the number of patients in the population who had never been tested. Therefore we estimated the test coverage in a national cohort of pregnant women and used this to estimate the prevalence in the adult population. Apart from immigrants, major populations with chronic hepatitis B in Denmark are PWID and MSM. It is very likely that these populations have lower test rates than pregnant women. For PWID, we have recently estimated the HCV test coverage rate to 54%, and we believe this to be comparable to their HBV test rate as these tests are usually performed simultaneously among drug users [9]. For MSM, we have not been able to find any data on test rate, but MSM have been targeted for HBV screening and vaccination for decades. However when compared to the estimated absolute size of these populations in Denmark and their estimated prevalence of HBsAg (497,000 immigrants: 2,7% HBsAg; 50,000,MSM: 1–3% HBsAg; 13,000 PWID: 2–4% HBsAg), a 10% change in test rate for MSM and PWID will add only 150 and 16 cases to the total estimate, indicating that our estimate is rather robust to variation in test rates in these groups. Calculating the total Danish population with chronic hepatitis B based on subpopulation sizes and prevalence of chronic hepatitis B resulted in a total of 16,000 persons (0.36% of the adult population), suggesting that our estimate of the diagnosed population (67%) may be too high. Private practitioners participating in the study on pregnant women reported that 58% of cases had been known before the survey, and using this proportion, our national estimate would rise to 12,626 [8]. Correspondingly, an estimate from the United States (US) reported only 35% diagnosed HBV patients [22].

We found that HBV was evenly distributed among men and women and prevalence of infection decreased with age. The majority of patients in our study were diagnosed before the age of 40 years. The cohort with the pregnant women was almost completely younger than 40 years; therefore our estimate of test coverage may not be valid in the older population. Our estimates corresponded to a prevalence of 0.53% for persons under 25 years-old, 0.39% for persons 25 to 39 years-old and 0.13% for persons 40 years and older. In particular,

we expect the test rate among male immigrants to be lower, as this group has less contact to the health care system than pregnant women. Our total estimate is sensitive to this because a 10% change in test rates represents 1,000–1,300 cases. This may also explain why our register-based estimate was 20% smaller than the estimate based solely on the screening programme of pregnant women (13,500 cases in Denmark) [8].

The even sex distribution and falling prevalence with age in our study results are different from most published studies where up to two thirds were men and prevalence increased with age. In Sweden, a national serosurvey performed in 1991 found only 0.06% infected, but increasing exposure with age (anti-HBc positives), 60% females, and no significant geographical variation [23]. In Germany, the prevalence of chronic hepatitis B was 0.6% in 1998, with a three times higher prevalence among males and exposure (anti-HBc positives) increasing with age [24]. In France (metropolitan areas), HBsAg prevalence was 0.65%, and males were five times more likely to be infected [25]. Finally, in the US from 1999 to 2008, the National Health and Nutrition Examination Survey (NHANES) survey reported an adult prevalence of 0.38%, with an odds ratio for males of 2.3 and a maximum at 50 to 59 years of age [24]. Thus our estimated prevalence was higher than the 1991 Swedish study but lower than the French and German screening programmes.

Conclusion

We estimated the prevalence of chronic hepatitis B in the adult population in Denmark to be 0.24%, confirming the low prevalence previously estimated. However, one third of the infected were undiagnosed, and the national registers showed low coverage, with only 17% of identified hepatitis B patient attending specialised clinical care. These data suggest that screening for hepatitis B should be improved and that Denmark is far from fulfilling the intention that all identified patients with chronic hepatitis B should attend appropriate specialist care. Our study is six years old, but unfortunately ongoing research suggests that this has not improved significantly since.

Acknowledgements

Peer Brehm Christensen received a grant from The Danish Agency for Science, Technology and Innovation (FSS 09–061687) for this study.

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References

4. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J ViralHepat. 2004;11(2):97-107. http://dx.doi.org/10.1046/j.1365-2893.2003.00487.x PMid:14996343
5. McMahon B. The natural history of chronic hepatitis B virus infection. Hepatology. 2009;49(5 Suppl):45-55. http://dx.doi.org/10.1002/hep.22898 PMid:19399792
6. Moelbak K. Smitsomme sygdomme 2011. [Infectious diseases 2011]. EPI-NYT. 2012;1. 4 Jan 2012. Danish. Available from: http://www.ssi.dk/Aktuelt/Nyhedsbreve/EPI-NYT/2012/Uge%201%20-%202012.aspx
7. National Board of Health. 2013 Vejledning om HIV (human immundefekt virus), hepatitis B og C virus. Forebyggelse af blodbåren smitte, diagnostik og håndtering i sundhedsvæsenet og på andre arbejdspladser. [2013 Guidance on HIV (human immunodeficiency virus), hepatitis B and C virus. Prevention of bloodborne infection, diagnostic and handling in the health system and other places of work]. Copenhagen: Sundhedsstyrelsen; 2013. Danish. Availabe from: http://www.sst.dk/publ/Publ2013/03mar/HIVogHepBogCvejl.pdf
8. Christensen PB, Clausen MR, Krarup H, Laursen AL, Schlichting P, Weis N. Treatment for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection - Danish national guidelines 2011. Dan Med J. 2012;59(6):C4465 PMid:22677253
9. Hansen N, Cowan S, Christensen PB, Weis N, DANHEP styregruppen. [Reporting chronic hepatitis B and C in Denmark.] UgeskrLaeger. 2008;170(18):1567-70. Danish. PMid:18454929
10. National Board of Health. Vejledning om forebyggelse mod viral hepatitis – Juni 2002. [Guidance on the prevention of viral hepatitis – June 2002]. Copenhagen: Sundhedsstyrelsen; 2002. Danish. Available from: http://www.sst.dk/publ/Publ2002/hepatitis/html/index.htm
11. Harder KM, Cowan S, Eriksen MB, Krarup HB, Christensen PB. Universal screening for hepatitis B among pregnant women led to 96% vaccination coverage among newborns of HBsAg positive mothers in Denmark. Vaccine. 2011;29(50):9303-7. http://dx.doi.org/10.1016/j.vaccine.2011.10.028 PMid:22019756
12. Christensen PB, Hay G, Jepsen P, Omland LH, Just SA, Krarup HB, et al. Hepatitis C prevalence in Denmark –an estimate based on mutable national registers. BMC Infect Dis. 2012;12:178. http://dx.doi.org/10.1186/1471-2334-12-178 PMid:22866925 PMCid:PMC3447638
13. Christensen PB, Krarup HB, Niesters HG, Norder H, Schaffalitzky de Muckadell OB, et al. Outbreak of Hepatitis B among injecting drug users in Denmark. J ClinVirol. 2001;22(1):133-41. http://dx.doi.org/10.1016/S1386-6532(01)00175-5
14. Liang TJ. Hepatitis B: The virus and disease. Hepatology 2009;49(5 Suppl):13-21. http://dx.doi.org/10.1002/hep.22881 PMid:19399811 PMCid:PMC2809016
15. European Monitoring Centre for Drugs and Drug addiction (EMCDDA). Methodological guidelines to estimate the prevalence of problem drug use on the local level. Lisbon: EMCDDA; 1999. Available from: http://www.emcdda.europa.eu/html.cfm/index58064EN.html
16. Hook EB, Regal RR. Capture-recapture methods in epidemioloy: methods and limitations. Epidemiol Rev. 1995;17(2):243-64. PMid:8654510
17. Schwarz G. Estimating the dimension of a model. Ann Statist. 1978;6(2):461-4. http://dx.doi.org/10.1214/aos/1176344136
18. Gemmell I, Millar T, Hay G. Capture-recapture estimates of problem drug use and the use of simulation based confidence intervals in a stratified analysis. J Epidemiol Community Health. 2004;58(9):758-65. http://dx.doi.org/10.1136/2003.008755 PMid:15310802 PMCid:PMC1732890
19. Regal RR, Hook EB. Goodness-of-fit based confidence intervals for estimates of the size of a closed population. Stat in Med. 1984;3(3):287-91. http://dx.doi.org/10.1002/sim.4780030310
20. StatBank Denmark. Population and elections. Copenhagen: Statistics Denmark. [Accessed 17 Nov 2013]. Available from: www.statistikbanken.dk
21. Gjörup IE, Smith E, Borgwardt L, Skinhøj P. Twenty-year survey of the epidemiology of hepatitis B in Denmark: effect of immigration. Scand J Infect Dis 2003;35(4):260-4. http://dx.doi.org/10.1080/00365540310000111 PMid:12839156
22. Rimseliene G, Nilsen Ø, Kløvstad H, Blystad H, Aavitsland P. Epidemiology of acute and chronic hepatitis B virus infection in Norway 1992-2009. BMC Infect Dis. 2011;11:153. http://dx.doi.org/10.1186/1471-2334-11-153 PMid:21615904 PMCid:PMC3123571
23. Lok AS, McMahon BJ. Chronic hepatitis B:update 2009. Hepatology 2009;50(3):661-2. http://dx.doi.org/10.1002/hep.23190 PMid:19714720
24. Chao A, Tsay PK, Lin SH, Shau WY, Chao DY. The applications of capture-recapture models to epidemiological data. Stat Med. 2001;20(20):3123-57. http://dx.doi.org/10.1002/sim.996 PMid:11590637
25. Committee on the Prevention and Control of Viral Hepatitis Infection; Institute of Medicine. Colvin HM, Mitchell AE, editors. Hepatitis and liver cancer: a national strategy for prevention and control of hepatitis B and C. Washington: The National Academies Press; 2010. ISBN: 9780309146289. Available from: http://www.nap.edu/catalog/12793.html
26. Christenson B, Bottiger M, Grillner L. The prevalence of hepatitis B in Sweden; a statisicalserosurvey of 3381 Swedish inhabitants. Epidemiol Infect. 1997;119(2):221-5. http://dx.doi.org/10.1017/S0950268897007838 PMid:9363020 PMCid:PMC2808843
27. Thierfelder W, Hellenbrand W, Meisel H, Schreier E, Dortschy R. Prevalence of markers for hepatitis A, B and C in the German population. Results of the German National Health Interview and Examination Survey 1998. Eur J Epidemiol. 2001;17(5):429-35. http://dx.doi.org/10.1023/A:1013792013184 PMid:11855576
28. Meffre C, Le Strat Y, Delarocque-Astagneau E, Dubois F, Antona D, Lemasson JM, et al. Prevalance of Hepatitis B and Hepatitis C virus infection in France in 2004: Social factors are important predictors after adjusting for known risk factors. J Med Virol. 2010;82(4):546-55. http://dx.doi.org/10.1002/jmv.21734 PMid:20166185
29. Ioannou GN. Hepatitis B virus in the United States: Infection, exposure, and immunity rates in a nationally representative Survey. Ann Intern Med. 2011;154(5):319-28. http://dx.doi.org/10.7326/0003-4819-154-5-201103010-00006 PMid:21357909

A validation of the use of names to screen for risk of chronic hepatitis B in Victoria, Australia, 2001 to 2010

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Citation style for this article:
MacLachlan JH, Wang YJ, Cowie BC. A validation of the use of names to screen for risk of chronic hepatitis B in Victoria, Australia, 2001 to 2010. Euro Surveill. 2013;18(47):pii=20638. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20638

Article submitted on 11 December 2012 / published on 21 November 2013

The burden of chronic hepatitis B (CHB) is increasing in Australia, particularly in those born in the Asia-Pacific region, and nearly half are undiagnosed. Primary care clinicians have a key role in diagnosing CHB, however identification of patients at risk is hindered by lack of awareness and limited information on country of birth in patient records. This study evaluates the potential of a validated list of names associated with Asian country of birth as a screening tool to predict risk of CHB, by comparing it with surveillance records for all people diagnosed with CHB or salmonellosis in Victoria from 2001 to 2010, and analysed using standard screening tools. Name list match was associated with CHB notification, with over 60% of cases having one name matching the list (sensitivity), and nearly one third matching both given name and surname; less than 15% and 2% of salmonellosis notifications matched for one name and both names, respectively (false positives). These results show that more than half of notified cases of CHB would have been identified by this name list, and that it could be used in support of initiatives to improve diagnosis of patients with diseases associated with country of birth when limited information is available.

Introduction

The global prevalence of chronic hepatitis B (CHB) has been estimated at 350 million people, with the greatest burden amongst those living in Asia and the Pacific [1]. Despite comprising only around 5% of the Australian population [2], migrants from the Asia-Pacific region represent nearly 40% of estimated 218,000 Australians living with CHB [3,4]. Without treatment, 15–40% will suffer serious complications of liver disease [5] including primary liver cancer, the fastest increasing cause of cancer mortality in Australia [6].

Early detection of CHB enables positive interventions for individual patients and the wider community. Effective antiviral treatment can significantly reduce the complications of chronic infection such as cirrhosis and hepatocellular carcinoma (HCC) [6,7], and diagnosis in an individual facilitates screening and vaccination of susceptible contacts. Such screening and treatment initiatives have been demonstrated to be cost-effective [8,9]. Clinical guidelines recommend routine screening for those born in intermediate (2–8%) and high (>8%) CHB prevalence countries [5,10], however undiagnosed CHB is common [11,12]. It has recently been estimated that 45% of those living with CHB in Australia have not been diagnosed [3].

The need for improved identification and management of CHB in the primary healthcare setting is well recognised [13], however, the lack of information on country of birth in patient records in Australian general practices is a substantial barrier to systematic identification of those most at risk [14]. Improving recording of country of birth is important, and educating clinicians in which patients should be routinely offered testing is a key consideration [15]. However, it is likely that further decision support and prompting regarding testing for hepatitis B virus (HBV) is necessary, given the existing large number of undiagnosed Australians with CHB despite these recommendations and education programmes that have been in place for years.

The linking of country of birth to patient name is a method that has previously been used for determination of ethnicity using a list of names derived from census records, and has been shown to be predictive of country of birth for both Hispanic [16] and Asian American [17-19] patients. In addition, clinical indicators (such as body mass index) were similar between self-identified and name list-identified groups, suggesting that this method identified a representative sample of the population within each ethnicity [19].

In addition, software tools such as Nam Pehchan and OnoMAP have been used in the United Kingdom to assign ethnicity based on names for notified cases of CHB [20] and cancer registry records [21]. However,

there has been no examination of this approach in the Australian context, nor, to our knowledge, has there been an assessment of the utility of a name list as a screening tool for risk of having a chronic communicable disease associated with birth country.

This analysis aimed to determine whether a considerable proportion of people attending general practices would be effectively identified using a name list as a screening tool, by examining the sensitivity and specificity of the name list when compared with notifications. More broadly, this study aimed to bridge the gap in evidence and evaluate the utility of the name list in identifying risk of CHB associated with country of birth, to promote and support systematic diagnosis in general practice.

Methods

Asian-Pacific name list

The list of names used in this analysis was derived in the United States from Social Security and Medicare administration records containing country of birth information on a pool of over 400 million applicants, with the original aim of creating a method for classification of ethnicity within the broad group of Asian Americans (the full process of which is described in reference [17]).

Individual name lists were derived for the six major Asian ethnic groups in the United States: Chinese (including those from Hong Kong and Taiwan), Japanese, Filipino, Korean (North and South), Indian and Vietnamese. Names were chosen for inclusion on the basis of their predictive quality, based on association with the specific country of birth and frequency, i.e. names were only included if the majority of people of a certain name were associated with a given origin, and names occurring less than five times were excluded.

The full list contains a total of 20,693 unique names, each associated with a specific country of birth but aggregated for the purpose of this analysis as predictive of birth in any of the countries included.

Data matching: surveillance notifications

Infection with HBV is notifiable to the Department of Health in Victoria, with notification including limited patient demographic and disease information required of both the diagnosing clinician and laboratory within five days [22]. Notifications are reported as either newly acquired (acute infection) or unspecified (chronic infection) according to patient history and serological evidence. The case definition for hepatitis B notification in Australia requires detection of hepatitis B surface antigen (HBsAg) or hepatitis B DNA, with acute infections differentiated by the presence of high levels of IgM to hepatitis B core antigen (anti-HBc) and/or demonstrated absence of prior infection [23].

Table 1

Screening test construct for name list analysis

Sensitivity	Proportion of chronic hepatitis B notifications with a name match
Specificity	Proportion of salmonellosis notifications without a name match
Positive predictive value	Proportion of matches that were chronic hepatitis B notifications
Negative predictive value	Proportion of non-matches that were salmonellosis notifications

Notification data for CHB were extracted from the Victorian Notifiable Infectious Disease Surveillance (NIDS) database by staff from the Communicable Diseases Prevention and Control Unit, Department of Health, Victoria, and compared with the name list to produce a de-identified dataset with a variable indicating a name match. Notified cases of salmonellosis were subjected to the same matching procedure with the name list and used as a control group. Salmonellosis is an acute gastroenteritis with a short incubation period and no particular association with country of birth [24].

Records were assessed for completeness in reporting, and basic demographic characteristics (median age, sex ratio, proportion born overseas) analysed for both diseases.

To determine the effectiveness of the list for the identification of persons at risk of CHB, we tested the name list as a screening tool (see Table 1). Notification data were used as the source of diagnosed cases, with notifications for CHB representing true positives, and notified cases of salmonellosis representing true negatives (analogous to a gold standard diagnostic test); the presence of a name matching the supplied list in a given case was considered a positive result in the screening test. This construct was used to calculate sensitivity and specificity of the name list when using an algorithm that matched both given name and surname ('match both') and one that matched either given name or surname ('match either').

As the positive and negative predictive values (PPV and NPV) of a screening tool are dependent on the prevalence of disease in the target population, and the sample of notifications used here included roughly equal numbers of hepatitis B and salmonellosis notifications, PPV and NPV needed to be adjusted to the prevalence of hepatitis B that would be expected in the screened population. CHB prevalence has been demonstrated in a recent serosurvey to vary considerably by geographic region, largely related to the proportion of residents who were born in endemic areas [25]. Estimates of 1.5%, 3% and 6% prevalence were selected to reflect the expected number of people living with CHB attending

a clinical practice within a general, moderate and high prevalence area, respectively. Adjusted PPV and NPV values were calculated using the following formulae:

$$PPV = \frac{\text{Se} * \text{Pr}}{(\text{Se} * \text{Pr}) + (1 - \text{Sp})(1 - \text{Pr})}$$

$$NPV = \frac{\text{Sp} * (1 - \text{Pr})}{(\text{Sp} * (1 - \text{Pr})) + (1 - \text{Se})(\text{Pr})}$$

where Se is sensitivity, Sp is specificity, and Pr is prevalence.

Statistical analysis

Sensitivity was estimated according to the 'match either' algorithm by sex, age group and across the time period of notifications used. For those notifications where country of birth information was available, sensitivity measures were calculated individually for each of the six name list countries, as well as for the 10 most commonly identified countries of birth that were not originally used to develop the name list.

The chi-square test was used to test the significance of differences in sensitivity according to notification type (CHB compared to salmonellosis), sex, age group, year of notification, as well as differences in country of birth reporting according to sex and presence of name list match. The Wilcoxon rank sum test was used to evaluate differences in age distribution between groups. Exact binomial 95% confidence intervals (CI) were calculated around screening test measures. Data were handled and graphically presented using Microsoft Excel, with statistical analyses conducted using Stata 11.

Ethics

Ethical approval for this research was granted by the Royal Australian College of General Practitioners' National Research and Evaluation Ethics Committee as a component of a broader study (NREEC 10 – 011).

Results

Between 2001 and 2010, there were 17,438 notifications of chronic HBV infection to the Victorian Department of Health, and 14,865 notifications for salmonellosis infection. Notifications differed in age distribution according to disease, with those diagnosed with salmonellosis generally younger (median age 25 years (interquartile range (IQR): 8–45 years) compared with 35 years (IQR: 27–46 years) for HBV, $p<0.001$) and less likely to be male (47.7% of salmonellosis cases were male, compared with 54.2% of CHB cases, $p<0.001$).

The majority of notifications for salmonellosis (83%) were patients born in Australia; however despite representing only around a quarter of the total Victorian population [26], those born overseas made up the vast majority (91%) of CHB notifications. Completeness of this information was similar for salmonellosis and CHB, with greater than 99% of notifications reporting sex and age of cases, but less than one in five recording country of birth.

The sensitivity of the name list varied substantially depending on the type of match assessed (Table 2). While around 60% of those with a notification for CHB had either a given name or a surname matching the name list, just under one third had both names matching the list. In contrast, less than 15% and 2% of salmonellosis notifications matched one name and both names, respectively ($p<0.001$ for both comparisons).

Specificity was correspondingly higher for matching both names instead of either name; in those with salmonellosis notification (i.e. not at increased risk of CHB), only 1.8% of persons were identified as being at risk based on this name list (specificity of 98.2%). This proportion, a measure of false positives, increased to nearly 15% when matching either given name or surname (specificity decreased to 86.4%).

The differing sensitivity and specificity values for the two types of match are reflected in the positive and negative predictive values, with a patient who matched both names much more likely to have a diagnosis of CHB than one who matched either name (PPV in a high prevalence population 51.8% for both names, compared with 22.3% for either name). The inverse was true for the NPV, which increased with improving sensitivity; however, the difference was much less marked, with the proportion of non-matches who were not CHB (true negatives) only increasing from 95.7 to 97.2% when matching either name instead of both (Table 2).

As expected, PPV was heavily impacted by reduced CHB prevalence. Using an average CHB prevalence (1.5%), PPV was calculated to be 6.39% for matching either name and 20.4% for matching both, while using moderate prevalence resulted in PPV values of 12.2% (match either) and 34.2% (match both). As expected, PPV was greatest in high prevalence areas, at 22.3% (match either) and 51.8% (match both). Prevalence had little impact on NPV, with all estimates above 95% regardless of CHB prevalence or match type (see Table 2).

Although demonstrating no trend over time (data not shown), the sensitivity of the name list differed substantially by age group, being only 33.6% in those younger than 10 years compared with 61.0% in those aged 10 years or older ($p<0.001$, Figure). Sensitivity was also slightly higher in women (62.3% compared with 59.5% in men, $p<0.001$).

The sensitivity of the name list varied substantially by country of birth. The vast majority (over 96%) of those with CHB born in China and Vietnam were identified

Table 2

Sensitivity, specificity, and positive and negative predictive values based on estimated prevalence of chronic hepatitis B, by type of match, Victoria, 2001–2010 (n=32,303)

	Both surname and given names		Either surname or given name	
Number of CHB cases matching list Sensitivity (95% CI)	5,279 of 17,438 30.3% (30.0–31.0%)		10,594 of 17,438 61.0% (60.0–61.5%)	
Number of salmonellosis cases not matching list Specificity (95% CI)	14,598 of 14,865 98.2% (98.0¬–98.4%)		12,847 of 14,865 86.4% (85.9–87.0%)	
Prevalence of CHB	PPV	NPV	PPV	NPV
1.5%	20.4%	98.9%	6.39%	99.3%
3.0%	34.2%	97.9%	12.2%	98.6%
6.0%	51.8%	95.7%	22.3%	97.2%

CHB: chronic hepatitis B; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value.

as matching either name on the list, and these two countries alone made up around three quarters of total CHB notifications with a name list match. Sensitivity was moderate for those born in Korea (76.0%), India (60.4%) and the Philippines (48.5%), as well as Asia-Pacific countries not originally used to derive the name list, such as Malaysia, Singapore, East Timor and Laos (Table 3).

Analysis of factors potentially associated with the country of birth not being reported in the notification dataset found no difference according to sex; however those with no country of birth recorded were on average older, and more likely to have a name matching the list than those with a country of birth recorded (sensitivity of 39.5% compared with 32.7%, p<0.001, Table 4).

Discussion

When assessed as a screening tool, the name list evaluated here detected the majority (61%) of the 17,438 notified cases of CHB in Victoria, Australia between 2001 and 2010. Sensitivity and PPV were highest when either name was matched, at the cost of reduced specificity and NPV. Predictive values varied according to the estimated prevalence of CHB among primary care practices. Women and those in older age groups with CHB were more likely to match the name list, and the list was most sensitive for those born in Vietnam and China, with moderate sensitivity for other name list and a number of non-name list countries.

Figure

Proportion of chronic hepatitis B notifications matching name list (either surname or given name) by age group, with 95% confidence intervals (n=20,693)

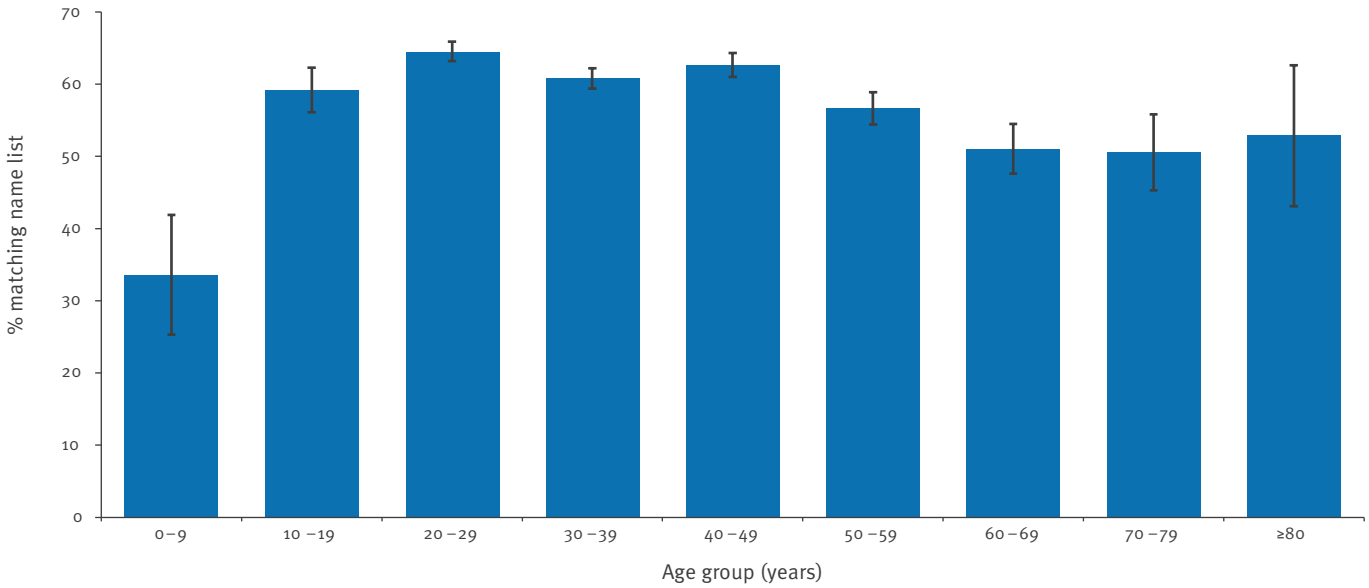

Table 3

Proportion of chronic hepatitis B notifications matching name list (either surname or given name), by country of birth, Victoria, 2001–2010 (n=2,167)

Country of birth	Number of CHB notifications	Number of CHB notifications matching list	Proportion matching name list ('sensitivity')	Proportion of total CHB notifications with match (n=1,584)
China[a]	690	665	96.4%	42.3%
Vietnam	351	339	96.6%	21.4%
Philippines	99	48	48.5%	3.04%
Korea[a]	76	58	76.0%	3.67%
India	53	32	60.4%	2.02%
Japan	<5[b]	<5[b]	100%	<0.32%[b]
TOTAL (name list[b])	**1,269**	**1,142**	**90.0% (1,142)**	**72.62% (1,150)**
Australia	255	60	23.5%	3.85%
Malaysia	76	51	67.1%	3.23%
Burma	122	42	36.9%	2.85%
Sudan	161	43	26.7%	2.72%
Cambodia	61	25	41.0%	1.58%
Singapore	35	23	65.7%	1.45%
Afghanistan	51	22	43.1%	1.39%
Thailand	70	17	24.3%	1.08%
Indonesia	48	16	33.3%	1.01%
Somalia	19	11	57.9%	0.70%

CHB: chronic hepatitis B.

[a] For the purposes of the name list derivation, Chinese names included those born in the People's Republic of China, Taiwan and Hong Kong, and Korean names included both the Republic (South) and Democratic People's Republic (North).

[b] Suppressed for people born in Japan due to low numbers and excluded from name list total.

The use of surveillance data in this analysis provided a very large sample of over 33,000 notifications, resulting in narrow confidence intervals around sensitivity and specificity estimates as well as substantial power to detect differences over time and between subgroups.

It is difficult to ascertain what proportion of diagnosed cases are notified to health authorities, or if this varies according to disease, clinic, or patient demographics, but reporting is a legal requirement and compliance is thought to be reasonably high, particularly for laboratories [27]. However, relying on passive surveillance data limited control over quality and completeness, demonstrated by the high proportion of notifications with no country of birth reported, limiting sub-analysis by country. The finding that records without a specified country of birth were more likely to match the name list may also indicate a bias in non-reporting towards those from Asia-Pacific countries.

This validation study also necessarily limited evaluation of the screening value of the name list to those who have already been identified and diagnosed, and therefore the results may not be generalisable to the undiagnosed population that the screening test would be applied to. The evidence of differences in name list sensitivity according to demographic factors such as age and specific country of birth indicate that the effectiveness of the name list screening tool is dependent on the characteristics of the population.

In addition, other analyses of notifications data in Victoria have shown that a notable proportion of diagnoses arise from targeted testing programmes (such as antenatal and humanitarian migrant screening), which may be associated with birth in countries on the name list and affect resultant sensitivity estimates. The effect of targeted screening programmes on the representativeness of notification data has been observed previously, with women aged 20 to 29 years and migrants from countries such as Sudan and Burma (Myanmar) making up a greater than expected proportion of CHB notifications in Victoria due to, respectively, antenatal and humanitarian entrant screening [4,28]. As the migrants from countries on the name list currently entering the country are not usually part of humanitarian migration streams, they are under-represented in notifications and therefore this may have underestimated the sensitivity of the name list in detecting the population with CHB. The higher sensitivity of the name list for those born in China and Vietnam, observed here and in other studies [17,19], is particularly valuable, as

Table 4

Country of birth recording of chronic hepatitis B and salmonellosis cases according to demographic factors and presence of name list match (for all notifications), Victoria, 2001–2010 (n=32,303)

	Country of birth recorded		p value
	Yes	No	
Age in years, median (IQR)	29 (21–41)	32 (22–46)	<0.001
% male	53.5%	52.5%	0.133
% matching name list (either given name or surname)	32.7%	39.5%	<0.001
TOTAL	6,378	27,114	

IQR: interquartile range.

people born in these two countries combined represent more than a third of people living with CHB in Australia [13,28] and a substantial proportion of migrants with CHB in other settings [29].

The screening test construct used here is also limited by the categorisation of salmonellosis notifications as those without disease, when in fact these people may have undiagnosed CHB. However, given that the majority of notifications for salmonellosis occurred among those born in Australia and among young children, the prevalence of undiagnosed CHB in this population is likely to be considerably lower than in the general population (e.g. less than 1%) [3] and would therefore not have a had a substantial effect on estimates of sensitivity and specificity.

Much of the difference in name list sensitivity according to age can be explained by the differing migration and demographic patterns according to country of birth. Those born in Asian countries made up a much smaller proportion of notifications in those aged 0 to 9 years compared with other regions of birth. In addition, migrants from the Middle East/North Africa and Sub-Saharan Africa regions are more likely to be younger than 15 years than those from Asian countries [26]. The name list may also be identifying younger people with Asian names who were born in Australia and whose risk of CHB may be lower, particularly since the implementation of universal infant vaccination.

This analysis is the first to investigate the validity of the name list to identify CHB cases in an Australian setting. The name list may have the potential for application in other countries where migrants born in Asia experience a disproportionate burden of CHB, and this validation process could be carried out in jurisdictions with similar communicable disease surveillance systems. These results support the application of this name list predictive tool in general practice management software to trigger testing, an initiative that is currently being piloted in practices in Melbourne, Victoria situated in areas identified with a high prevalence of CHB [25]. The higher PPV of the name list as a screening tool when applied in higher prevalence populations suggests that practices serving communities with a higher burden of CHB would be optimal sites for implementing this approach.

The use of computer programmes to trigger testing in primary care based on patient characteristics has been shown to be effective in various contexts [30,31] and may be particularly effective in this case, given the need expressed by Australian clinicians for improved knowledge about HBV, particularly regarding whom to test [32,33]. The results of this pilot project will allow assessment of the practical utility of the name list as a screening tool, and estimation of the sensitivity of the list in a previously untested clinical cohort, as opposed to a surveillance registry of people known to be infected. Post-implementation assessment could also provide the opportunity for improvement such as variation of match algorithm to balance sensitivity and specificity, or expansion to other countries.

The implementation of this screening in primary care settings with high CHB prevalence could help to improve access to preventive care, which is particularly imperative given the generally lower uptake of these programmes (for example cancer screening) among Australia's migrant populations [34,35]. Supporting improved delivery of primary care-based opportunistic testing also minimises the potential for stigmatisation of minority groups that could result from broader public campaigns highlighting their increased risk of a chronic infectious disease.

Despite differences in the migration patterns between the United States (where the name list was developed) and Australia, the six ethnicities represented in the list make up 65% of the total Asian-born population of Victoria [2], and estimates put the total burden of chronic hepatitis B in migrants from the name list countries at 60,000 to 100,000 people nationally [13,28]. However, there is still potential for inclusion of a more complete selection of countries that people living with CHB in Australia have migrated from, such as Thailand, Fiji and Indonesia [4,13]. This novel screening concept could also be applied to other diseases (communicable and non-communicable) that are associated with country of birth or ethnicity, possibly involving the development of name lists for other regions.

Systematically increasing diagnostic testing through the application of any screening process, including this name list, must consider the cost-effectiveness of doing so. There has been increasing evidence that screening and appropriate treatment for CHB is cost-effective; a recent study from the United States [36]

found that routine screening for CHB may be cost-effective down to prevalence levels as low as 0.3%. This is lower than the average Australian prevalence of 1.02% [3], and substantially lower than the prevalence of CHB in several parts of Melbourne [25].

In conclusion, the name list evaluated here shows potential as a screening tool to trigger testing of at-risk patients for HBV in primary care situations, being associated with CHB notifications and identifying a considerable proportion of those diagnosed. Although the links between name and country of birth, and country of birth and disease risk have been individually established, this analysis bridges the gap by clarifying the direct association between name and disease, a finding that may have relevance for public health screening initiatives in the future.

Acknowledgements

The authors wish to acknowledge the contribution of Ellen Donnan and Trevor Lauer, Department of Health Victoria, who extracted and de-identified the surveillance notifications for comparison with the name list.
Prof. Dallas English provided helpful comments on analytical methods for an earlier version of this paper, which was produced as part of a thesis for the Master of Science (Epidemiology) degree at the University of Melbourne.

Conflict of interest

YJW was a member of the Adult Hepatitis B Advisory Board for GlaxoSmithKline Australia and Bristol-Myers Squibb.

References

1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J. Viral Hepat. 2004;11(2):97–107. http://dx.doi.org/10.1046/j.1365-2893.2003.00487.x PMid:14996343
2. Australian Bureau of Statistics (ABS). Victoria: Country of birth of person by sex, 2006. Canberra: ABS; 2007.
3. MacLachlan JH, Allard N, Towell V, Cowie BC. The burden of chronic hepatitis B virus infection in Australia, 2011. Aust N Z J Public Health. 2013;37(5):416-22. http://dx.doi.org/10.1111/1753-6405.12049 PMid:24090323
4. Williams S, Vally H, Fielding J, Cowie B. Chronic hepatitis B surveillance in Victoria, 1998-2008: instituting a 21st century approach to an old disease. Aust N Z J Public Health. 2011;35(1):16-21. http://dx.doi.org/10.1111/j.1753-6405.2010.00611.x PMid:21299695
5. Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009;50(3):661-2. http://dx.doi.org/10.1002/hep.23190 PMid:19714720
6. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol. 2010;53(2):348-56. http://dx.doi.org/10.1016/j.jhep.2010.02.035 PMid:20483498
7. Asia-Pacific Working Party on Prevention of Hepatocellular Carcinoma. Prevention of hepatocellular carcinoma in the Asia–Pacific region: Consensus statements. J Gastroenterol Hepatol. 2010;25(4):657-63. http://dx.doi.org/10.1111/j.1440-1746.2009.06167.x PMid:20492323
8. Robotin MC, Kansil M, Howard K, George J, Tipper S, Dore GJ, et al. Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than cancer screening. J Hepatol. 2009;50(5):990-8. http://dx.doi.org/10.1016/j.jhep.2008.12.022 PMid:19303657
9. Veldhuijzen IK, Toy M, Hahné SJM, De Wit GA, Schalm SW, de Man RA, et al. Screening and early treatment of migrants for chronic hepatitis B virus infection is cost-effective. Gastroenterology. 2010;138(2):522-30. http://dx.doi.org/10.1053/j.gastro.2009.10.039 PMid:19879275
10. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. Centers for Disease Control and Prevention: MMWR Recomm Rep. 2008;57(RR-8):1-20.
11. Cohen C, Evans AA, London WT, Block J, Conti M, Block T. Underestimation of chronic hepatitis B virus infection in the United States of America. J Viral Hepat. 2008;15(1):12-3. PMid:18088239 PMCid:PMC2229201
12. Vyas M, Rohde S. Bridging the gap between viral hepatitis and liver cancer: policy recommendations of the European expert group for better control of liver cancer by optimally managing viral hepatitis. Brussels: Rohde Public Policy; 2012.
13. National Hepatitis B Strategy 2010 - 2013. Canberra: Australian Government Department of Health and Ageing; 2010. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-national-strategies-2010-hepb/$File/hepb.pdf
14. Dev A, Nguyen J, Munafo L, Hardie E, Iacono L. Chronic hepatitis B - a clinical audit of GP management. Aust Fam Physician. 2011;40(7):533-8. PMid:21743864
15. National hepatitis B testing policy. Canberra: Australian Government Department of Health and Ageing; 2012. Available from: http://testingportal.ashm.org.au/resources/HBV/HBV_TESTING_POLICY_FORMATTED_V1.1_PRINT.pdf
16. Word DL, Perkins RC, Division USB of the CP. Building a Spanish Surname List for the 1990's: A New Approach to an Old Problem. Population Division, Washington: United States Census Bureau; 1996.
17. Lauderdale DS, Kestenbaum B. Asian American Ethnic Identification by Surname. Popul Res Policy Rev. 2000;19(3):283–300. http://dx.doi.org/10.1023/A:1026582308352
18. Nanchahal K, Mangtani P, Alston M, dos Santos Silva I. Development and validation of a computerized South Asian Names and Group Recognition Algorithm (SANGRA) for use in British health-related studies. J Public Health Med. 2001;23(4):278-85. http://dx.doi.org/10.1093/pubmed/23.4.278 PMid:11873889

19. Wong EC, Palaniappan LP, Lauderdale DS. Using name lists to infer Asian racial/ethnic subgroups in the healthcare setting. Med Care. 2010;48(6):540-6. http://dx.doi.org/10.1097/MLR.0b013e3181d559e9 PMid:20421828 PMCid:PMC3249427

20. Hahne S, Ramsay M, Balogun K, Edmunds WJ, Mortimer P. Incidence and routes of transmission of hepatitis B virus in England and Wales, 1995-2000: implications for immunisation policy. J Clin Virol. 2004;29(4):211-20. http://dx.doi.org/10.1016/j.jcv.2003.09.016 PMid:15018847

21. Ryan R, Vernon S, Lawrence G, Wilson S. Use of name recognition software, census data and multiple imputation to predict missing data on ethnicity: application to cancer registry records. BMC Med Inform Decis Mak. 2012;12:3. http://dx.doi.org/10.1186/1472-6947-12-3 PMid:22269985 PMCid:PMC3353229

22. Hepatitis B. In: Blue Book. Victoria: Department of Health. [Accessed 12 Sep 2011]. Available from: http://ideas.health.vic.gov.au/bluebook/hepatitis-b.asp

23. Australian national notifiable diseases case definitions - hepatitis B (unspecified). Canberra: Australian Government Department of Health and Ageing. [Accessed 18 Nov 2013]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/content/cda-surveil-nndss-casedefs-cd_hepbun.htm

24. Salmonellosis. In: Blue Book. Victoria: Department of Health. [Accessed 12 Jul 2012]. Available from: http://ideas.health.vic.gov.au/bluebook/salmonellosis.asp

25. Cowie B, Karapanagiotidis T, Enriquez A, Kelly H. Markers of hepatitis B virus infection and immunity in Victoria, Australia, 1995 to 2005. Aust N Z J Public Health. 2010;34(1):72-8. http://dx.doi.org/10.1111/j.1753-6405.2010.00477.x PMid:20920109

26. Australian Bureau of Statistics (ABS). Victoria: Country of birth (major groups) by age and sex, 2006. Canberra: ABS; 2007.

27. Fielding J. Infectious diseases notification trends and practices in Victoria, 2009. Victorian Infectious Diseases Bulletin. 2010;13(3):85-90. Available from: http://docs.health.vic.gov.au/docs/doc/231C2E6AA5C657F4CA2578C4000C7B42/$FILE/VIDB-13-3-web.pdfe

28. Cowie B. The linguistic demography of Australians living with chronic hepatitis B. Aust N Z J Public Health. 2011;35(1):12-5. http://dx.doi.org/10.1111/j.1753-6405.2010.00634.x PMid:21299694

29. Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. Hepatology. 2012;56(2):422-33. http://dx.doi.org/10.1002/hep.24804 PMid:22105832

30. Walker J, Fairley CK, Walker SM, Gurrin LC, Gunn JM, Pirotta MV, et al. Computer reminders for Chlamydia screening in general practice: a randomized controlled trial. Sex Transm Dis. 2010;37(7):445-50. PMid:20375930

31. Shojania KG, Jennings A, Mayhew A, Ramsay CR, Eccles MP, Grimshaw J. The effects of on-screen, point of care computer reminders on processes and outcomes of care. Cochrane Database Syst Rev. 2009;(3):CD001096. PMid:19588323

32. Wallace J, McNally S, Richmond J, Hajarizadeh B, Pitts M. Challenges to the effective delivery of health care to people with chronic hepatitis B in Australia. Sex Health. 2012;9(2):131–7. PMid:22498156

33. Guirgis M, Yan K, Bu YM, Zekry A. A study into general practitioners' knowledge and management of viral hepatitis in the migrant population. Intern Med J. 2012;42(5):497-504. http://dx.doi.org/10.1111/j.1445-5994.2011.02440.x PMid:21299780

34. Anikeeva O, Bi P, Hiller JE, Ryan P, Roder D, Han G-S. The health status of migrants in Australia: a review. Asia Pac J Public Health. 2010;22(2):159-93. http://dx.doi.org/10.1177/1010539509358193 PMid:20457648

35. Weber MF, Banks E, Smith DP, O'Connell D, Sitas F. Cancer screening among migrants in an Australian cohort; cross-sectional analyses from the 45 and Up Study. BMC Public Health. 2009;9:144. http://dx.doi.org/10.1186/1471-2458-9-144 PMid:19442312 PMCid:PMC2693134

36. Eckman MH, Kaiser TE, Sherman KE. The cost-effectiveness of screening for chronic hepatitis B infection in the United States. Clin Infect Dis. 2011;52(11):1294–306. http://dx.doi.org/10.1093/cid/cir199 PMid:21540206 PMCid:PMC3097367

Molecular epidemiology of hepatitis C virus genotypes and subtypes among injecting drug users in Hungary

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Citation style for this article:
Tresó B, Takács M, Dencs Á, Dudás M, Pár A, Rusvai E. Molecular epidemiology of hepatitis C virus genotypes and subtypes among injecting drug users in Hungary. Euro Surveill. 2013;18(47):pii=20639. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20639

Article submitted on 04 December 2012 / published on 21 November 2013

The aim of this study was to determine the geographical distribution of hepatitis C virus genotypes/subtypes among people who inject drugs (PWID) recruited at 22 needle exchange sites and drug outpatient services in all seven Planning and Statistical Regions of Hungary. Of 198 such PWID, 147 (74.2%), 45 (22.7%) and six (3.0%) carried genotype 1, 3 or 4, respectively, and 31 (72.1%) of the 43 genotype 1 sequences were of subtype 1a. Genotype 3 was significantly more prevalent in provincial towns than in the capital, Budapest. Injecting for a longer period and an older age both correlated with a higher prevalence of genotype 3, suggesting possible future changes in genotype distribution. The distributions of hepatitis C virus genotypes/subtypes differed significantly between the tested PWID and the general population. The identification of genotype 3 reflected its worldwide occurrence among PWID. Our results underline the importance of genotyping before treatment, especially among people who have ever injected drugs in Hungary.

Introduction

The hepatitis C virus (HCV) may rarely cause symptomatic acute hepatitis. The infection becomes persistent in ca. 85% of these cases, and its persistence may be responsible for liver cirrhosis, end-stage liver disease and hepatocellular carcinoma. HCV has been suggested to have six genotypes, which differ from each other by 31–33% at the nucleotide level and are further classified into several subtypes [1]. These genotypes have different susceptibility to treatment [2]. Each genotype and subtype exhibits a certain geographical distribution, e.g. genotypes 1, 2 and 3 occur virtually worldwide. On the American continent subtype 1a is the most prevalent, in Europe it is subtype 1b. Genotype 4 is mainly present in North and Central Africa and in the Middle East [3]. Genotype 3 originates from Asia, but subtype 3a is widely distributed among people who inject drugs (PWID) around the world [4]. In Hungary, subtype 1b has been reported in 85%, subtype 1a in 4.5%, and genotype 3 in 0.5% of chronic HCV carriers among the general population, with mixed infections in the remainder [5]. A similar genotype distribution, but without mixed infections, has been observed in southern Hungary [6].

Since the screening of blood products for HCV was introduced in Europe in the 1990s, HCV transmission has become closely associated with the sharing of injection equipment among PWID [7]. In Hungary, 126 acute HCV cases were reported to the National Center for Epidemiology (NCE) from 2006 to 2010. In 72 cases, the epidemiological investigations revealed potential risk factors, and injection drug use was reported in 20 of these patients [8,9]. The seroprevalence of HCV among PWID is high (22.6% in 2008) relative to similar age groups in the general population (<1%) [10,11].

No data are available on HCV genotypes in Hungarian PWID. The aims of the present study were therefore to determine the genotype and subtype distributions in this group, to predict possible changes in such distributions, and to examine the phylogenetic relatedness of the HCV sequences.

Methods

Patients and samples

From 2006 to 2011, capillary blood samples were collected through the use of self-retracting single-use lancets from 2,133 PWID appearing at 22 needle exchange sites and drug outpatient services in all seven Planning and Statistical Regions of Hungary(Central and Western Transdanubial Regions were underrepresented relative to their inhabitants). Participation was voluntary; a meal ticket was offered to motivate contribution. The samples were dried on Guthrie cards (Macherey-Nagel GmbH), and sent to the NCE. The dried blood spots (DBSs) were stored at 20 °C until analysis. From PWID who donated multiple samples during the study period, only one sample was included in the analysis. As a comparison group (referred to as the general population), 89 treatment-naïve HCV carriers seen by hepatologists were randomly selected between 2006 and

2011from all Statistical Regions of the country (evenly represented relative to PCR-positive PWID).

This study was approved by the Ethics Committee of the NCE.

Serology

Each DBS, cut out for serology, was placed into 200 µl of PBS containing 0.05% TWEEN 20 and 0.08% Na-azide, vortexed and eluted overnight at 4 °C. For anti-HCV antibody detection, HCV Ab (Dia.Pro) ELISA was used. The results were confirmed by Innotest HCV Ab IV ELISA or HCV Inno-LIA (Innogenetics).

Questionnaire

After informed consent had been obtained from the PWID, they voluntarily completed anonymous questionnaires on risk behaviour relating to the transmission of HCV, with the help of trained social workers. The questionnaire had been compiled on the basis of the recommendations of the European Monitoring Centre for Drugs and Drug Addiction. The determined genotype/subtype was linked to the corresponding questionnaire through a unique anonymous identification code.

Detection of HCV RNA, sequencing, genotyping and subtyping

Each DBS was placed into 500 µl of TRI REAGENT BD (Sigma), 166 µl of RNase/ DNase-free water (Gibco) and 14 µl of 5 N acetic acid (Reanal). Tubes were vortexed, and incubated for 1 h at room temperature. Further steps were carried out according to the Sigma instructions. Pellets were dissolved in 8 µl of water and subjected to reverse transcription through the use of a GeneAmp RNA PCR kit with random hexamers (Applied Biosystems). The protocol was modified: the final concentration of each dNTP was 0.4 mM. The presence of HCV RNA was determined by a previously reported nested PCR, which detects all known genotypes with primers specific for the 5'UTR [12]. PCR products were purified and directly sequenced as described earlier [12]. HCV subtyping was carried out via Line Probe Assay (LIPA; Siemens Versant HCV Genotype 2.0 Assay).

Phylogenetic analysis

For the analysis of the NS5B coding region of genotype 3 viruses, the published primers [13] were modified as follows:

- HCV3a outer sense: 8,504–8,527 (5'ACAATCACTTGTTACATCAARGCC),
- HCV3a outer antisense: 9,051–9,072 (5'TCTACTGGAGAGTAACTGTGGA),
- HCV3a inner sense: 8,556–8,575 (5'GGRACCCGGACTTTCTTGTC),
- HCV3a inner antisense: 9,012–9,033 (5'CCATGGAGTCTTTCAATGATTG).

The PCR conditions were not changed [13]. The products were purified and directly sequenced [12]. NS5B nucleotide sequences obtained from PWID have been deposited in GenBank (accession numbers JQ821321–JQ821345). These and other sequences from 11 countries were analysed and phylogenetic trees were constructed as described earlier [12], with the difference that the Jukes-Cantor model was selected, and subtype 3b isolate (accession number D49374) was used as an outgroup.

Statistical analysis

All analyses were conducted using STATA 11 software (StataCorp. 2010. Stat Statistical Software: Release 11. College Station, TX: StataCorp LP).

Baseline characteristics of study participants (age, sex, geographical distribution, duration of drug use, type of drug) and HCV genotypes and subtypes were compared using the chi-squared test or Fisher's exact test, as appropriate. Association between injecting drug use and HCV genotype/subtype was assessed by computing crude odds ratios (ORs). Bivariable analysis was performed by using the Mantel–Haenszel summary chi-squared statistics to further explore any potential confounding effect. Effect modification was assessed by comparing ORs across the strata, and by the use of the test of homogeneity. A multivariable logistic regression model was used to determine the adjusted odds ratios (AOR) with 95% confidence interval (CI). In the statistical analysis, a p value of <0.05 was considered indicative of a significant difference.

Results

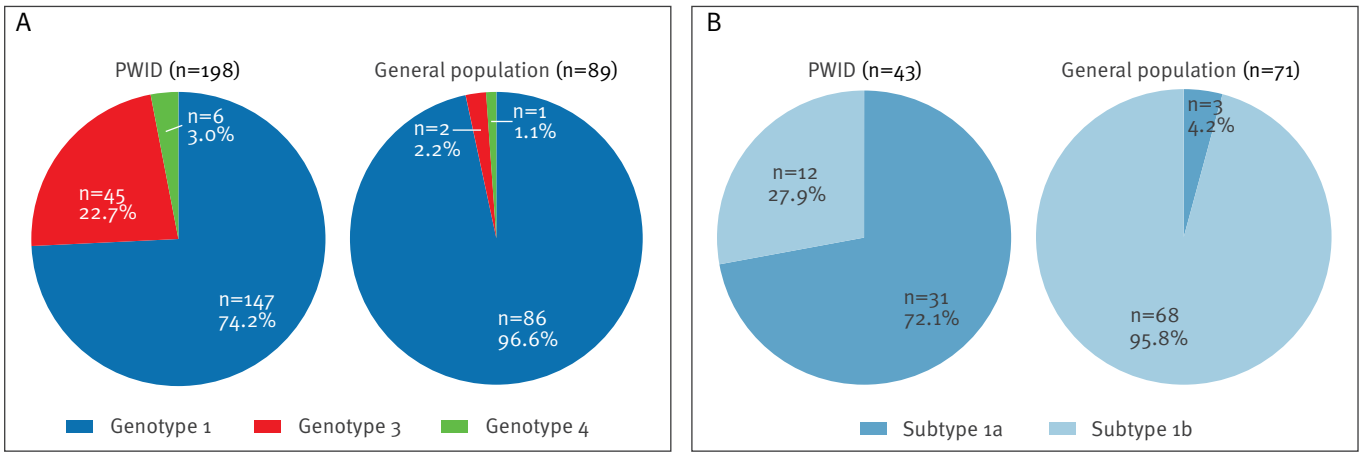
Of the 2,133 PWID tested, 509 proved to be positive for anti-HCV antibodies. Viral RNA was detected in 211 (65%) of 323 HCV antibody-positive samples that were available for PCR analysis. RNA-positive samples were obtained in six of the seven Regions. For 198 of the 211 PCR-positive samples conclusive genotyping results were obtained. Among those 198 PWID, 74.2% (n=147) were infected with genotype 1, 22.7% (n=45) with genotype 3, and 3.0% (n=6) with genotype 4. Of the 89 HCV RNA-positive patients from the general population sample, 96.6% (n=86), 2.2% (n=2) and 1.1% (n=1) carried genotype 1, 3 or 4, respectively (Figure, panel A). The prevalence of genotype 3 among PWID was significantly higher than in the general population ($p<0.001$). The frequency of genotype 1 was significantly lower ($p<0.001$) among PWID, while that of genotype 4 was similar in both groups.

Subtyping was performed for 91 samples from PWID. The HCV subtype was identified in 79 samples, in six cases the assay did not reveal precisely whether genotype 1 or 6 was present, and all of the six genotype 4 viruses were genotypable, but not subtypable with LIPA.

Of the 147 samples from PWID with HCV genotype 1, 43 were subtyped: 31 were found to be of subtype 1a, and 12 of subtype 1b, with no significant geographical difference in subtype distribution between the capital and elsewhere. In the general population, three subtype 1a

Figure

Distribution of hepatitis C virus genotypes (A) and subtypes of genotype 1 (B) among people who inject drugs and the general population, Hungary, 2006–2011



PWID: people who inject drugs.

and 68 subtype 1b viruses were detected, again with no significant difference between Budapest and elsewhere. Subtype 1a was significantly more frequent among PWID than in the general population (p<0.001, Figure, panel B). Of the 45 genotype 3 viruses detected in PWID, 36 were subtyped, and all were of subtype 3a. Genotype 3 was significantly more prevalent in the provincial towns (p<0.001).

Genotype 3 was significantly more prevalent among those who had been injecting drug for a longer period of more than five years or belonged to older age groups (25–34 and >34 years), than among those who had started injecting more recently (less than five years before testing) or belonged to younger age groups (Table).

After data were adjusted to age and geographical distribution, the difference in the prevalence of genotype 3 HCV remained significant between PWID and the general population (p<0.001, AOR: 52.88, 95% CI: 11.21–249.39). Multivariable logistic regression confirmed that among PWID, genotype 3 were significantly more prevalent in provincial towns than in Budapest after the data were adjusted to age (≤34 or >34 years) and duration of drug use (p<0.001, AOR: 0.22, 95% CI: 0.10–0.47).

A correlation was observed between the HCV genotype and the type of drug injected (opiate: n=145, other: n=47, unknown: n=6). Genotype 3 was significantly associated with opiate drug use (39/145 versus 5/47, p=0.022), although after adjusting the data to the duration of injection drug use and geographical distribution, the assumed difference was not confirmed (p=0.053, AOR: 3.22 95% CI: 0.99–10.54).

Phlyogenetic analysis of the NS5B regions revealed that the HCV genotype 3 sequences of Hungarian PWID did not form a separate clade, but certain sequences were grouped together, forming at least three subclusters (data not shown).

Discussion

This study has furnished the first data on the HCV genotype and subtype distributions among PWID in Hungary. Approximately one third (2,133 individuals) of the estimated population of Hungarian PWID [8] was examined. We consider these individuals as representative of the overall population of PWID in Hungary. We used DBS, which can also be collected by trained social workers. The willingness to donate DBS is better than in the case of venous puncture [14]; moreover, it permits large-scale field studies because sample storage and transportation do not require a special infrastructure [15]. In agreement with other authors [16,17], we have demonstrated that DBSs samples are suitable for molecular epidemiological investigations of HCV in the population of PWID. The use of DBSs has the limitation that some samples may give false-negative results [18], but this is not likely to have a significant influence on the genotype and subtype prevalence data.

The genotype and subtype distributions of HCV were found to differ between PWID and the general population. The abundance of genotype 3 and subtype 1a among PWID was in accordance with data on PWID in industrialised nations worldwide [4,19-22]. Since genotype 3 and subtype 1a are rare in the general Hungarian population [5,6], we assume that Hungary is involved in the worldwide epidemic of these genotypes among PWID, and that genotype 3 and subtype 1a may possibly have entered the Hungarian population of PWID from abroad. Genotype 3 proved to be significantly more frequent among PWID who entered the study in

Table

Prevalence of hepatitis C virus genotypes among people who inject drugs, by age and duration of drug use, Hungary, 2006–2011 (n=198)

Age group (years)	Genotype 1	Genotype 3	Genotype 4
	n (%)	n (%)	n(%)
<25	35 (89.7)	1 (2.6)	3 (7.7)
25–34	74 (81.3)	17 (18.7)	0 (0.0)
>34	38 (55.9)	27 (39.7)	3 (4.4)
Exact p	<0.001[a]	<0.001[a]	0.021
Duration of drug injection use (years)	**n (%)**	**n (%)**	**n (%)**
<5	33 (94.3)	1 (2.9)	1 (2.9)
≥5	111 (69.8)	43 (27.0)	5 (3.1)
Unknown	3 (75.0)	1 (25.0)	0 (0.0)
Exact p	0.002	0.001	1.000

[a] with strong evidence of linear trend.

the provincial towns than in Budapest. This observation suggests that PWID communities with different genotype frequencies exist in Hungary.

Three of the four HCV genotype 4-infected PWID outside Budapest were residents of the same town, Veszprém (ca. 64,000 inhabitants). Only four PWID in Veszprém were found to be positive for HCV: three of them carried genotype 4 and one genotype 3. Although few viruses were genotyped, our data suggested a possible epidemic of HCV genotype 4 among PWID in Veszprém. In contrast, all five HCV RNA-positive individuals detected in the general population of Veszprém carried genotype 1. HCV genotype 4 is often associated with drug injection use in Europe [23].

A shorter duration of drug injection use was found to correlate with a higher prevalence of genotype 1 and a lower prevalence of genotype 3. The prevalence of genotype 1 was significantly higher in the youngest age group (<25 years old). Younger PWID are most likely to present with a more recently acquired infection. These data suggest that the prevalence of HCV genotypes may drift towards genotype 1 in the future among Hungarian PWID. In contrast, the genotype recently emerging among PWID in the Czech Republic is genotype 3 [22]. No other publication was found about changes in genotype distributions in other neighbouring countries.

The correlation between the HCV genotype and the type of drug injected was not confirmed after adjusting the data to the duration of injection drug use and geographical distribution. Consequently, the correlation between opiate use and infection with genotype 3 was probably due to an association of opiate use with the users' older age and the duration of drug use.

The prevalence of different genotypes that Gervain et al. observed in the general population in Hungary was similar to our results [5]. Importantly, none of the individuals in our study was infected with more than one genotype or subtype, either in the general population or among the PWID, whereas Gervain et al. did identify mixed infections [5]. This difference might be due to the use of different versions of the LIPA kit for subtyping.

Phylogenetic analysis of the NS5B nucleotide sequences of the genotype 3 viruses confirmed previous findings that genotype 3 HCVs from PWID in different geographical areas do not form well-defined clades [4]. However, some clear sub-clusters with strong bootstrap values were apparent in the Hungarian sequences, suggesting that the individuals in the sub-clusters were infected by each other, probably through unsafe practices of drug injection.

The limitations of our study include that we had HCV PCR-positive samples only from six of the seven Statistical Regions. Also, when genotyping is carried out by sequencing a region of the 5' UTR, genotypes 1 and 6 are not distinguishable. However, genotype 6 is prevalent only in the area of Hong Kong [3] and, of the 45,462 sequences in the HCV sequence database for Europe, only six strains belonged to genotype 6 [24]. Moreover, 43 of the 49 type 1/6 viruses from PWID subtyped by hybridisation in this study were of genotype 1, and none of them were shown to be of genotype 6. Further limitations are that only 49 of the 147 genotype 1 HCV of PWID were subtyped, and that we did

not sequence the whole genomes, thus recombinant viruses may not have been recognised if they were present, and may have been misclassified.

The determination of HCV genotypes in PWID is of more than epidemiological significance. More than 95% of the HCV carriers in the Hungarian general population are infected with HCV genotype 1. The current National Treatment Protocol specifies that genotyping is not compulsory before treatment and is strongly recommended only for foreign nationals living in Hungary [25]. Our findings lead us to propose that the Treatment Protocol should be modified to include Hungarian PWID in addition to foreigners. Since genotype 3 is relatively susceptible to treatment and is common among PWID, it is possible that the shorter treatment time (24 versus 48 weeks) and the higher cure rate (>75% versus ca. 45%) can help convince people who have ever injected drugs to accept and complete a course of treatment, and would also reduce costs. We assume that genotyping and subtyping will remain or become a more important tool for individualised therapy in the future in view of upcoming treatments with direct acting agents [26].

Acknowledgements

This study was supported by DIAGNOSTICUM Inc., Hungary and the Hungarian Research Fund grant OTKA-81454 (A. Pár). The authors are grateful to Prof. Éva Gönczöl for her critical reading of the manuscript. We thank Judit Krisztina Horváth MD, MSc (Office of the Chief Medical Officer of State in Hungary) for help with statistical analysis. The work of those who collected the samples, and the excellent technical assistance of the staff at the NCE are highly appreciated.

References

1. Simmonds P, Bukh J, Combet C, Deléage G, Enomoto N, Feinstone S, et al. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology. 2005;42(4):962-73. http://dx.doi.org/10.1002/hep.20819 PMid:16149085
2. Rosen HR. Clinical practice. Chronic hepatitis C infection. N Engl J Med. 2011;364(25):2429-38. http://dx.doi.org/10.1056/NEJMcp1006613 PMid:21696309
3. Noorali S, Pace DG, Bagasra O. Of lives and livers: emerging responses to the hepatitis C virus. J Infect Dev Ctries. 2011;5(1):1-17. PMid:21330735
4. Morice Y, Cantaloube JF, Beaucourt S, Barbotte L, De Gendt S, Goncales FL, et al. Molecular epidemiology of hepatitis C virus subtype 3a in injecting drug users. J Med Virol. 2006;78(10):1296-303. http://dx.doi.org/10.1002/jmv.20692 PMid:16927280
5. Gervain J, Simon Jr G, Simon J; Hungarian Viral Hepatitis Group. Genotype distribution of hepatitis C virus in the Hungarian population with chronic viral hepatitis C Eur J Gastroenterol Hepatol. 2003;15(4):449-50. http://dx.doi.org/10.1097/00042737-200304000-00021 PMid:12655271
6. Müller Z, Deák J, Ross RS, Nagy E, Kovács L, Roggendorf M, et al. Hepatitis C virus genotypes in Hungarian and Austrian patients with chronic hepatitis C. J Clin Virol. 2003;26(3):295-300. http://dx.doi.org/10.1016/S1386-6532(02)00045-8
7. European Centre for Disease Prevention and Control (ECDC). Annual Epidemiological Report 2011. Reporting on 2009 surveillance data and 2010 epidemic intelligence data. Stockholm: ECDC; 2011. Available from: http://ecdc.europa.eu/en/publications/Publications/1111_SUR_Annual_Epidemiological_Report_on_Communicable_Diseases_in_Europe.pdf
8. Bozsonyi K, Csesztregi T, Dudás M, Horváth GC, Keller É, Koós T, et al. 2010 National Report to the EMCDDA by the Reitox National Focal Point. Hungary. New developments, trends and in-depth information on selected issues. Lisbon: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). [Accessed 3 Dec 2012]. Available from: http://drogfokuszpont.hu/wp-content/uploads/nr_10_en.pdf
9. Csesztregi T, Dudás M, Felvinczi K, Horváth GC, Huszár L, Koós T, et al. 2011 National Report to the EMCDDA by the Reitox National Focal Point. Hungary. New developments, trends and in-depth information on selected issues. Lisbon: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). [Accessed 3 Dec 2012]. Available from: http://drogfokuszpont.hu/wp-content/uploads/national_report_2011_hungary.pdf
10. Bánhegyi D, Böröcz K, Kertész A, Melles M, Milassin M, Pechó Z, et al. Tájékoztató a betegellátás során a vérrel és testváladékokkal terjedő vírusfertőzések megelőzéséről. Epinfo. 2003;10(2. különszám):1-39.
11. Tresó B, Barcsay E, Tarján A, Horváth G, Dencs A, Hettmann A, et al. Prevalence and Correlates of HCV, HVB, and HIV Infection among Prison Inmates and Staff, Hungary. J Urban Health. 2012;89(1):108-16 http://dx.doi.org/10.1007/s11524-011-9626-x PMid:22143408 PMCid:PMC3284587
12. Dencs A, Hettmann A, Martyin T, Jekkel C, Bányai T, Takács M. Phylogenetic investigation of nosocomial transmission of hepatitis C virus in an oncology ward. J Med Virol. 2011;83(3):428-36. http://dx.doi.org/10.1002/jmv.21983 PMid:21264863
13. Cochrane A, Searle B, Hardie A, Robertson R, Delahooke T, Cameron S, et al. A genetic analysis of hepatitis C virus transmission between injection drug users. J Infect Dis. 2002;186(9):1212-21. http://dx.doi.org/10.1086/344314 PMid:12402190
14. Hickman M, McDonald T, Judd A, Nichols T, Hope V, Skidmore S, et al. Increasing the uptake of hepatitis C virus testing among injecting drug users in specialist drug treatment and prison settings by using dried blood spots for diagnostic testing: a cluster randomized controlled trial. J Viral Hepat. 2008;15(4):250-4. http://dx.doi.org/10.1111/j.1365-2893.2007.00937.x PMid:18086182
15. Abe K, Konomi N. Hepatitis C virus RNA in dried serum spotted onto filter paper is stable at room temperature. J Clin

Microbiol. 1998 Oct;36(10):3070-2.
PMid:9738072 PMCid:PMC105116

16. Hope VD, Hickman M, Ngui SL, Jones S, Telfer M, Bizzarri M, et al. Measuring the incidence, prevalence and genetic relatedness of hepatitis C infections among a community recruited sample of injecting drug users, using dried blood spots. J Viral Hepat. 2011;18(4):262-70. http://dx.doi.org/10.1111/j.1365-2893.2010.01297.x PMid:20456636
17. Mahfoud Z, Kassak K, Kreidieh K, Shamra S, Ramia S. Distribution of hepatitis C virus genotypes among injecting drug users in Lebanon. Virol J. 2010;7:96. http://dx.doi.org/10.1186/1743-422X-7-96 PMid:20465784 PMCid:PMC2885342
18. Tuaillon E, Mondain AM, Meroueh F, Ottomani L, Picot MC, Nagot N, et al. Dried blood spot for hepatitis C virus serology and molecular testing. Hepatology. 2010;51(3):752-8. PMid:20043287
19. Pybus OG, Cochrane A, Holmes EC, Simmonds P. The hepatitis C virus epidemic among injecting drug users. Infect Genet Evol. 2005;5(2):131-9. http://dx.doi.org/10.1016/j.meegid.2004.08.001 PMid:15639745
20. Seme K, Poljak M, Lesnicar G, Brinovec V, Stepec S, Koren S. Distribution of hepatitis C virus genotypes in Slovenia. Scand J Infect Dis. 1997;29(1):29-31. http://dx.doi.org/10.3109/00365549709008660 PMid:9112294
21. Vince A, Iscić-Bes J, Zidovec Lepej S, Baća-Vrakela I, Bradarić N, Kurelac I, et al. Distribution of hepatitis C virus genotypes in Croatia--a 10 year retrospective study of four geographic regions. Coll Antropol. 2006;30 Suppl 2:139-43. PMid:17508487
22. Krekulová L, Rehák V, Strunecký O, Němecek V. [Current situation and trends in the hepatitis C virus genotype distribution among injecting drug users in the Czech Republic]. Epidemiol Mikrobiol Imunol. 2009;58(2):84-9. Czech. PMid:19526922
23. Chlabicz S, Flisiak R, Lapinski TW, Kowalczuk O, Wiercinska-Drapalo A, Pytel-Krolczuk B, et al. Epidemiological features of patients infected with HCV genotype 4 in Poland: Epidemiology of HCV genotype 4 in Poland. Hepat Mon. 2011;11(3):191-4. PMid:22087142 PMCid:PMC3206688
24. HCV sequence database. [Accessed 28 Feb 2012]. Available from: http://hcv.lanl.gov/content/sequence/HCV/ToolsOutline.html
25. Infektológiai Szakmai Kollégium. [Infectious Diseases Advisory Board]. A Nemzeti Erőforrás Minisztérium szakmai protokollja a C hepatitis antivirális kezeléséről. [The Ministry of National Resources' professional protocol for hepatitis C antiviral treatment]. Egészségügyi Közlöny. [Official Bulletin of the Ministry of National Resources in Hungary]. 2011;61(7):1393-401.
26. Kronenberger B, Zeuzem S. New developments in HCV therapy. J Viral Hepat. 2012;19 Suppl 1:48-51. http://dx.doi.org/10.1111/j.1365-2893.2011.01526.x PMid:22233414 xxx

Spatial and temporal analysis of human infection with avian influenza A(H7N9) virus in China, 2013

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Citation style for this article:
Liu W, Yang K, Qi X, Xu K, Ji H, Ai J, Ge A, Wu Y, Li Y, Dai Q, Liang Q, Bao C, Bergquist R, Tang F, Zhu Y. Spatial and temporal analysis of human infection with avian influenza A(H7N9) virus in China, 2013. Euro Surveill. 2013;18(47):pii=20640. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20640

Article submitted on 22 July 2013 / published on 21 November 2013

Descriptive and geographic information system methods were used to depict the spatial and temporal characteristics of the outbreak of human infection with a novel avian influenza A(H7N9) virus in mainland China, the peak of which appeared between 28 March and 18 April 2013. As of 31 May 2013, there was a total of 131 reported human infections in China, with a cumulative mortality of 29% (38/131). The outbreak affected 10 provinces, with 106 of the cases being concentrated in the eastern coastal provinces of Zhejiang, Shanghai and Jiangsu. Statistically significant spatial clustering of cumulative human cases was identified by the Cuzick–Edwards' k-nearest neighbour method. Three spatio-temporal clusters of cases were detected by space–time scan analysis. The principal cluster covered 18 counties in Zhejiang during 3 to 18 April (relative risk (RR): 26.39;p<0.0001), while two secondary clusters in March and April covered 21 counties along the provincial boundary between Shanghai and Jiangsu (RR: 6.35;p<0.0001) and two counties in Jiangsu (RR: 72.48;p=0.0025). The peak of the outbreak was in the eastern coastal provinces of Zhejiang, Shanghai and Jiangsu that was characterised by statistically significant spatio-temporal aggregation, with a particularly high incidence in March and April 2013.

Introduction

A novel avian influenza A(H7N9) virus emerged in China in February 2013, causing an outbreak of human infections characterised by rapidly progressive severe illness and fatal outcome [1,2]. After the first case of human infection was confirmed in the Minhang district of Shanghai on 31 March 2013, the disease gradually spread to the three neighbouring provinces of Zhejiang, Jiangsu and Anhui during the following four weeks. The number of cases was very low in this period but then began to increase rapidly, which raised serious concern throughout the world [3]. The Chinese government responded swiftly and the containment measures applied (shutting down live poultry markets) effectively controlled the outbreak – an approach strongly commended by the international community [4,5]. To date, the influenza A(H7N9) virus has not been detected in people or birds outside China.

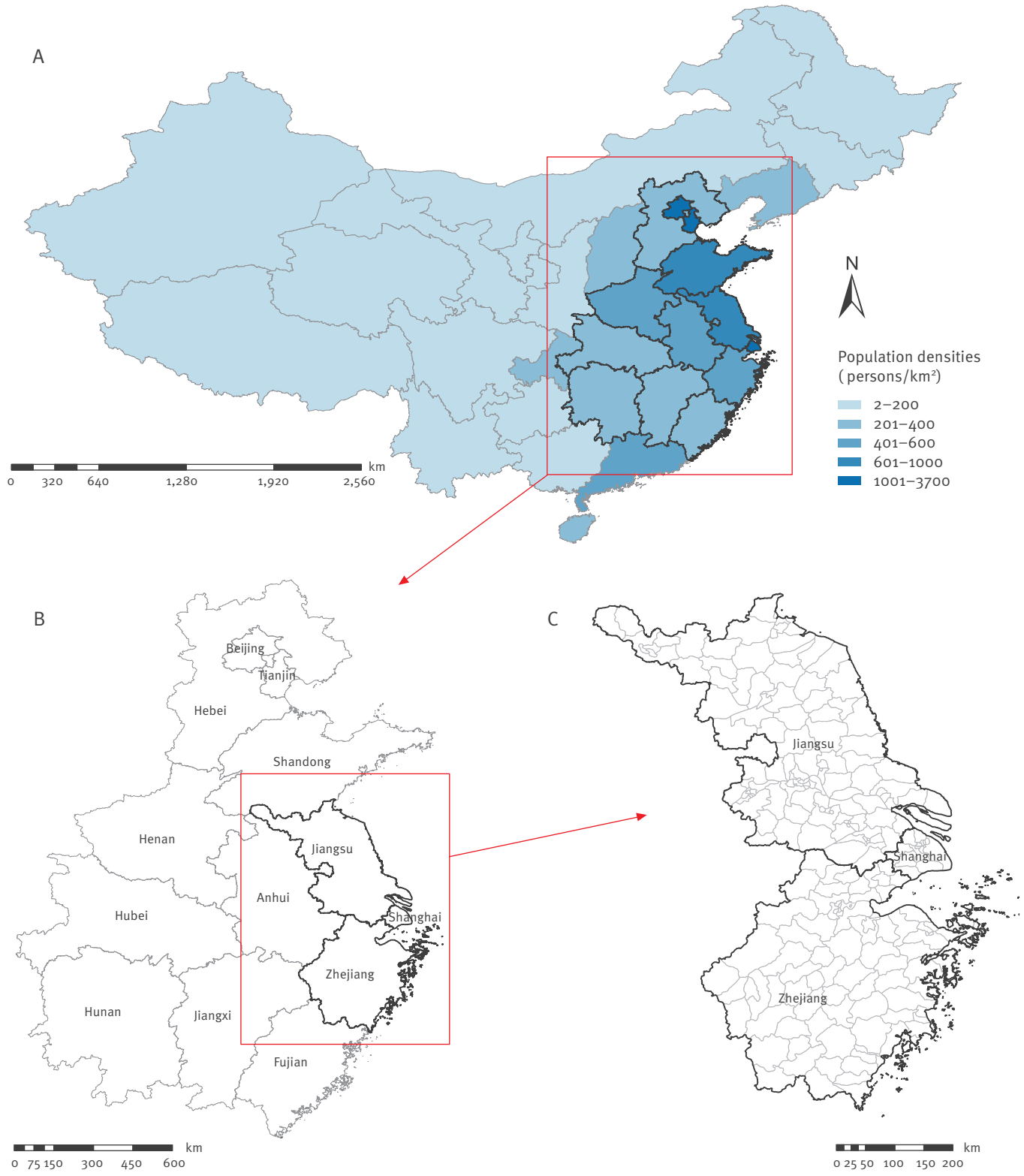
Currently, the outbreak has entered in a stationary state in China and new infections appear only rarely [6]. However, scientists and authorities are still concerned that there might be a risk of a pandemic developing [6]. Strong efforts to date have been made to understand this new virus and substantial progress in epidemiology, diagnosis, therapy and aetiology of the infection has been achieved [1,7-12]. However, much remains to be discovered [13], particularly with regard to the spatial and temporal pattern of this emerging infectious disease. Understanding such patterns is essential for effective surveillance and control. A sound description of the dynamic progress of the outbreak is needed to refine control strategies and optimise resource allocation.

Advances in geographic information system (GIS) and related technologies have fostered new opportunities for examining diseases. As a distinct, useful tool for spatio-temporal analysis, GIS has been widely applied in controlling emerging infectious diseases, such as severe acute respiratory syndrome (SARS) [14,15], avian influenza A(H5N1) [16] and influenza A(H1N1) pdm2009 [17].

In the present study, we concurrently used descriptive analysis and GIS methods to depict the spatial and temporal characteristics of the outbreak of human infection with influenza A(H7N9) virus in mainland China. This work was conducted with the expectation that the results might provide some clues for further epidemiological research and help scientists and health authorities to more effectively target and improve their surveillance and control efforts in the future.

Figure 1

Population densities in mainland China (A)[a] and spatio-temporal cluster analysis of human cases of influenza A(H7N9) virus infection in three eastern provinces, China (B and C)



[a] Data for 2011 [19].
Source of maps: [20].

Methods

Case definition

The case definition was based on *The diagnosis and treatment programs of human infection with influenza A(H7N9) virus*[18] issued by National Health and Family Planning Commission of the People's Republic of China, in which a confirmed case of human infection with influenza A(H7N9) virus is defined as a patient with influenza-like illness, or a suspected case with respiratory specimens, testing positive for the influenza A(H7N9) virus by one of the following laboratory diagnostic tests: isolation of influenza A(H7N9) virus or real-time reverse transcription polymerase chain reaction (rRT-PCR) assay for influenza A(H7N9) virus.

A suspected case is defined as a person presenting with unexplained acute lower respiratory illness with fever (≥38 °C) and cough, shortness of breath or difficulty breathing or infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure (hypoxemia, severe tachypnoea), and either (i) positive laboratory confirmation of an influenza A virus infection but insufficient laboratory evidence for influenza A(H7N9) virus infection because of lack of specimens or (ii) epidemiologically linked to a confirmed influenza A(H7N9) case, but without any respiratory specimens available for influenza A(H7N9) virus testing [18].

Data source

As of 31 May 2013, a total of 131 confirmed human infections with influenza A(H7N9) virus including 38 deaths had occurred in mainland China. For each case, we collected the following data: sex, age, place of residence (postal address), the date of symptom onset and, in case of fatal outcome, the date of death. This information was extracted from the influenza A(H7N9) outbreak reporting released by National Health and Family Planning Commission of the People's Republic of China. We obtained population data from the *Scientific Data Sharing Center of Public Healt*h [19], developed by Chinese Center for Disease Control and Prevention. The maps were downloaded from the National Geomatics Center of China [20].

Study areas and study period

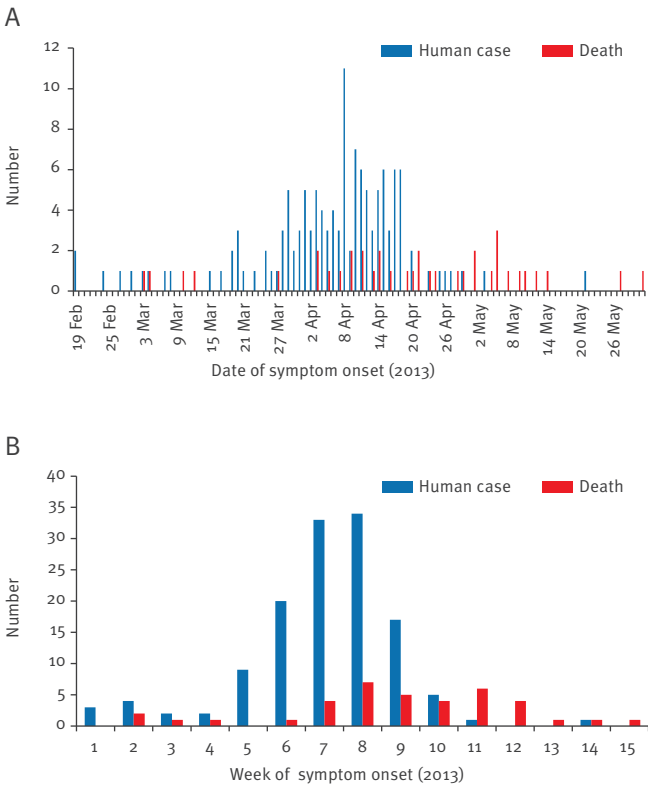
A total of 10 provinces in east China, representing more than a million square kilometres and approximately 570 million inhabitants (Figure 1) reported cases of influenza A(H7N9) virus infection. The study period was from 19 February to 31 May 2013.

Statistical analysis

Descriptive statistics were used to illustrate the characteristics of the population distribution and temporal distribution of the cases of human influenza A(H7N9) virus infection and related deaths. Pearson correlation analysis was conducted to examine the presumed association between the incidence of human infection and population density at the county level using SAS software version 8.1 (SAS Institute Inc., Cary, NC, United States).

Figure 2

Daily (A) and weekly[a] (B) distribution of human cases of influenza A(H7N9) virus infection (n=131) and related deaths (n=38), China, 19 February–31 May 2013



[a] Week 1 started 19 February 2013.

Spatial autocorrelation analysis

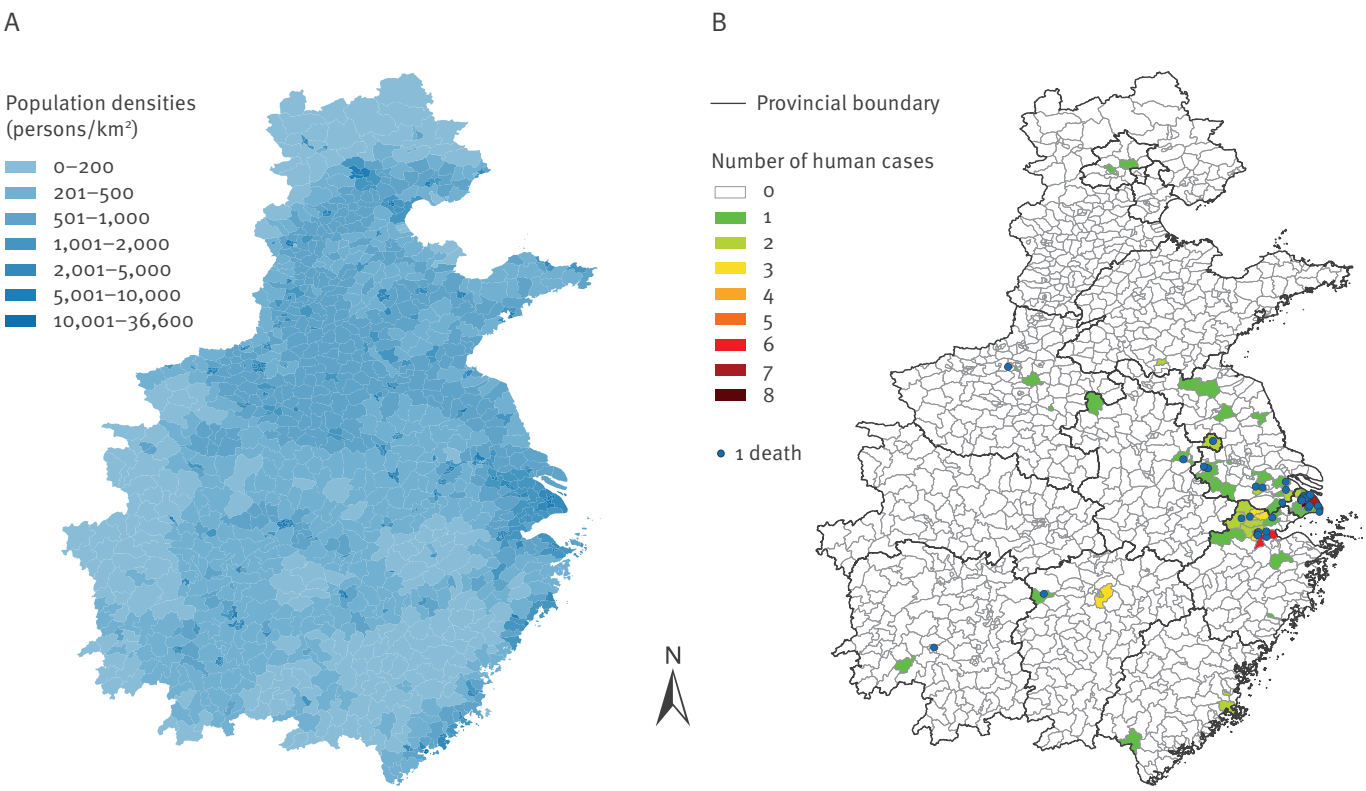
Spatial autocorrelation provides an analysis of the degree of the dependency among various observations in geographical space [21]. In this study, the Cuzick–Edwards' k-nearest neighbour method was used to identify the possibility of spatial clustering [22]. Existence of potential spatial clustering was analysed at each of the first 10 neighbourhood levels, and the overall p value was adjusted for multiple comparisons with the Simes approach based on ClusterSeer software version 2.5.1 (BioMedware, Ann Arbor, MI, United States).

Space–time scan statistic

SaTScan software version 9.0 [23] was employed to conduct a retrospective space–time scan statistic to identify whether or not the human influenza A(H7N9) virus infections were randomly distributed over space and time in Zhejiang, Shanghai and Jiangsu, the three eastern coastal provinces with the highest number of cases. The method is based on the use of a cylindrical

Figure 3

Population density at county level[a] (A) and spatial distribution of human cases of influenza A(H7N9) virus infection (n=131) (B) in 10 eastern provinces, China, 19 February–31 May 2013



[a] Data for 2011 [19].
Source of maps: [20].

window, which represents the circular geographical base of a cylinder, the height of which corresponds to time. The null hypothesis assumes that the relative risk (RR) of human infections is the same within the window compared with outside it. In this study, the human influenza A(H7N9) virus infections were assumed as having a Poisson distribution in each location. The spatial size of scan window was limited to 25% of the total population and the length of time was limited to half of the whole study period. The statistical significance of each cluster was based on comparing the log likelihood ratio (LLR) against a null distribution obtained through Monte Carlo simulation, with the number of replications set to 999 and the significance level set as 0.05. The window with the maximum LLR was deemed the cluster least likely to be due to chance. Other windows with a statistically significant LLR were considered as secondary clusters [24,25].

Results

Demographic characteristics of cases

During the study period, a total of 131 confirmed human cases were reported, 93 of which were male (71%) and 38 female (29%). The age of the cases ranged from two to 91 years, with a median of 61 years. Male cases aged 60 years or older accounted for 39% (51/131) of all cases. Of the 131 cases, 38 (29%) had died from the infection. Full data were not available for one case, but of the remaining 37 fatal cases, 29 were male and 8 female. Their ages ranged from 27 to 91 years, with a median of 67 years, with 28 aged 60 years or older. The sex-related mortality was 31% (29/93) for the male cases and 21% (8/38) for the female cases. No statistically significant difference was observed between the two groups (chi-square test statistic: 1.3660;p=0.2425). The interval between the date of symptom onset and the date of death ranged from six to 67 days, with a median of 20 days.

Temporal characteristics of cases

We divided the study period into 15 weeks of seven days (with week 1 starting 19 February 2013) except the last week, which included only four days (i.e. 28–31 May 2013) and calculated the number of cases for each week (Figure 2). The first two cases developed symptoms simultaneously on 19 February. The outbreak was highly sporadic in the four weeks after the first cases developed symptoms, with just 11 sporadic cases, after which the number of cases increased substantially.

Weeks 5 to 9 (19 March–22 April) included the great majority of cases (n=113), with most of the mortality occurring during weeks 7 to 12 (2 April–13 May). There was a peak of incidence between 28 March and 18 April, with76% (100/131) of all cases. From week 10, the incidence decreased rapidly. Only two cases occurred in May, the last month of the study period.

Spatial characteristics

In the study period, 10 provinces successively reported human infections of influenza A(H7N9) virus. More than 80% of cases (106/131) occurred in Zhejiang, Shanghai and Jiangsu, the three eastern coastal provinces. At the county level, just 70 counties had ever reported cases, accounting for approximately 7% (70/971) of the total number of counties in the 10 provinces, most of which are located along the provincial boundaries among Zhejiang, Jiangsu and Shanghai. Of these 70 counties, 43 had only one case, while five had five or more (Figure 3). Although a relatively high population density was observed in the regions with human infections, the Pearson correlation analysis (r: 0.17;p=0.1702) suggested that there was no statistically significant association between the incidence and population density. The Cuzick–Edwards' test identified statistically significant spatial clustering of cases, not only for each level of neighbourhoods, but also for a summary test at the significance level of 0.05, implying that the distribution of human cases was spatially autocorrelated.

Dynamic progress of the outbreak

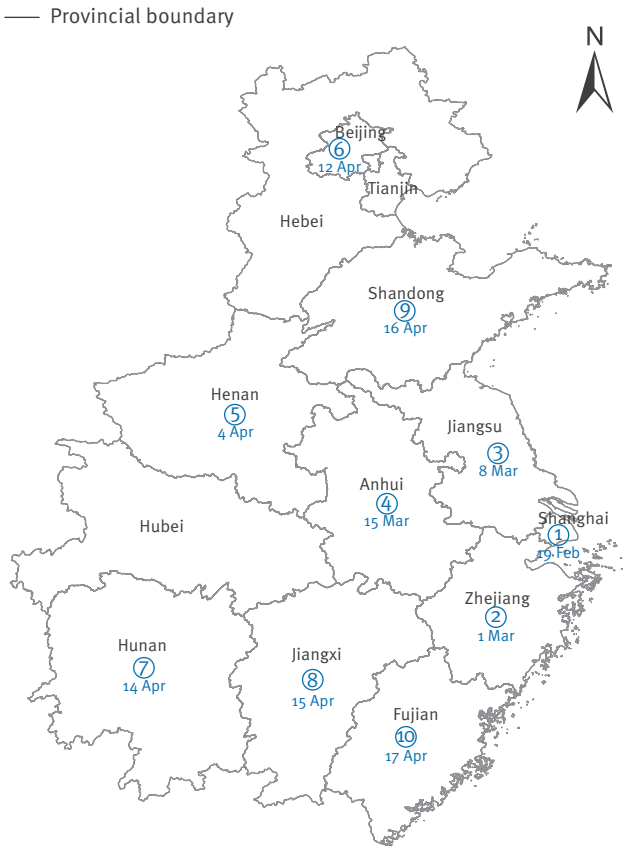
Cases of confirmed influenza A(H7N9) virus infection were initially very rare in weeks 1–4 (19 February–18 March). The outbreak started in Shanghai and spread to Zhejiang, Jiangsu, and Anhui in this period. A period of high incidence appeared subsequently between weeks 5 and 9 (19 March–22 April). In this stage, the outbreak gradually spread to another six provinces: Henan, Beijing, Hunan, Jiangxi, Shandong and Fujian, in that order. But Zhejiang, Jiangsu and Shanghai were the most affected areas, with 87 cases. After that, the outbreak decreased rapidly. In the last six weeks of the study period, only seven new infections occurred and the outbreak did not spread to any other provinces. Notably, no infections occurred during this period in the highly endemic regions of Zhejiang, Shanghai and Jiangsu. No infections occurred from weeks 12 to 13 (7–20 May) throughout the study area. For details, see Figure 4.

Spatio-temporal cluster analysis

Figure 5 shows the results of the space–time scan statistic analysis in the three eastern coastal provinces, which had the highest number of human cases. Three clusters were detected: one principal and two secondary. The principal cluster (LLR:77.72) had a RR of 26.39: it included 37 cases and covered 18 counties in Zhejiang, lasting from 3 to 18 April. One of the secondary clusters, with an LLR of 25.06, included 21 counties (17 in Shanghai and four in Jiangsu). With 28 cases, it lasted from 25 March to 11 April and had a RR of 6.35.

Figure 4

Spatial diffusion of human cases of influenza A(H7N9) virus infection in 10 eastern provinces, China, 19 February–31 May 2013 (n=131)



The numbers in circles represent the order in which cases appeared in the provinces. The dates shown are the dates of symptom onset of the first case in the province.

Source of map: [20].

The other secondary cluster (LLR:16.37) covered just two counties in Jiangsu: it lasted from 4 to 8 April, had five cases, with a RR of 72.48.

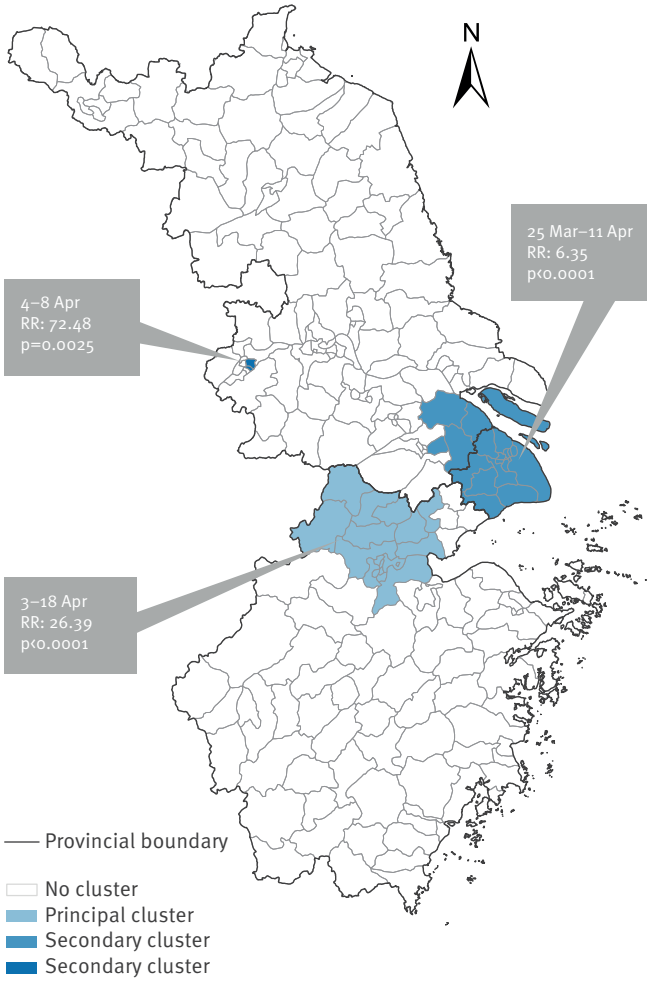
Discussion

The outbreak of human infection with influenza A(H7N9) virus has attracted considerable attention because it is an emerging infectious disease caused by a novel, reassortant avian-origin influenza virus [26,27]. As this virus does not have the ability to be transmitted from person to person, it is unlikely to lead to a pandemic, but gene sequences analysis has indicated that it is better adapted than other avian influenza viruses to infect mammals [9,28]. Scientists are therefore concerned about the possibility of a pandemic if there is further gene mutation [29,30].

In the study period, the outbreak caused 131 confirmed human infections in mainland China. As reported

Figure 5

Spatio-temporal clusters of human cases of influenza A(H7N9) virus infection at county level in Zhejiang, Shanghai and Jiangsu provinces, China, 19 February–31 May 2013 (n=106)



RR: relative risk.
Source of map: [20].

previously [2], most cases were male, mainly aged 60 years or older. In contrast, the influenza A(H5N1) virus mainly affected children, adolescents and young adults (aged between 4 and 29 years, with a median of 18 years) [31]. As of 31 May, 38 cases of influenza A(H7N9) virus infection had died, with accumulative mortality of 29%, much higher than the 21% (17/82) in a previous report on the outbreak [2]. In comparison with the influenza A(H1N1)pdm2009 virus infections (mortality: 2.5%), the mortality of cases of influenza A(H7N9) virus infection was higher[32], although it was clearly lower than that of cases of highly pathogenic avian influenza A(H5N1) virus infection (mortality: 56%) [31]. As shown in a former case study [2], most of the human cases of influenza A(H7N9) virus infection had a severe illness (77/82), while others manifested as mild illness (4/82). In addition, a four year-old child in Beijing was identified as an asymptomatic carrier of influenza A(H7N9) virus [33]. This has been the only asymptomatic infection of influenza A(H7N9) virus to date. Thus, human infections with influenza A(H7N9) virus may result in fatal disease, mild illness as well as silent infection.

Our study shows that the influenza A(H7N9) outbreak in mainland China can be divided into 3 stages: early (weeks1–4), high-incidence (weeks5–9) and late stationary (weeks10–15). In the early stage, the outbreak was considered as non-threatening and highly sporadic. However, the high-incidence stage (in March–April) represented a peak, with 76% (100/131) of the cases during this stage. Furthermore, the three spatio-temporal clusters of cases identified were all during this period. Increased surveillance and control should be carried out in this period in future, to find out if there is an association with climate. In the late stationary stage, transmission was effectively controlled, leading to the ending of the outbreak in the most severely affected areas. This is now believed to be mainly due to the closure of live poultry markets [5].

Some studies have claimed that climatic factors, particularly temperature, have a clear impact on seasonal influenza outbreaks [34,35]. The weather in eastern China is very cold between December and January, and temperatures begin to rise in late February. It is usually relatively warm in March and April, and starts to get hot from May. The temporal characteristics of human infections with influenza A(H7N9) virus suggest that temperature has some association with incidence of this disease. The prevailing mild climate may have been particularly suitable for influenza A(H7N9) virus infection since there was an increase in the number of cases in March–April. If there is a relationship, attention must be paid as there could be a potential outbreak in the same period (March–April) in the future.

The outbreak was limited to 10 provinces in eastern China. In-depth studies of the factors driving the spatial diffusion of cases are essential to prevent future outbreaks. It is notable that when the first human infections appeared in Beijing and Henan, there were no cases in the neighbouring provinces. What is the reason for this? Were the two regions new, natural foci of the influenza A(H7N9) virus strain? Alternatively, and perhaps more probable, could they be attributed to the regional poultry trade or migration of infected wild birds? These possibilities need to be further studied.

The three coastal provinces of Zhejiang, Shanghai and Jiangsu were the most severely affected areas. Understanding the main factors causing this spatial concentration is critical in the approach to control this type of emerging disease. Some studies report that the spatial distribution of human infection with highly pathogenic avian influenza A(H5N1) is mainly associated with human population density, poultry density, elevation and the proportion of land covered by water

bodies [16,36]. However, our study suggests that population density does not influence the spatial pattern of human infection with influenza A(H7N9) virus. Further studies are needed to confirm whether or not there are other counterintuitive correlations involved in the spatial distribution of human infection due to this virus.

The SatScan method has become an increasingly popular adjunct for exploring the spatio-temporal distribution of infectious diseases [37]. We selected this method in the hope of identifying clustering of cases and found three clusters in the three coastal provinces with a high incidence, which were proposed to be the most probable place of the viral reassortment [12,38]. Two of the identified clusters represent the most important hotspots of the outbreak in China and were found in the counties along the boundaries between these three provinces. Surveillance should be focused on these regions to identify any future emergence of this or other new virus strains and monitor possible further mutation or reassortment that may alter the risks to animals or humans. The third cluster covered just two counties within Jiangsu province and was situated far from the other two clusters. In addition, its duration was very short. The risk factors that contribute to clustering warrant further study.

This study, using spatio-temporal methods in conjunction with classic descriptive analysis, found evidence of clustering, in both space and time. The results can provide clues for further developments and serve as a reference and basis for the surveillance and control of human infection with influenza A(H7N9) virus in the future.

Acknowledgements

This work was supported by the Jiangsu Province Health Development Project with Science and Education (ZX201109, RC2011085 and RC 2011094), and the research project of Jiangsu preventive medicine (NO.YZ201020).

Conflict of interest

None declared.

Authors' contributions

Wendong Liu and Kun Yang contributed equally to this study. Correspondence to Yefei Zhu and Fenyang Tang. Yefei Zhu and Fenyang Tang designed the study; Wendong Liu, Kun Yang, Xian Qi, KeXu, Hong Ji, Jing Ai, Aihua Ge, Ying Wu, Yuan Li, Qigang Dai, Qi Liang and Changjun Bao collected, analyzed and interpreted data; Wendong Liu, Kun Yang, and Yefei Zhu drafted the article; Robert Bergquist revised the manuscript. All authors reviewed and revised the first and final drafts of this manuscript.

References

1. Gao R, Cao B, Hu Y, Feng Z, Wang D, Hu W,et al. Human infection with a novel avian-origin influenza A (H7N9) virus. N Engl J Med. 2013;368(20):1888-97. http://dx.doi.org/10.1056/NEJMoa1304459 PMid:23577628
2. Li Q, Zhou L, Zhou M, Chen Z, Li F, Wu H,et al. Preliminary report: epidemiology of the avian influenza A (H7N9) outbreak in China. N Engl J Med. 2013 Apr 24. [Epub ahead of print]. http://dx.doi.org/10.1056/NEJMoa1304617PMCid:PMC3652256
3. Alcorn T. As H7N9 spread in China, experts watch and wait. Lancet. 2013;381(9875):1347. http://dx.doi.org/10.1016/S0140-6736(13)60868-5
4. Hvistendahl M. Influenza. A decade after SARS, China's flu response wins cautious praise. Science. 2013;340(6129):130. http://dx.doi.org/10.1126/science.340.6129.130 PMid:23580499
5. The Lancet Infectious Diseases. A proportionate response to H7N9. Lancet Infect Dis.2013;13(6):465. http://dx.doi.org/10.1016/S1473-3099(13)70134-8
6. Alcorn T. China's H7N9 outbreak slows but experts remain wary. Lancet Respir Med. 2013;1(4):286. http://dx.doi.org/10.1016/S2213-2600(13)70092-4
7. Ai J, Huang Y, Xu K, Ren D, Qi X, Ji H, et al. Case-control study of risk factors for human infection with influenza A(H7N9) virus in Jiangsu Province, China, 2013. Euro Surveill. 2013;18(26):pii=20510.Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20510 PMid:23827526
8. Baas C, Barr IG, Fouchier RA, Kelso A, Hurt AC. A comparison of rapid point-of-care tests for the detection of avian influenza A(H7N9) virus, 2013. Euro Surveill. 2013;18(21):pii=20487. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20487
9. Chen Y, Liang W, Yang S, Wu N, Gao H, Sheng J, et al. Human infections with the emerging avian influenza A H7N9 virus from wet market poultry: clinical analysis and characterisation of viral genome. Lancet. 2013;381(9881):1916-25. http://dx.doi.org/10.1016/S0140-6736(13)60903-4
10. Han J, Niu F, Jin M, Wang L, Liu J, Zhang P, et al. Clinical presentation and sequence analyses of HA and NA antigens of the novel H7N9 viruses. Emerg Microbes Infect. 2013;2:e23. http://dx.doi.org/10.1038/emi.2013.28 PMCid:PMC3675404
11. Hu Y, Lu S, Song Z, Wang W, Hao P, Li J, et al. Association between adverse clinical outcome in human disease caused by novel influenza A H7N9 virus and sustained viral shedding and emergence of antiviral resistance. Lancet. 2013;381(9885):2273-9. http://dx.doi.org/10.1016/S0140-6736(13)61125-3
12. Liu D, Shi W, Shi Y, Wang D, Xiao H, Li W, et al. Origin and diversity of novel avian influenza A H7N9 viruses causing human infection: phylogenetic, structural, and coalescent analyses. Lancet. 2013;381(9881):1926-32. http://dx.doi.org/10.1016/S0140-6736(13)60938-1
13. Cohen J. Influenza. New flu virus in China worries and confuses. Science. 2013;340(6129):129-30. http://dx.doi.org/10.1126/science.340.6129.129 PMid:23580498
14. Meng B, Wang J, Liu J, Wu J, Zhong E. Understanding the spatial diffusion process of severe acute respiratory syndrome in Beijing. Public Health. 2005;119(12):1080-7 http://dx.doi.org/10.1016/j.puhe.2005.02.003 PMid:16214187
15. Lai PC, Kwong KH, Wong HT. Spatio-temporal and stochastic modelling of the severe acute respiratory syndrome (SARS). Geospat Health. 2013. Forthcoming.
16. Martin V, Pfeiffer DU, Zhou X, Xiao X, Prosser DJ, Guo F, et al. Spatial distribution and risk factors of highly pathogenic avian influenza (HPAI) H5N1 in China. PLoSPathog. 2011;7(3):e1001308. http://dx.doi.org/10.1371/journal.ppat.1001308 PMid:21408202 PMCid:PMC3048366
17. Lee SS, Wong NS. The clustering and transmission dynamics of pandemic influenza A (H1N1) 2009 cases in Hong Kong. J Infect. 2011;63(4):274-80. http://dx.doi.org/10.1016/j.jinf.2011.03.011 PMid:21601284
18. National Health and Family Planning Commission of the People's Republic of China (NHFPC).Diagnostic and treatment protocol for human infections withavian influenza A (H7N9) (2nd edition, 2013). Beijing: NHFPC; 11 Apr 2013.Available from: http://www.moh.gov.cn/yjb/bmdt/201304/9e989ebaodod4500ba5dbb89c3bd7829.shtml

19. Chinese Center for Disease Control and Prevention (CDC). [Sex-age specific population of each county in mainland China in 2011]. Beijing: Chinese CDC. Scientific Data Sharing Center of Public Health. [Accessed 20 June 2013]. Chinese. Available from: http://www.phsciencedata.cn/Share/ky_sjml.jsp?id=454aaff4-a4ba-41e3-accc-fefc06900a43
20. National GeomaticsCenter of China (NGCC).[Maps].Beijing: NGCC. [Accessed 15 June 2013]. Chinese. Available from: http://ngcc.sbsm.gov.cn/article/sjcg/dtxz/
21. Lai PC, So FM, Chan KW. Spatial epidemiological approaches in disease mapping and analysis. Boca Raton, FL: CRC Press; 2008.
22. Cuzick J, Edwards R. Spatial clustering for inhomogeneous populations. J R Stat Soc Series B Stat Methodol. 1990;52:73-104.
23. Kuldorff M, Information Management Services, Inc. SaTScan v9.0: software for the spatial and space-time scan statistics. Boston, MA: SaTScan; 2010. [Accessed 10 Mar 2011].Available from: http://www.satscan.org/download.html
24. Kulldorff M, Nagarwalla N. Spatial disease clusters: detection and inference. Stat Med. 1995;14(8):799-810. http://dx.doi.org/10.1002/sim.4780140809
25. Kulldorff M. A spatial scan statistic. Commun Stat Theory Methods. 1997;26(6):1481-96. http://dx.doi.org/10.1080/03610929708831995
26. Horby P. H7N9 is a virus worth worrying about. Nature. 2013;496(7446):399. http://dx.doi.org/10.1038/496399a PMid:23619655
27. Uyeki TM, Cox NJ. Global concerns regarding novel influenza A (H7N9) virus infections. N Engl J Med. 2013;368(20):1862-4. http://dx.doi.org/10.1056/NEJMp1304661 PMid:23577629
28. Belser JA, Gustin KM, Pearce MB, Maines TR, Zeng H, Pappas C, et al. Pathogenesis and transmission of avian influenza A (H7N9) virus in ferrets and mice. Nature.2013;501(7468):556-9. http://dx.doi.org/10.1038/nature12391 PMid:23842497
29. Tharakaraman K, Jayaraman A, Raman R, Viswanathan K, Stebbins NW, Johnson D,et al. Glycan receptor binding of the Influenza A Virus H7N9 hemagglutinin. Cell. 2013;153(7):1486-93. http://dx.doi.org/10.1016/j.cell.2013.05.034 PMid:23746830
30. Kageyama T, Fujisaki S, Takashita E, Xu H, Yamada S, Uchida Y,et al. Genetic analysis of novel avian A(H7N9) influenza viruses isolated from patients in China, February to April 2013. Euro Surveill. 2013;18(15):pii=20453.Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20453 PMid:23594575
31. Fiebig L, Soyka J, Buda S, Buchholz U, Dehnert M, Haas W. Avian influenza A (H5N1) in humans: new insights from a line list of World Health Organization confirmed cases, September 2006 to August 2010. Euro Surveill. 2011;16(32):pii=19941. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19941 PMid:21871222
32. Yu H, Feng Z, Uyeki TM, Liao Q, Zhou L, Feng L, et al. Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China. Clin Infect Dis. 2011;52(4):457-65. http://dx.doi.org/10.1093/cid/ciq144 PMid:21220768 PMCid:PMC3060897
33. Butler D. H7N9 bird flu poised to spread. Nature. 15 April 2013.
34. Lowen AC, Mubareka S, Steel J, Palese P. Influenza virus transmission is dependent on relative humidity and temperature. PLoS Pathog. 2007;Oct 19;3(10):1470-6 http://dx.doi.org/10.1371/journal.ppat.0030151 PMid:17953482 PMCid:PMC2034399
35. Tamerius J, Nelson MI, Zhou SZ, Viboud C, Miller MA, Alonso WJ. Global influenza seasonality: reconciling patterns across temperate and tropical regions. Environ Health Perspect. 2011;119(4):439-45. http://dx.doi.org/10.1289/ehp.1002383 PMid:21097384 PMCid:PMC3080923
36. Kuo HI, Lu CL, Tseng WC, Li HA. A spatiotemporal statistical model of the risk factors of human cases of H5N1 avian influenza in South-east Asian countries and China. Public Health, 2009;123(2):188-93. http://dx.doi.org/10.1016/j.puhe.2008.10.012 PMid:19144364
37. Kulldorff M, Heffernan R, Hartman J, Assunção R, Mostashari F. A space–time permutation scan statistic for disease outbreak detection. PLoS Med. 2005;2(3):e59. http://dx.doi.org/10.1371/journal.pmed.0020059 PMid:15719066 PMCid:PMC548793
38. Xiong C, Zhang Z, Jiang Q, Chen Y. Evolutionary characteristics of A/Hangzhou/1/2013 and source of avian influenza virus H7N9 subtype in China. Clin Infec Dis.2013;57(4):622-4. http://dx.doi.org/10.1093/cid/cit294 PMid:23650290

Special Eurobarometer: Use of antibiotics declining in the European Union but much work still needed

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Citation style for this article:
Eurosurveillance editorial team. Special Eurobarometer: Use of antibiotics declining in the European Union but much work still needed. Euro Surveill. 2013;18(47):pii=20641. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20641

Article published on 21 November 2013

According to the Special Eurobarometer 407, 'Antimicrobial resistance' published in November 2013, most Europeans (84%) are aware that the overuse of antibiotics makes them ineffective [1]. However, the general knowledge of Europeans about antibiotics remains quite low and results in the misuse of these drugs. When asked questions about antibiotics and how they work, 49% of respondents replied that antibiotics kill viruses whereas 40% correctly replied that antibiotics do not kill viruses. More than one in ten (11%) could not answer the question. Only slightly more than half of those polled (52%) could reply correctly that antibiotics are not* effective against colds and influenza. Most respondents (66%) are aware that the use of antibiotics can cause side-effects but nearly one fifth (19%) cannot answer the question. The above responses illustrate the challenge of those who try to make Europeans have a more prudent attitude towards antibiotic use.

The survey concludes that media campaigns are efficient sources of information but that they need to be targeted better in order to reach the desired audience and that the public regard healthcare workers and pharmacies as trusted sources of information for advising on the proper use of antibiotics.

The Eurobarometer is an instrument used by the European Commission to map public opinion in the European Union (EU). The standard Eurobarometer is based on about 1,000 face-to-face interviews per Member State and reports are published twice a year. Special Eurobarometer reports such as the above are based on in-depth thematical studies [2].

- The 2013 Special Eurobarometer used the same questions and addressed the same objectives as a previous one published in 2010 [3]. It aimed to:
- map the use of antibiotics in the EU: how often users took them, how they were obtained and why they were taken;
- measure how much the public knows about the effectiveness of antibiotics and the risks linked to their inappropriate use
- determine the impact of antibiotic awareness campaigns.

Encouraging findings are that the use of antibiotics has declined among respondents who reported having taken antibiotics in the last 12 months from 40% in 2009 to 35% in 2013; still there is a two-fold difference in this percentage among EU countries The large majority of those who used antibiotics in the time covered by the survey got them from a healthcare provider but 3 % of users obtained them without prescription. Antimicrobial resistance represents a serious threat to public health and patient safety and is a worldwide problem [4].

The European Antibiotic Awareness Day (EAAD) is a European health initiative, coordinated by the European Centre for Disease Prevention and Control (ECDC) since 2008, which aims to provide a platform and support for national campaigns on the prudent use of antibiotics. The European Commission adopted an 'Action plan against the rising threats against Antimicrobial Resistance' in 2011 [5]. One important aim of the action plan is to conduct research about effective ways to fight antimicrobial resistance and to ensure that antimicrobials are used appropriately.

*Erratum:

The sentence 'Only slightly more than half of those polled (52%) could reply correctly that antibiotics are not* effective against colds and influenza.' was corrected on 22 November 2013.

References

1. European Commission. Special Eurobarometer 407 'Antimicrobial resistance'. TNS Opinion &Social, at the request of the European Commission, Directorate-General for Health and Consumers. 2013. Available from: http://ec.europa.eu/public_opinion/archives/ebs/ebs_407_en.pdf
2. European Commission. Public Opinion. Available from: http://ec.europa.eu/public_opinion/index_en.htm
3. European Commission. Special Eurobarometer 338 'Antimicrobial resistance'. Survey commissioned by the Directorate-General for Health and Consumers and coordinated by the Directorate-General Communication ("Research and Political Analysis" Unit). 2010. Available from http://

ec.europa.eu/health/antimicrobial_resistance/docs/ebs_338_en.pdf.

4. Eurosurveillance editorial team. CDC publishes report on antibiotic resistance threats in the United States for the first time. Euro Surveill. 2013;18(38):pii=20588. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20588
5. Communication from the Commission to the European Parliament and the Council. Action plan Against the rising threats from Antimicrobial Resistance. Available from: http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf