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Reduction of acute hepatitis B through vaccination of adolescents with no decrease in chronic hepatitis B due to immigration in a low endemicity country

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Summary

With a hepatitis B prevalence of 0.3%, Switzerland is a country with low endemicity. Unlike most other countries, Switzerland's recommendation for vaccination against hepatitis B has since 1998 focused on adolescents aged 11 to 15 years rather than on infants, in addition to risk groups since 1982. This paper describes the evolution of the incidence of acute hepatitis B virus (HBV) infection and newly reported chronic cases in Switzerland, as well as their epidemiological features, in order to discuss the implications for the control of hepatitis B through vaccination. Data from mandatory notifications by physicians and laboratories between 1988 and 2015 were analysed for acute and chronic HBV infection. Crude and stratified incidence and notification rates (IR, NR), and incidence and notification rate ratios (NRR, IRR) by year were calculated by means of a Poisson regression. Acute HBV incidence peaked in 1992 at 7.5 cases per 100 000 population and subsequently declined by 11% annually (IRR 0.89, p <0.001) to the lowest rate of 0.4/100 000 in 2015. The decrease in incidence accelerated after the introduction of vaccination for adolescents (IRR 0.93, p <0.001 vs 0.91, p <0.001), and was more pronounced in the targeted age groups (IRR 0.90, p <0.001 vs 0.84, p <0.001 for age 15–19 years and IRR 0.92, p <0.001 vs 0.83, p <0.001 for age 20–24). The use of injectable drugs as an assumed source of exposure decreased from 58.1% to 1.9% of all exposures between 1988–1991 and 2012–2015, while sexual contact with an infected person increased from 10.3% to 67.9%. The NR of chronic cases decreased until 1995, then stabilised at around 15/100 000. A growing majority of the chronic cases originated abroad (58.4% in 1988–1991 and 82.2% in 2012–2015), and the NR was significantly higher for foreigners than for Swiss nationals (NRR 7.92, p <0.001), especially when compared with the IRR of 1.51 (p <0.001) for acute cases. The introduction of universal vaccination of adolescents combined with vaccination of risk groups and other nonvaccine-related measures has brought acute HBV infection under control in Switzerland. However, the rate of new notifications of chronic HBV infection has remained stable, largely as a result of the immigration of people chronically infected prior to arrival. The burden of disease is thus likely to increase, requiring the strengthening of secondary prevention of chronic HBV infection, in addition to renewed efforts to vaccinate people and their families originating from countries with high endemicity, and persons who frequently change sexual partners.

Key words: *hepatitis B; epidemiology; surveillance; incidence; vaccination; immigrants*

Introduction

Worldwide, 240 million people are chronically infected with hepatitis B virus (HBV), with 14 million of them living in Europe [1, 2]. Every year, 780 000 people, including 36 000 in Europe, die of complications of chronic HBV infection (cirrhosis and liver cancer). Between 80 and 90% of children infected during their first year of life develop a chronic infection, compared with 5% in adults. Between 20 and 30% of chronically infected adults will go on to develop cirrhosis or liver cancer [1].

With an estimated prevalence of 0.3%, or 24 500 chronically infected individuals, Switzerland is a low endemicity region, as are western Europe and North America [3]. In contrast, southern, central and eastern Europe, sub-Saharan Africa and East Asia are high endemicity regions in which 5 to 10% of the adult population is chronically infected [1]. In these regions, infection generally occurs at birth or during infancy, whereas in low endemicity regions it most often occurs during adulthood.

Because of immigration, countries with a generally low prevalence may have foreign populations or populations of foreign origin with HBV prevalence similar to that of their country of origin. Switzerland has attracted a large number of immigrants since the 1950s, first mainly from southern Europe, later of increasingly diverse origin. In 2014, 161 000 foreigners moved to Switzerland, representing a net migration of 79 000 individuals [4]. In that year, foreigners made up 24.3% of the

total population of 8.24 million. More than half of them came from regions with intermediate to high endemicity. Not included in these 2 million foreigners are Swiss citizens with a foreign origin (11.1% of the adult population), foreigners who had recently applied for asylum (23 800 in 2014) and people living illegally in Switzerland (estimated at 76 000 in 2015) [5].

HBV is transmitted by percutaneous or mucosal exposure to blood and other bodily fluids of an infected person, including perinatal transmission. A safe and effective vaccine for primary prevention of HBV infection has been available since 1982. Since 1992, the World Health Organization has recommended including the vaccination of infants against hepatitis B in all national vaccination programmes, or, alternatively, the vaccination of adolescents in low endemicity countries [6].

In Switzerland, vaccination of risk groups, particularly health professionals, people who frequently change sexual partners, injecting drug users (IDUs), and people originating from countries with intermediate to high endemicity started in 1982 and was officially recommended in 1989. Systematic HBV surface antigen (HBsAg) screening in pregnant women has been recommended since 1996 (at least 97% were screened recently [7–9]). More than 80% of health professionals had been vaccinated by the early 1990s. This targeted strategy was not successful in other risk groups, particularly IDUs [10]. This is why the Federal Office of Public health (FOPH) issued in 1998 a national recommendation for universal voluntary vaccination covered by compulsory health insurance, which was primarily targeted at adolescents (aged 11–15 years) and comprised a two- or three-dose series of vaccinations delivered by school health services or private medical practices [11]. The possibility for catch-up vaccinations at any age was also recommended, and vaccination in infancy was mentioned as an alternative. Switzerland and Hungary are the only two countries in western and central Europe to recommend vaccination of adolescents, compared with 22 countries that recommend vaccination of infants. Six northern countries with low endemicity recommend vaccination of risk groups only [12].

The vaccination coverage rate at age 16 years, with at least two doses of a hepatitis B vaccine, achieved 41% (95% confidence interval [CI] 38.3–43.3) in Switzerland in 1999–2003, 70% (95% CI 68.4–71.7) in 2008–2010 and 68% (95% CI 66.5–69.5) in 2011–2013 [13]. The introduction of hexavalent paediatric vaccines including the HBsAg component has led to a growing proportion of children being vaccinated during their first year of life (coverage rate of 43% at the age of 2 years with three doses in 2011–2013).

The aim of this article is to describe the epidemiology of cases of acute and chronic HBV infection reported in Switzerland between 1988 and 2015 in terms of age, sex, nationality, origin and assumed sources of exposure, and to evaluate the impact of universal vaccination of adolescents on the incidence of the disease.

Materials and methods

Surveillance of HBV infection through mandatory notification

In Switzerland, laboratories and physicians have been obliged to report individual cases of HBV infection to the cantonal medical officer and the FOPH since 1988. Laboratories must first report all positive results (anti-HBV core antigen IgM, HBsAg, HBV e-antigen and detection of HBV DNA). Afterwards the attending physician completes a detailed notification form including clinical manifestations, and assumed sources and place of exposure. The FOPH classifies the cases in a centralised database. All reports are saved on a named basis to avoid creating several cases for the same patient. Patients living abroad are excluded. No informed consent is required, since notification of hepatitis cases is mandatory under the Swiss federal law.

Case definition

The case definition of acute HBV infection is met if the following three criteria are fulfilled: presence of at least one of the four laboratory markers mentioned above, reporting of jaundice of recent onset and absence of indications suggesting a chronic infection (case known for over a year, case considered chronic by the doctor, ascites, cirrhosis or hepatocellular carcinoma). Acute cases are also defined by a documented seroconversion within the last year prior to notification. All other laboratory-confirmed cases of HBV infection are considered to be chronic, including cases for which only a laboratory report is available.

Population data

The annual Swiss population statistics by sex, age and nationality (no data available on origin) that were used as denominators were provided by the Federal Statistical Office. Since the risk of HBV infection is primarily correlated with origin (immigrants from a region of intermediate to high endemicity, vertical and horizontal transmission in Switzerland from parents originating from such a region) rather than with present nationality [14], the evolution of the case proportions according to their origin was also analysed. Origin was defined as country of origin reported by the physician, or set equal to nationality if the origin was missing (physicians often specified the origin only when it differed from nationality).

Statistical analysis

We conducted separate analyses of the acute and chronic HBV cases reported through the Swiss mandatory notification system between 1988 and 2015. Analyses included the first notification year and four-year notification periods, sex, age, nationality, origin, assumed place of infection and assumed sources of exposure. The crude incidence rate (IR) and the incidence rate ratio (IRR) by year were calculated by means of a Poisson regression for the acute infection, using Stata version 14.0. The same was done for newly diagnosed chronic infection by using the notification rate (NR) and the notification rate ratio (NRR). Specific IR, NR, IRR and NRR were also calculated for data stratified by sex, age group, linguistic region and nationality. An IRR or NRR >1 was considered a significant increase, an IRR or NRR <1 a significant rate decrease if $p < 0.05$ (z test). Differences between proportions were considered significant if $p < 0.05$ (chi-squared test and nonparametric test for trend across ordered groups).

Results

Notification of hepatitis B virus infection

Between 1988 and 2015, 36 126 cases of HBV infection were reported in Switzerland. Of these, 5 603 were classified as acute (15.5%) and 30 523 as chronic infection (84.5%), including 5 321 cases (14.7%) for which there was no information on clinical symptoms. The annual number of reported cases of acute HBV (range 31–510) and chronic HBV (range 852–1 372), as

well as annual IR for acute, and annual NR for chronic and total HBV are shown in figure 1.

Acute hepatitis B virus cases

The annual IR of reported acute HBV cases increased markedly between 1988 and 1992, from 4.8 to 7.5 cases per 100 000 population (IRR 1.08, p <0.001), reaching an all-time high before it decreased almost continuously to its lowest level in 2015 with 0.4/100 000 (IRR for 1992–2015 0.89, p <0.001) (fig. 1).

Most acute HBV cases were male (72.0%; table 1), with a significantly higher overall IR (4.0/100 000) compared with females (1.5/100 000; IRR 0.37, p <0.001). The yearly IR for males was between 1.4 and 5.2 times higher than for females. The IR for females tended to decrease regularly over the whole period, whereas it rose sharply for males until 1992 (10.6/100 000) before declining rapidly until 1996, after which it fell more irregularly and slowly (fig. 2).

Case numbers and IRs varied greatly with age. Overall, the highest case numbers between 1988 and 2015 were found in the age group 20 to 24 years (24.5%), followed by the age group 25 to 29 years (16.7%), with children under 15 years accounting for 3.0% of cases (table 1). After the early 1990s, the annual IR decreased almost continuously over time for all age groups (table 2, fig. 3).

After the introduction of adolescent vaccination in 1998, the annual decrease in IR accelerated (IRR 0.93, p <0.001 before and IRR 0.91 after, p <0.001; table 2). The decline was particularly pronounced in the age groups directly affected by the vaccination programme, with an annual decrease in IR from 10 to 16% for adolescents aged 15 to 19 years, and from 8 to 17% for young adults aged 20 to 24 years. Such a steep IR decline was also observed in children and in adults aged 25 to 34 years, but to a lesser extent. Between 1988–1991 and 2012–2015, the IR decreased by 97.3 to 100% for the age groups between 5 and 24 years (table 2).

The IR decrease of acute HBV cases was accompanied by a continuous rise in the median age of cases from 25 years in 1988–1991 (interquartile range 21–33) to 47 years in 2012–2015 (34–57). The peak IR shifted from the age group 20 to 24 years (27.1 and 29.5 cases per 100 000 population in 1988–1991 and 1992–1995, respectively), to the age group 50 to 59 years in 2012–2015 (1.1/100 000; table 2).

The 1988–2015 IR of acute infection was significantly lower in the French-speaking part of Switzerland compared with the German-speaking part (2.2 vs 2.9 cases per 100 000 population; IRR 0.75, p <0.001; table 1). This difference was due to a substantially higher IR in the German-speaking part until 1995. At 2.8/100 000, the IR in the Italian-speaking part of Switzerland was similar to the IR in the German-speaking part.

Out of the 85.6% of all acute HBV cases where the origin was known, 1389 cases (29.0%) were of foreign origin (table 1), 81.3% of them from Europe, mainly former Yugoslavia, Italy and Turkey. The case proportion of foreign origin increased from 27.5 to 41.8% (p <0.001) between 1988–1991 and 2012–2015, and that of non-European origin from 3.9 to 11.1% (p <0.001). Overall, the IR for people of foreign nationality was significantly higher than for Swiss nationals, including those naturalised (IRR 1.51, p <0.001). Overall, 68.1% of the acute cases under 15 years of age were of foreign origin, usually infected abroad (82.0%), compared with 27.8% of the older cases (p <0.001). Among children, however, the number of acute HBV cases, as well as the proportion of children with a foreign background, has strongly declined over time.

The presumed place of exposure (available since 1999) was reported for 59.5% of the acute cases notified between 1999 and 2015 (table 1). Of these, 66.5% had been exposed in Switzerland, with a slightly decreasing trend over time, and 33.5% abroad.

At least one exposure was mentioned in 65.8% of acute cases. Use of injectable drugs was the most frequent source of exposure, mentioned 1853 times (40.9% of the total of 4531 known exposures), and followed by sexual contact with an infected person (32.0%) and other types of contact (16.8%). Other source of exposure – iatrogenic, surgery, dental care, nonmedical profession and perinatal transmission (6.4%); blood transfusion and dialysis (2.7%); exposure as a healthcare professional (1.2%) – were mentioned less frequently. Of the 834 men possibly infected as a result of sexual contact and whose sexual preference was known, 306 (36.7%) were men who have sex with men (MSM).

Figure 4 shows a strong decrease over time in the proportion of exposures linked to the use of injectable drugs, from 58.1% in 1988–1991 to 1.9% in 2012–2015. The importance of contacts other than sexual (often within families) also declined before increasing again in 2012–2015 (15.1%). Sexual exposure, on the other hand, has increased remarkably over time, reaching 69.7% in 2004–2007 before stabilising, as has the importance of other sources of exposure, albeit to a lesser degree (maximum of 13.7% in 2008–2011). A detailed analysis of sexual exposure reveals that its proportion has increased steadily from 7.1% in 1988–1991 to 83.3% in 2012–2015 in the age group 15–24 years, while a peak of 72.5% was reached in 2004–2007 for older cases. Thus, sexual contacts were the major source of infection among the few acute HBV cases reported in recent years in the age group who potentially received the vaccination as adolescents. However, the number of people infected through sexual contact was recently much higher among those aged 25–44 years or 45 years and over than among those aged 15–24 years (33 and 34, respectively, vs 5 for the period 2012–2015).

The epidemiological features of acute cases reported recently (2011–2015) enable us to define the typical profile of persons prone to be infected today (table 3). They are men of middle to mature age, originating from Switzerland and infected in Switzerland through heterosexual contact. Of the cases for whom origin and place of exposure are known, 68.1% of recent cases originating from Switzerland were infected in Switzerland, compared with 47.4% of those originating abroad (p <0.05). However, the risk of acute infection is currently slightly higher for people with foreign nationality than for Swiss nationals (IRR 1.39, p <0.05). This risk is similar when the place of exposure is assumed to be in Switzerland, and higher, although not statistically significant, when exposure took place abroad (IRR 1.46, p = 0.24). Compared with the German-speaking part of Switzerland, this risk is higher in the Italian-speaking part (IRR 2.15, p <0.001) and lower in the French-speaking part (IRR 0.73, p <0.05).

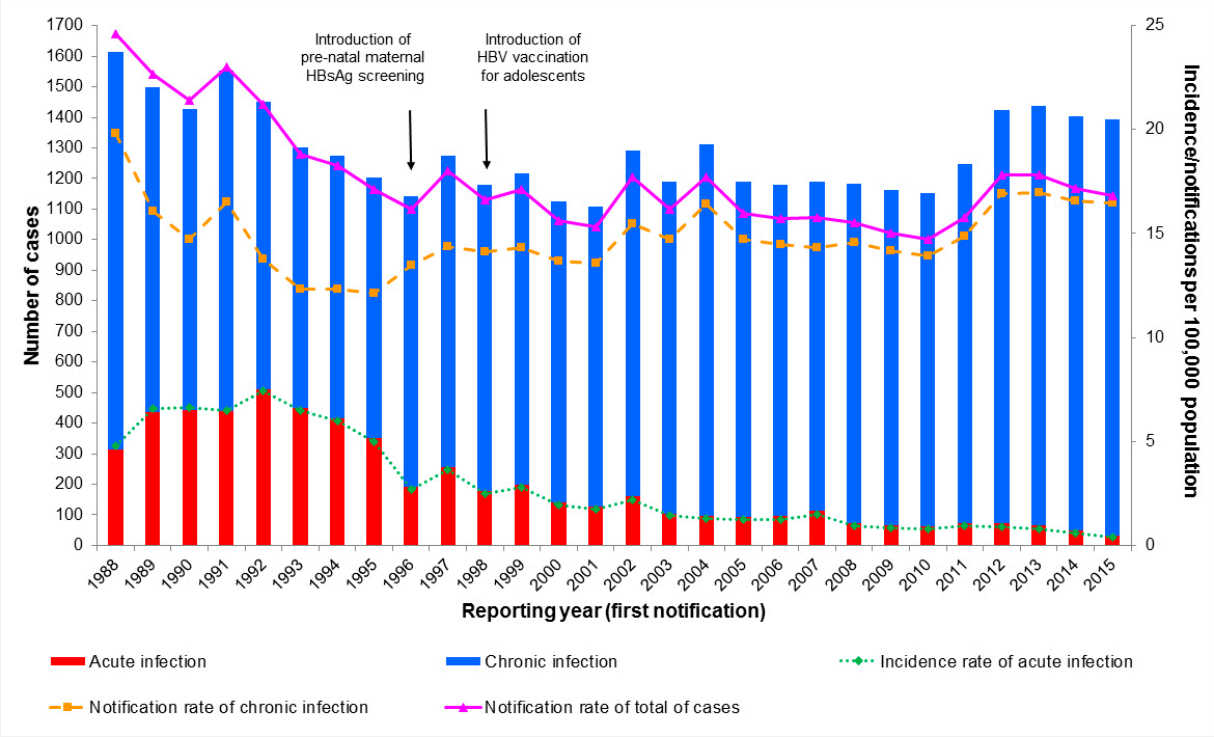

Figure 1: Notified acute and chronic hepatitis B virus infection with annual incidence and notification rates, Switzerland, 1988–2015. HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus.

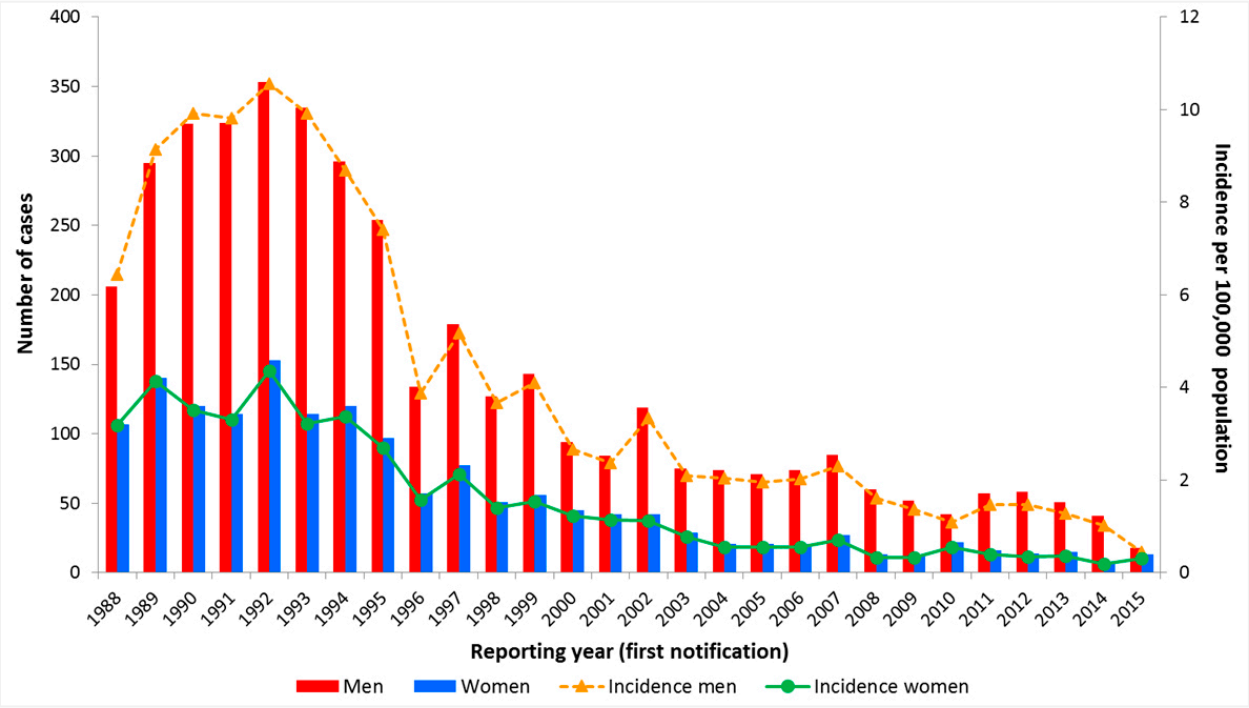

Figure 2: Notified acute hepatitis B virus infection with annual incidence rates by sex, Switzerland, 1988–2015.

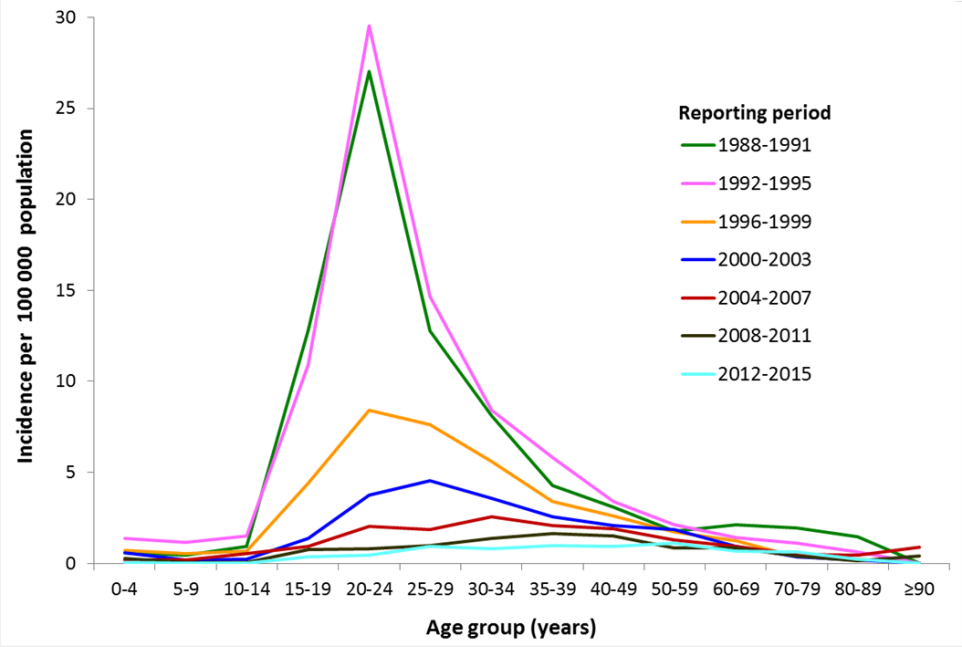

Figure 3: Incidence rate of acute hepatitis B virus infection by age and notification period, Switzerland, 1988–2015.

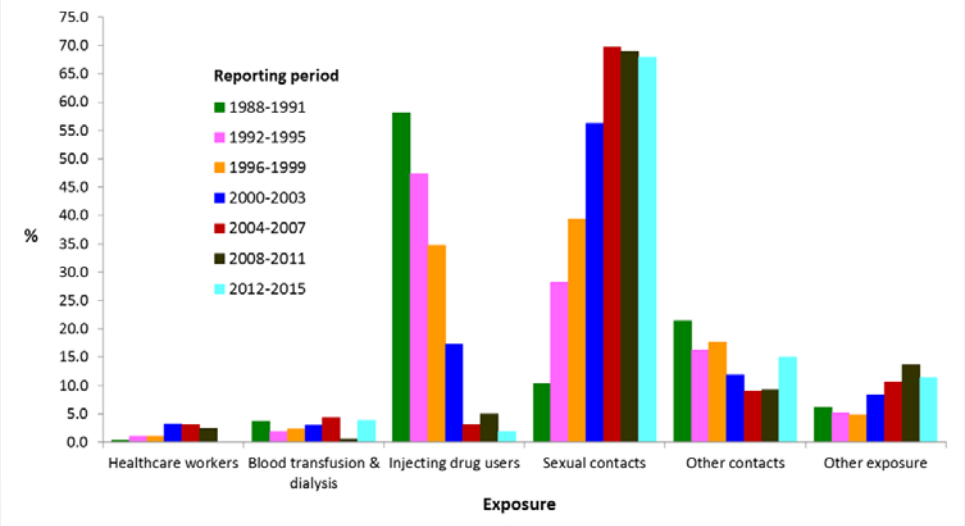

Figure 4: Assumed exposure of acute hepatitis B virus infection by notification period, Switzerland, 1988–2015 (100% = total known exposures by period, including multiple exposures)

Chronic hepatitis B virus cases

Between 1988 and 1995, the NR of chronic HBV decreased from 19.8 to 12.1 cases per 100 000 population (NRR 0.94, p <0.001). It subsequently stabilised at around 15.0/100 000, before increasing to around 17.0/100 000 between 2012 and 2015 (fig. 1).

Most chronic cases were men (57.0%; table 1), whose overall NR was significantly higher (17.1/100 000) than for women (12.4/100 000; NRR 0.72, p <0.001). While the NR decreased strongly for men between 1988 and 1995, it increased slightly for women. Since 1995, the men's annual NR was only 1.1 to 1.5 times higher than the women's, compared with the previous period, when it was 1.4 to 2.7 times higher.

At the time of the first notification, 8.5% of chronic cases were under 20 years old, 58.2% between 20 and 39 years, 26.3% between 40 and 59 years and 7.0% were 60 years or older (table 1). Overall, the NR was at its highest among persons aged 25 to 29 years (34.7/100 000), followed by the age group 20–24 years (33.3/100 000) and the age group 30–34 years (29.9/100 000).

The trend in NR of chronic infection between 1988 and 2015 varied according to age at the time of the first notification. The notification rate significantly decreased for the group aged 0–24 years, was stable for the age group 25–29 years and significantly increased for the age group 30–69 years (table 4). The median age of chronic cases increased continuously from 29 years (interquartile range 23–40) to 37 years (28–48) between 1988–1991 and 2012–2015.

In contrast to acute infection, the NR of chronic HBV was higher in the Italian-speaking (20.2/100 000; NRR 1.52, p <0.001) and French-speaking parts of Switzerland (18.4/100

000; NRR 1.39, p <0.001) than in the German-speaking region (13.2/100 000; table 1).

Out of 22 962 (75.2%) chronic HBV cases with a known origin, 74.3% were of foreign origin (table 1). Among all chronic cases aged less than 15 years, 84.5% were of non-Swiss origin. Between 1988–1991 and 2012–2015, the proportion of chronic cases of foreign origin increased from 58.4 to 82.2% (p <0.001); those of non-European origin increased from 18.4 to 45.7% (p <0.001), those of African origin from 9.7 to 23.7% (p <0.001) and those of Asian origin from 7.9% to 20.5% (p <0.001). The proportion of non-Swiss Europeans, on the other hand, decreased to 35.4% in 2012–2015, having peaked at 45.6% (p <0.001) in 1996–1999. Between 1988 and 2015, the NR for chronic HBV cases was significantly higher among people of non-Swiss nationality than among the Swiss (NRR 7.92, p <0.001). The cumulative NR for 1988–2015 by canton correlated with the mean proportion of foreigners in the canton (correlation coefficient: 0.88, p <0.001). Because the proportion of foreigners is higher in the Italian-speaking (25.7%) and French-speaking (25.6%) parts of Switzerland than in the German-speaking part (17.8%), this correlation largely explained differences in the NR of chronic HBV infection between linguistic regions.

The assumed place of exposure was reported for just 30.5% of the chronic cases notified between 1999 and 2015 (table 1). Of these, 71.3% said that they had been exposed abroad. This proportion increased from 64.0 to 76.1% between 1999–2003 and 2011–2015 (p <0.001).

At least one source of exposure was mentioned for 26.8% of the chronic cases. Nonsexual contact (generally within the family) was the most frequent source of exposure (28.3% of 9504 known exposures), followed by other sources of exposure (26.2%), which included perinatal transmission, sexual contact (24.1%), use of injectable drugs (10.7%), blood transfusion and dialysis (6.3%) and exposure as a healthcare professional (4.4%). The proportion of exposures through sexual contact increased over time, while the proportion through use of injectable drugs, and blood transfusion and dialysis declined. Most of the cases (95.2%) in the 0- to 15-year-old group for whom the source of exposure was known involved perinatal transmission or transmission within the family during infancy, or origin in a region of intermediate to high endemicity.

Table 1: Comparison of characteristic features of acute and chronic hepatitis B virus cases reported, Switzerland, 1988–2015.

	Acute infections			Chronic infections			p-value[a]	OR[b]
	n	%	IR[c]	n	%	NR[d]		
Reporting period								
1988–1991	1634	29.2	6.1	4462	14.6	16.6	<0.001	
1992–1995	1726	30.8	6.2	3503	11.5	12.5		
1996–1999	825	14.7	2.9	3992	13.1	14.0		
2000–2003	531	9.5	1.8	4181	13.7	14.3		
2004–2007	394	7.0	1.3	4477	14.7	14.9		
2008–2011	275	4.9	0.9	4469	14.6	14.2		
2012–2015	218	3.9	0.7	5439	17.8	16.6		
Total	5603	100.0	2.7	30523	100.0	14.9		
Sex								
Male	4024	72.0	4.0	17170	57.0	17.1	<0.001	
Female	1568	28.0	1.5	12952	43.0	12.4		
Total	5592	100.0		30122	100.0			
Age								
0–4 years	61	1.1	0.6	304	1.0	2.7	<0.001	
5–9 years	42	0.8	0.4	277	0.9	2.5		
10–14 years	63	1.1	0.6	356	1.2	3.1		
15–19 years	526	9.4	4.4	1641	5.4	13.6		
20–24 years	1368	24.5	10.5	4336	14.3	33.3		
25–29 years	932	16.7	6.4	5034	16.6	34.7		
30–34 years	689	12.3	4.4	4660	15.3	29.9		
35–39 years	467	8.4	2.9	3647	12.0	22.9		
40–49 years	674	12.1	2.2	5026	16.6	16.1		
50–59 years	390	7.0	1.5	2949	9.7	11.3		
60–69 years	229	4.1	1.1	1300	4.3	6.5		
70–79 years	102	1.8	0.7	616	2.0	4.3		
80 years and over	36	0.6	0.4	218	0.7	2.5		
Total	5579	100.0		30364	100.0			
Origin								
Swiss	3407	71.0	n.a.[e]	5891	25.7	n.a.[e]	<0.001	
Foreign	1389	29.0	n.a.[e]	17071	74.3	n.a.[e]		
Total	4796	100.0		22962	100.0			

Table 1 (cont.)								
Region of Switzerland								
German-speaking	4250	75.9	2.9	19287	63.4	13.2	<0.001	
French-speaking	1110	19.8	2.2	9358	30.8	18.4		
Italian-speaking	243	4.3	2.8	1770	5.8	20.2		
Total	5603	100.0		30415	100.0			
Assumed place of exposure (since 1999)								
Switzerland	640	39.6	0.5	1713	8.8	1.3	<0.001	
Abroad	322	19.9	0.3	4254	21.7	3.3		
Unknown	655	40.5	0.5	13618	69.5	10.5		
Total	1617	100.0	1.2	19585	100.0			
Assumed source of exposure[f]								
Healthcare professions	53	0.8	n.a.[g]	414	1.3	n.a.[g]	<0.001	0.26
Blood transfusion / dialysis	123	1.9	n.a.[g]	603	1.9	n.a.[g]	<0.001	0.41
IDU	1853	28.7	n.a.[g]	1018	3.2	n.a.[g]	<0.001	5.77
Sexual contact	1449	22.5	n.a.[g]	2288	7.2	n.a.[g]	<0.001	1.48
Other contact	761	11.8	n.a.[g]	2694	8.5	n.a.[g]	<0.001	0.51
Other	292	4.5	n.a.[g]	2487	7.8	n.a.[g]	<0.001	0.19
Unknown and missing	1918	29.7	n.a.[g]	22331	70.1	n.a.[g]		
Total	6449	100.0	n.a.[g]	31835	100.0	n.a.[g]		

IDU = injecting drug users; IR = incidence rate; n.a. = not available; NR = notification rate; OR = odds ratio
[a] For proportions
[b] Odds ratio calculated on the total number of cases for which at least one exposure is available
[c] Incidence rate per 100 000 population
[d] Notification rate per 100 000 population
[e] Not available because denominators for Swiss population by origin do not exist
[f] Several exposures possible
[g] Not available because several exposures were possible

Table 2: Annual incidence development of acute hepatitis B virus infection per 100 000 population by age in Switzerland, 1988–2015.

	Incidence per 100 000 population							**IRR (continuous years)**			**Variation of incidence (%) between 1988–1991 and 2012–2015**
Age group (years)[a]	**1988–1991**	**1992–1995**	**1996–1999**	**2000–2003**	**2004–2007**	**2008–2011**	**2012–2015**	**1988–2015**	**1988–1998[b]**	**1998–2015[b]**	
0–4	0.57	1.36	0.73	0.58	0.20	0.26	0.06	0.93**	1.05	0.89*	−89.5
5–9	0.46	1.17	0.53	0.18	0.19	0.06	0.00	0.89**	0.97	0.78**	−100.0
10–14	0.93	1.51	0.67	0.23	0.52	0.06	0.00	0.90**	1	0.87*	−100.0
15–19	12.82	10.91	4.40	1.35	0.95	0.77	0.34	0.86**	0.90**	0.84**	−97.3
20–24	27.05	29.53	8.43	3.73	2.01	0.78	0.45	0.86**	0.92**	0.83**	−98.3
25–29	12.76	14.68	7.64	4.56	1.85	0.97	0.91	0.89**	0.95**	0.87**	−92.9
30–34	8.09	8.43	5.58	3.56	2.58	1.36	0.82	0.92**	0.97	0.91**	−89.9
35–39	4.27	5.82	3.38	2.58	2.07	1.63	0.97	0.94**	0.99	0.93**	−77.3
40–49	3.09	3.41	2.59	2.08	1.88	1.50	0.94	0.96**	0.97*	0.94**	−69.6
50–59	1.75	2.10	1.71	1.86	1.27	0.86	1.10	0.97**	0.98	0.96**	−37.1
60–69	2.13	1.42	1.23	0.94	0.95	0.85	0.67	0.96**	0.91*	0.97	−68.5
70–79	1.95	1.10	0.36	0.34	0.47	0.40	0.61	0.94**	0.81**	1.04	−68.7
80–89	1.48	0.63	0.21	0.20	0.44	0.16	0.22	0.91**	0.80*	0.98	−85.1
≥90	0.00	0.00	0.00	0.00	0.87	0.42	0.00	1.08	–	1.01	–
Total	6.08	6.17	2.89	1.81	1.31	0.87	0.66	0.91**	0.93**	0.91**	−89.1

IRR = incidence rate ratio
[a] Age of 24 cases not known
[b] Introduction of vaccination of adolescents aged 11 to 15 years in 1998
* p <0.05; ** p <0.001

Table 3: Features of recently reported acute hepatitis B virus cases, Switzerland, 2011–2015.

		n	% total	% without unknowns	IR[a]
Total		291	100.0		0.7
Sex	Male	225	77.3		1.1
	Female	66	22.7		0.3
Age	0–4 years	1	0.3		0.1
	5–9 years	0	0.0		0.0
	10–14 years	0	0.0		0.0
	15–19 years	8	2.8		0.4
	20–24 years	13	4.5		0.5
	25–29 years	26	8.9		1.0
	30–34 years	26	8.9		0.9
	35–39 years	30	10.3		1.1
	40–49 years	68	23.4		1.1
	50–59 years	59	20.3		1.1
	60–69 years	36	12.4		0.8
	70–79 years	20	6.9		0.7
	80 years and over	4	1.4		0.2
Origin	Swiss	160	55.0	60.4	n.a.[b]
	Foreign	105	36.1	39.6	n.a.[b]
	Unknown	26	8.9		
Region of Switzerland	German-speaking	209	71.8		0.7
	French-speaking	55	18.9		0.5
	Italian-speaking	27	9.3		1.6
Assumed place of exposure	Switzerland	115	39.5	62.8	0.3
	Abroad	68	23.4	37.2	0.2
	Unknown	108	37.1		0.3
Assumed source of exposure[c]	Healthcare profession	1	0.3	0.6	n.a.[d]
	Blood transfusion and dialysis	4	1.3	2.6	n.a.[d]
	IDU	6	2.0	3.9	n.a.[d]
	Sexual contact	104	34.3	67.5	n.a.[d]
	Other contact	21	6.9	13.6	n.a.[d]
	Other	18	5.9	11.7	n.a.[d]
	Unknown and missing	149	49.2		n.a.[d]
	Total	349	100.0	100.0	

IDU = injecting drug users; IR = incidence rate; n.a. = not available. [a] Incidence rate per 100000 population. [b] Not available because denominators for Swiss population by origin do not exist. [c] Several exposures possible. [d] Not available because several exposures were possible

Table 4: Development of the notification rate of chronic hepatitis B virus infection per 100 000 population by age, Switzerland, 1988–2015.

	1988–1991[a]	1992–1995		1996–1999		2000–2003		2004–2007		2008–2011		2012–2015		1988–2015
Age group (years)[b]	**NR**	**NR**	**NRR**	**NR**	**NRR**	**NR**	**NRR**	**NR**	**NRR**	**NR**	**NRR**	**NR**	**NRR**	**NRR (continuous years)**
0–4	7.0	3.5	0.50**	3.4	0.49**	2.8	0.40**	1.4	0.19**	0.5	0.08**	0.6	0.09**	0.91**
5–9	4.8	2.9	0.61*	3.5	0.73	2.5	0.53*	1.8	0.37**	1.0	0.21**	0.6	0.12**	0.93**
10–14	3.3	2.4	0.71	4.5	1.36	3.4	1.03	3.9	1.18	2.7	0.82	1.4	0.41**	0.98*
15–19	15.5	13.2	0.85	13.0	0.84	14.9	0.96	14.5	0.94	11.6	0.75*	12.8	0.83*	0.99*
20–24	41.8	31.0	0.74**	33.2	0.79**	33.9	0.81**	34.1	0.82**	31.6	0.76**	26.9	0.64**	0.99**
25–29	40.8	30.8	0.76**	32.7	0.80**	36.6	0.90*	35.4	0.87*	32.1	0.79**	35.1	0.86*	1.00
30–34	28.5	23.6	0.83*	29.0	1.02	28.6	1.00	30.7	1.08	33.4	1.17*	35.6	1.25**	1.01**
35–39	21.7	16.4	0.76**	20.9	0.96	21.5	0.99	23.1	1.06	24.7	1.14*	31.4	1.45**	1.02**
40–49	14.4	11.2	0.78**	13.8	0.96	16.0	1.11	17.5	1.22**	16.0	1.11*	21.8	1.51**	1.02**
50–59	9.4	7.7	0.82*	9.6	1.03	9.8	1.04	12.1	1.30*	12.4	1.3**	16.1	1.72**	1.03**
60–69	6.6	5.2	0.78*	5.8	0.87	5.4	0.81	6.0	0.91	6.4	0.96	8.9	1.34*	1.01*
70–79	5.0	3.6	0.73*	3.2	0.64*	4.2	0.85	4.1	0.83	4.1	0.82	5.8	1.17	1.00
80–89	3.0	2.4	0.81	2.5	0.82	2.5	0.83	2.3	0.74	2.9	0.96	3.6	1.17	1.00
≥90	3.9	0.0	0.00	0.6	0.16	1.1	0.27	0.0	0.00	0.8	0.22	1.1	0.29	0.97
Total	16.5	12.5	0.75**	14.0	0.84**	14.3	0.86**	14.9	0.89**	14.4	0.86**	16.7	1.00	1.00**

NR = notification rate; NRR = notification rate ratio. [a] Reference period. [b] Age of 159 cases not known. * p <0.05; ** p <0.001

Discussion

This article describes how the epidemiology of acute and chronic HBV infection has developed in Switzerland since mandatory notification was introduced in 1988. It also describes the impact of universal vaccination of adolescents, introduced in 1998, on the epidemiology of acute infection. The annual IR of acute infection decreased by 95.0% between its peak in 1992 and its lowest point in 2015, from 7.5 to 0.4 cases per 100 000 population. This decrease accelerated after the introduction of universal vaccination for adolescents; it was more pronounced in the targeted age groups, which contributed to the overall increasing age of notified cases over time. In contrast, the annual NR of chronic infection has remained stable at about 15 cases per 100 000 population. The epidemiology of acute and chronic infection differs greatly, with distinct developments. Acute infection primarily affected men of Swiss origin aged 20 to 39 years, principally as a result of exposure through use of injectable drugs in the 1990s and thereafter, since the early 2000s, as a result of sexual contact with an infected person. Chronic infection was mainly reported in people of foreign origin aged between 20 and 49 years at the time of first notification, men slightly more often than women, most of them with an unknown source of exposure (otherwise mostly through nonsexual contact). In contrast to acute infections, most chronic infections had been contracted abroad. The proportion of infected persons with a foreign background increased over time for both acute and chronic infection, reaching 41.8 and 82.2%, respectively, of the total in the 2011–2015 period.

These last years, the IR of acute HBV infection in Switzerland was similar to the average IR in the European Union [15]. The NR of chronic HBV infection, on the other hand, was higher in Switzerland than in Europe (15 vs 8 cases per 100 000 population). This rate varied considerably from one country to another and reflects primarily the differences between surveillance systems, and screening and diagnostic practices.

The annual IR of acute HBV infection was consistently higher for men than for women. The proportion of MSM among men presumably infected through sexual contact has increased over time, reaching 41.5% in 2000–2015. Since the late 1990s, more cases were reported among MSM than among women infected through sexual contact. In Europe, roughly one acute infection in ten is nowadays due to sexual relations between men [15].

The impact of universal child vaccination programmes on the prevalence of HBV is well established [16, 17]. Switzerland also saw a considerable decrease in the IR of acute HBV infection in the targeted age groups shortly after universal adolescent vaccination had been introduced [18]. However, in Switzerland, as in Italy and most western countries, the decrease in incidence started before universal vaccination of children or adolescents had been introduced [19, 20]. This drop was mainly the result of preventive measures introduced not only to contain HBV infection (through vaccination) but also human immunodeficiency virus (HIV) infection, particularly among IDUs [21]. Use of injectable drugs was the principal source of exposure in 1988–1995 but became a marginal factor from 2004–2007 onward. In contrast, in the mid-1990s, the prevalence of antibodies against the HBV core antigen reached 73.2% among patients treated in a substitution programme for heroin [22]. The virtual absence of new infection among IDUs had already been observed in the Netherlands in 2000 [23, 24]. In 2012, only 8.7% of acute cases in the European Union were due to the use of injectable drugs, showing a downward trend [15]. In addition to harm reduction strategies in IDU, improved medical precautions against iatrogenic HBV transmission, changes in sexual behaviour related to more awareness of HIV-related risks and at-risk group vaccination may have also played a role in the observed steep decrease of HBV infection before the introduction of widespread vaccination programmes.

The introduction of universal adolescent vaccination in Switzerland in 1998 accelerated the decrease of HBV incidence. This was mainly due to minimising the risk of sexual transmission, which had become the main source of infection since the late 1990s. The simultaneous increase in the proportion of children already vaccinated before the age of 2 years may have also contributed to this decline. It should be noted that targeting mainly adolescents rather than infants usually makes it more difficult to reach high vaccination coverage. For example, the 2011–2013 coverage among children aged 2 years was 95–97% for three doses of infant vaccines and 89% for the fourth dose recommended at 15–24 months, whereas it was only 68% among 16-year-olds for hepatitis B and 54% for human papilloma virus, two vaccinations recommended for adolescents [13].

The example of Switzerland, and also Catalonia [25], British Columbia [26] and Quebec [27], shows that it is possible to achieve a substantial level of containment of HBV in low endemicity countries through a combination of universal (pre-)adolescent vaccination, vaccination of risk groups and other measures that target blood-borne exposure. However, the reduction observed in Switzerland was less pronounced than in Quebec, which introduced vaccination earlier (1994) and for younger children (aged 8–10 years), achieved a higher level of vaccination coverage (85%) and introduced a programme of catch-up vaccination in high schools.

The IR and NR of HBV infection among foreigners was higher than among the Swiss. The difference was more pronounced for chronic (NRR 7.92) than for acute infection (IRR 1.51). In addition, the proportion of cases of foreign origin increased significantly over time for both acute and chronic infection. Often greater than the risk of perinatal transmission [28–30], the risk of infection through parents or siblings during the first few years of life observed in regions with intermediate to high endemicity tends to persist after the family has moved to a low endemicity region [31–34].

In the Netherlands, the incidence of acute infection was 2.7 times higher for immigrants from endemic countries than for Dutch/western nationals and remained 2.4 times higher for their children born in the Netherlands [35]. In Germany, a seroprevalence study confirmed that second-generation migrants also constitute an at-risk population [36]. However, almost no cases of acute HBV infection are currently being reported in Switzerland among the under-15-year-olds, including those of foreign origin. Nevertheless, there may still be a low level of undiagnosed transmission among children, who are generally asymptomatic.

Despite the steep decrease in local transmission of HBV since 1993 in Switzerland, the NR of chronic infection has remained stable on the long run. The persistence of HBV in Switzerland is increasingly and primarily due to the importation of chronic cases by populations migrating from regions with intermediate to high endemicity. The growing and often dominant role of migrant populations in the prevalence of chronic HBV in low endemicity countries has already been noted elsewhere [37–41]. More than 95% of chronic cases that enter the Australian population every year are due to migration and not to domestic cases subsequently becoming chronic [42]. In 2012, 59.3% of the cases reported in European Union (9.8% for acute

and 84.1% for chronic HBV infection) were classified as imported [15]. Moreover, it is likely that, as in the Netherlands, residual transmission in the heterosexual population may originate largely from a partner who comes from a high endemicity country [23]. Sexual transmission is facilitated by the fact that most chronically infected people are not aware of their infection [43]. However, only a minority of infections acquired in adulthood become chronic.

The immigration of chronically infected individuals has at least two implications. On the one hand, the burden of disease in terms of cirrhosis, liver cancer, liver transplants and mortality is likely to continue to increase for at least two decades if no changes are made to the detection strategy, the proportion of cases treated and the efficacy of the treatment [44, 45]. On the other hand, in Switzerland, as in many other low endemicity countries, the prevalence of HBV depends more on global than on national vaccination policies [37]. The growing number of countries including HBV in their vaccination schedules (half of them with a birth dose) and progress in vaccination coverage should gradually contain the prevalence of chronic hepatitis in immigrants [1]. A reduction in the global prevalence from 4.2 to 3.7% has already been observed between 1990 and 2005 [46].

Given the persistence of a pool of persons chronically infected with HBV in Switzerland, the risk of transmission remains. Additional efforts need to be made to increase the vaccination coverage through universal vaccination in childhood (infancy or adolescence) and catch-up in adults, as well as identification and vaccination of uninfected populations at higher risk of exposure, transmission or complications, as stated in the recommendations issued by the FOPH [3, 11, 47]. In view of the current HBV epidemiology, these recommendations should be applied particularly to people originating from countries with intermediate to high endemicity and their contacts, including and above all their children, to MSM and to persons who frequently change sexual partners. However, for Switzerland and other countries that have largely controlled the epidemic of acute HBV infection, the main challenge is now to address the current epidemic of chronic infection. In order to further minimise the burden of disease, secondary prevention (i.e., detection in risk groups, evaluation and possibly treatment of chronic cases) should also be strengthened [3].

The strength of this analysis lies in the long surveillance period of 28 years during which the entire population living in Switzerland has been observed, in the distinction made between acute and chronic infection, and in the mandatory notification of all positive laboratory results, which increases the sensitivity of surveillance. Physicians completed a detailed form for a large proportion (86.4%) of cases reported by the laboratories. The full identity of patients was documented in each report, which made it possible to eliminate duplicate reports.

This report has several limitations. HBV infection is often asymptomatic, and there is no systematic screening programme in place except for some specific populations. Many cases have thus not (yet) been diagnosed. The criteria used to classify cases as acute or chronic changed during the entire surveillance period. However, the absence of a shift in the incidence of acute infection between 2007 and 2008, when case definitions were last modified, suggests that these changes have only had a limited effect on the way cases were classified. In the absence of clinical information, 14.7% of cases were considered to be chronic. For legal and data protection reasons, cases of hepatitis B and C for which the FOPH had not received a new report during the last 10 years were anonymised at the start of 2012. It was therefore no longer possible to assign some of the repeated reports to previously reported cases, and this led to chronic cases being duplicated. This is the main reason for the increase in the number of chronic HBV cases observed since 2012. A similar increase was recorded for hepatitis C. In our study the proportion of immigrants among reported chronic HBV infection might be biased upward due to diagnostic activity: targeted testing is recommended for persons originating from high endemicity countries. However, prevalence studies confirm that the foreign population in Switzerland was already more exposed to HBV than Swiss nationals 20 years ago [48]. In 2003–2004, 4.5% of patients born in Switzerland compared with 14.4% in those born abroad were positive for anti-HBc in the emergency department of a university hospital [49]. In 2005–2006, the overall prevalence of HBsAg was 0.7% for pregnant women, but 84% of positive women had been born abroad [50].

Conclusion

During 28 years of observation, the incidence of acute HBV infection in Switzerland has decreased continually in all age groups, but particularly in those targeted by universal vaccination of adolescents. This reduction is the result of the gradual introduction of measures aimed at preventing vertical, parenteral, sexual and nosocomial transmission of the virus, including vaccination of risk groups and, at a later stage, also of adolescents. The same tendency was anticipated, though with a delay, for the notification of chronic cases, but this has not been observed because of immigration from countries with intermediate to high endemicity. Mainly because of the current and future burden of chronic cases, Switzerland still requires the strengthening of secondary prevention of chronic HBV infection. Nevertheless, universal vaccination coverage must also be improved, as well as vaccination of people and their children originating from countries with increased endemicity, and persons who frequently change sexual partners.

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Authors' contributions
JR and VMS conducted the data collection and cleaning. JR analysed and interpreted data and wrote the manuscript. VMS and CS provided information about screening and vaccination and contributed to the interpretation of data and to the discussion section. SB, VMS, CS and JR contributed to the critical revision of the manuscript and approved the final version.

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