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Hepatitis B in Saint Petersburg, Russia (1994-1999): a descriptive epidemiological analysis

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Introduction

Hepatitis B (HB) represents a major health problem in most of the world. The World Health Organization estimates that about 350 million people are carriers of the HB virus (HBV) and that annually about 0.9 million deaths are caused by hepatitis B (though a recent alternative estimate brings this down to about 0.5 million (unpublished observation, Gay NJ et al, 2002)). Essentially a relatively virulent pathogen borne by bodily fluids, HBV transmission can occur via a multitude of routes. Perinatal transmission may occur from an infected mother to her child. Horizontal transmission from person-to-person (mostly from child-to-child) may occur at any time when very small amounts of saliva or blood are transferred via small skin wounds (e.g. impetigo, scabies lesions, abrasions, leg ulcers or infected insect bites). Transmission may also occur during homo- and heterosexual intercourse for which the rate of sexual partner change and receptive anal intercourse are important risk factors. Finally, parenteral transmission occurs when the virus spreads by penetration of the skin with an infected object, i.e. by needle stick, mucous membrane splash, tatooing, ear piercing, etc. Health care workers and injecting drug users are generally considered key risk groups for this transmission route. Most of the HBV disease burden is due to long-term chronic sequellae of HB, which can culminate in severe inflammation of the liver, leading to cirrhosis and hepatocellular carcinoma. As chronic HB does not become symptomatic until many years (often decades) after the infection, the link with the initial cause, infection with HBV, is often not made.

Highly effective and safe HB vaccines have been available since 1981, but because of the high price compared to other established vaccines, most countries have been slow to introduce it on a large scale. During the last five to ten years there has been a spectacular increase in the number of countries opting for widespread HB vaccination using the vaccine on a large scale, mainly because the vaccine price dropped substantially. Ironically, at first mainly low endemic countries introduced universal HB vaccination, because poverty and HB endemicity are strongly correlated. As of March 2002, 135 countries have initiated universal HB immunisation programmes in neonates, infants or adolescents. Still, many high endemicity countries have not introduced universal vaccination yet because of budgetary constraints and the presence of many competing interventions.

Russia is by far the largest country in the world, almost twice the size of Canada, the second largest country. Its population of 145 million is very unevenly distributed, with the most densely populated areas in the (European) Western part of the country. The endemicity of HB in the 89 territories of Russia ranges from intermediate to high (implying an HBV carrier rate of >2% and prevalence of all HBV markers of >20%). Between 1996 and 1997 up to 40 out of 63 reporting territories initiated at least one targeted vaccination strategy (mostly high risk newborns, health care workers and household contacts of index cases). These programmes achieved only low to moderate levels of vaccination coverage (e.g. for health care workers in 1997 on average 13%). In 1997, drug users were among the target groups in only one province. In just a few of the territories, universal HB vaccination was introduced in the year 2000, but till now vaccination coverage remained low (13.6% for all newborns and 41.6% for newborns from HBsAg-positive mothers). In this paper we discuss the changing pre-vaccination epidemiology of hepatitis B in one of its main territories and cities, Saint

Petersburg, home to a population of 4.7 million citizens. For Saint Petersburg we were able to use a uniquely detailed dataset, which allows for an analysis in depth of time, age and gender-related aspects of HB incidence. A report discussing the HBV epidemiology in Russia in general can be found elsewhere.[1]

Data and Methods

The system for reporting cases of viral hepatitis in Saint Petersburg (and indeed throughout the Russian Federation) offers an excellent opportunity to study the epidemiology of HBV in detail. By law, physicians and nurses have to refer all (jaundiced) acute symptomatic cases to a hospital. Since 1994, these cases are diagnosed as caused by hepatitis A, hepatitis B or hepatitis C by means of clinical diagnosis combined with highly sensitive and specific blood tests (the following markers are determined routinely: HBsAg, HBeAg, anti-HBe, anti-HBc IgM, anti-HCV, anti-HAV IgM). Additionally, on specific request of physicians markers for Hepatitis D virus infection (anti-HDV IgM or IgG) are often also determined.

All HBV cases are mandatorily reported by age in years, gender and date in months to a central registrar. However, the data set (1994-1999) was rebuilt into more detail for the purpose of the analysis presented in this study, which meant that all 13,136 original reporting cards were manually assessed. The primary data set thus consists of notified cases of acute symptomatic hepatitis B by exact age at infection and exact date of notification, over a period of 6 years (from 1994 to 1999). However, acute symptomatic infections present only part of the picture because most HB infections evolve asymptomatically or atypically. Indeed, the probability of showing clinical symptoms upon acute infection ranges from 5% to 15% in young children (< 5 years

old).[2,3,4] This probability gradually increases with increasing age at infection. Approximately one third of infected adults experience acute clinical illness at infection whilst in two thirds the illness is asymptomatic or presents only flu-like symptoms. In contrast, the probability of chronic HB infection is very high in infants and young children but decreases rapidly with age at infection and stabilises for those who incur an infection as adolescents or adults.[5,6,7] The highest carrier risk estimates vary roughly between 60% and 100% for infections acquired during the first 6 months of life. There is still considerable uncertainty about the carrier rate for older adults who become infected. Estimates vary between 0.1% and 10%, which underlines the need for further study on this particular subject.[8,9,7] Applying these two properties to the reported symptomatic cases we estimated the total number of HB infections by age at infection over time. For the age-dependent ratio of acute symptomatic to acute asymptomatic infections we used estimates derived from the literature.[2,3,4] For the relation between age at infection and probability of developing chronic HB infection we used an equation estimated by Edmunds et al. A graphic representation of both these relationships can be found elsewhere.[10] We used the two-sided t-test for independent samples to compare the age at infection for acute symptomatic, asymptomatic and chronic infections.[11]

On the basis of the detailed data, the ages at infection were compared using the LOESS smoother for both genders separately.[12,13] This allowed us to evaluate the change of the age at infection over time without making any parametric assumptions about the dependency between age at infection and time. Similarly, the number of HBV infections over time was investigated by fitting a LOESS model to each age group separately. We used Kernel density estimates to represent the gender-specific distribution of the age at infection.[14]

The estimates based on reported cases were validated by comparing them with data from a seroprevalence study conducted in Saint Petersburg in 1999. In that study, sera were collected from 100 'healthy' persons (50 male, 50 female) in each of the following age groups: < 1, 1-2, 3-6, 7-10, 11-14, 15-19, 20-24, 25-29, 30-39 and ≥40 years of age (total sample: 1000 sera). For the youngest age groups, the sample was taken primarily among children in the kindergartens and schools, and supplemented with sera from children entering the hospitals with acute non-infectious pathologies (e.g., trauma, emergency surgery, pneumonia). Sera from teenagers and young adults were obtained from a variety of schools (excluding nursing schools) as well as from hospitalized persons requiring urgent surgery. Sera from adults were obtained from primary blood donors, pregnant women and persons entering the hospitals with acute non-infectious pathologies. Clearly, it should be noted that this type of residual sampling could introduce selection bias. All sera were tested for anti-HBc. Anti-HBc-positive sera were also tested for HBsAg. Sera with indeterminable test results were retested. All testing was done with commercialized ELISA kits (produced by Organon Teknika in The Netherlands).

The force of infection (i.e. the per-susceptible rate of infection) was estimated from the seroprevalence study by using two non-parametric models: isotonic regression and local polynomials. The use of local polynomials to estimate the force of infection was introduced by Shkedy et al as an alternative to isotonic regression (see Keiding[15]). The main difference between both methods is that by using local polynomials a smooth function is estimated for both the force of infection and prevalence. Moreover, Shkedy et al showed that one can choose the smoothing parameter in such a way that the local mean square error of the force of infection is minimised. The theoretical

background of these models as applied to infectious diseases is described in a separate paper, in which the advantages and flexibility of local polynomial versus isotonic regression are discussed in detail, as well as demonstrated on a data set for hepatitis A.[16] **(Maybe refer also to the MUMPS/RUBELLA working paper?).** One issue that arises with non-parametric calculations of the force of infection is the accuracy of the estimate. In view of this we use non-parametric bootstrapping to estimate 95% pointwise confidence intervals for the force of infection estimated by local polynomials.[17]

Results

Figure 1 shows the annual age- and gender-specific number of reported acute symptomatic HB cases per 100,000 population. The data over the years seem to show a weak cyclic evolution, which was enforced in 1999 with a dramatic increase in incidence (on average 92 cases per 100,000 population in 1999). Accumulated from 1994 through 1999, 77% of the cases were between 15 and 30 years of age (35% were between 15 and 19 and 30% between 20 and 24 years), and 66% were male.

The total incidence (i.e. symptomatic and asymptomatic infections combined) is estimated as four to tenfold greater than the reported incidence (i.e. symptomatic infections alone). Overall we estimated the total number of infections over the six years combined at 38,848 (on average 265 infections per 100,000 population in 1999). Although the data in figure 2 are presented per age group, we used the exact age at infection (based on reporting date) to derive total incidence from symptomatic incidence. Figure 2 shows a declining incidence in the 1-6 year olds and quasi status quo for age groups above 40 years. It seems noteworthy that the group aged 50 to 59

years was born just before or during the second world war. These birth cohorts were very small compared to the other cohorts in the population. Furthermore, due to the specific circumstances during or in the aftermath of the war, these people may have been exposed to the virus and co-mortality relatively more and earlier in life compared with other age groups. More importantly for the present analysis, in all the intermittent age groups the incidence of infection has increased markedly between 1998 and 1999, after an initially slowly declining cycle between 1995 and 1997. The most dramatic increases were observed among the age groups of 15 to 19 and 20 to 29 year olds, for whom the already high incidence has tripled in 1999 (note the different scales for different age groups). From 1994 through 1999, we estimated that 3.4% of infections occurred in < 1 year olds, 2.9% in 1-9 year olds, 33.8% in 15-19 year olds, 29.1% in 20-24 year olds, 10.9% in 25-29 year olds, 9.5% in 30-39 year olds, 4.8% in 40-49 year olds, 1.8% in 50-59 year olds and 1.6% in ≥ 60 year olds. The share of infections under 1 year of age gained importance between 1994 and 1997 (from 2.5% to 9.8%) and diminished again in 1999 (to 0.7%) probably due to a steep increase in vaccination coverage among high risk newborns (from close to 0% in 1997 to over 80% in 1999 in Saint Petersburg). The share of 15 to 29 year olds has increased from 67.7% in 1994 to 85.1% in 1999 (with 48% of these in 15-19 year olds).

In what follows, the results are based on the total number of infections, as this is most relevant for public health.

The typical inverse relationship between average age at infection and force of infection, is also observed in this analysis through the incidence figures (see figure 3).[18] Given no drastic increase in the number of susceptibles, incidence increased over the period 1997-1999 due to a rise in the force of infection, implying that the average period of susceptibility per susceptible individual decreased (and hence the average

age at infection). The great rise in incidence in this period cannot be explained by a rise in the number of susceptibles. Indeed, the age cohorts currently at greatest risk of infection (15-40 years) are on average about twice the size of today's birth cohort. However, they are similar in size to cohorts aged 40 to 50 years. Therefore the number of susceptibles at risk has been stable, and possibly even declined due to strongly declining birth rates. This implies that the force of infection (a compound measure of the proportion of infectious people, the contact rate and the transmission probability during contact) must have increased substantially. Hence the frequency of hazardous contacts between susceptible and infectious people has increased. Figure 3 also shows that on average women are infected at an older age than men. This characteristic is observed consistently across all observed years for symptomatic as well as for asymptomatic infections. The gender-difference in average age at infection was always found to be significant (at 95%), except in 1998 (or in 1997 when considering only acute infections). As depicted in the lower panel of figure 3, the proportion of male infections is at nearly all time points significantly greater than 0.5, meaning that there are usually significantly more infections in men than in women. However, when an infection in a woman evolves chronically, it is relatively more often the consequence of a childhood infection than when an infection in a man leads to chronic infection, because there are more male than female adult infections, and about the same number of male and female childhood infections (see also figure 1). This explains why female carriers were on average infected at a younger age than male carriers, and the average age for this group has increased for both genders between 1998 and 1999 (from 11.5 to 19.1 years for women, and from 17.7 to 19.4 years for men). We estimated that the infections occurring between 1994 and 1999

directly gave rise to 3752 new carriers of HBV (63% male). In turn these will continue to be infectious to others for the remainder of their lives.

Returning to figures 2 and 3, it seems that the rise in incidence from 1998 on was caused predominantly by male acquisition of infections during adolescence and early adulthood (mostly by injecting drug use and by sexual intercourse) and further enforced by infections in women who acquired infection from mixing with infected men. Women would proportionally be more infected through sexual intercourse with male infected partners, and by starting injecting drug use at a relatively later age than their male counterparts. These intuitively logical deductions, suggesting a kind of jojo effect by which male infection leads the way for female infection would best be substantiated by behavioural studies on the subject.

Turning to the seroprevalence study, figure 4a shows the dispersion of HBV prevalence by age. As one might expect, there seems to be a moderate to strong (heteroscedastic) positive correlation between HBV prevalence and age. We considered the data unreliable for ages above 40 years, because of the disproportionately small sample size for this age group (see section data and methods) and the distinct possibility that this age group may have been subjected to time effects due to changing exposure to HBV (e.g. through improved safety of bloodbanks) or to background mortality in general (e.g. as a consequence of the second world war). This would seriously limit the appropriateness of these cross sectional data to document changes over time. We therefore truncated the data set at age 40 years. Figure 4b shows the force of infection, derived by both isotonic regression and isotonic local polynomials. Both methods yield similar, though not identical, patterns for the estimated prevalence and force of infection.

The bell shaped form of the force of infection in the youngest age group (<12 years), indicates that transmission at a young age is more often a consequence of horizontal than of perinatal transmission. Indeed, the force of infection attains its first (secondary) peak at age 2.5 and 6 years, estimated by local polynomials and isotonic regression, respectively. It declines to its first minimum at age 6.3 years (based on local polynomials) or at age 12 years (based on isotonic regression), when horizontal transmission declines and children are too young to be exposed through sexual and parenteral transmission. From age 13 years on, however, the force of infection rapidly increases to its maximum between ages 20 and 30 years (at age 23 when derived by regression, and at age 26.3 years when derived by local polynomials). From age 30 years on the force of infection rapidly declines again as people approach their late thirties.

There are, however, substantial differences in the age-specific force of infection for men and women. The general shape described above may hold for men, but not for women. Indeed, as described on the basis of the reported incidence data above, women experience the greatest force of infection at a later age than men. This supports the hypothesis that women contract the infection predominantly from sexual intercourse with men, who have been infected previously (probably by injecting drug use or homosexual intercourse). An alternative explanation may be that women start injecting drugs at a later age than their male counterparts. Note the relatively wide uncertainty interval, which may cast doubt on some aspects of the general shape of the force of infection, particularly for women. The use of these prevalence data is additionally restricted by the fact that, as argued above, the force of infection is likely to have increased recently through changed behaviour.

Discussion

This paper described the evolution of HBV incidence in Saint Petersburg in the second half of the 1990s. Particularly in 1999 the overall incidence almost doubled compared to the preceding years. The increase was predominantly caused by infections in young male adults (15-25 years of age). With the increase of incidence we observed a further decrease in average age at infection from 24.1 years in 1994 to 22.1 years in 1999 (despite a substantial reduction in infections under 1 year of age). On average, men contract the infection at a significantly younger age than women (in 1999, 21.8 versus 22.7 years, respectively). This observation allows for some speculation on the role of various transmission routes underlying the epidemiological changes. In view of the age at infection, the main routes of transmission seem obvious: parenteral transmission by injecting drug use and sexual transmission. If men and women mix assortative with regard to age, it seems plausible that men primarily are infected by other men, through shared infected needles and homosexual intercourse. Women would then be mostly infected by men through heterosexual intercourse (the probability of HBV transmission is less likely by heterosexual intercourse than by male homosexual intercourse, but remains very high for both). Female infection also occurs by injecting drug use, but (still) to a smaller extent than male infection. These speculations are supported by two related observations: (1) Injecting drug use continues to increase following the collapse of the Soviet Union. The number of injecting drug users in St Petersburg was estimated at 72,000 in 1998 (about 0.7 million in the whole of Russia).[19] Injecting drug use is documented as

being a predominantly male activity (about 65% of injecting drug users would be male); (2) The recent syphilis epidemic in Russia peaked in 1996-97, when we observe the proportion of female HBV infections to be highest. The fade out of the syphilis epidemic in 1999 also indicates more generally that the HBV epidemic in 1999 is only marginally the result of sexual transmission.

In sum, HBV transmission in Saint Petersburg occurs mainly within subgroups in the population (injecting drug users and people engaging frequently in unsafe sex), and occasionally between these groups (when an injecting drug user has unsafe sex with someone who is not injecting drugs). Our interpretation of the 1999 HBV incidence is that infections mainly occurred within the group of injecting drug users, which seems to continue to expand in size. We can therefore expect more infections in years to come sparked by between group infection and marked by an overall greater proportion of female infections due to sexual transmission.

It seems clear that any intervention strategy in the short term should comprise the prevention of unsafe injections among young adults. This will not only prevent HBV transmission, but also other infections including Human Immunodeficiency Virus (HIV). Indeed, in view of the similar transmission routes (and greater infectivity of HBV) the current analysis may give a maximum indication of the extent to which HIV is spreading. Hepatitis B may be as important a surrogate marker as hepatitis C, because it can also document sexual transmission routes. Nonetheless, injecting drug use is still considered the primary risk factor of HIV infections in Russia (around 80% of infections).

In addition to preventing unsafe injections, complementary HB vaccination strategies should target neonates and infants because an important part of the infections occur

already during childhood. A 1996 decree of the Ministry of Public Health of the Russian federation recommended hepatitis B vaccination of newborns in territories of high endemicity. In January 2002 this was expanded by a new decree recommending hepatitis B vaccination of all newborns and adolescents (13 years of age).

In 15 to 30-year-olds a great deal of the damage is already done and the additional benefit of vaccination may be limited compared to the additional benefit of promoting and providing other preventive measures (i.e. safe sex and needles).

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