Hepatitis B virus prevalence in first-time blood donors in Flanders, Belgium: impact of universal vaccination and migration

Short running head: Prevalence and risk factors of HBV

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ABSTRACT

Background: Transfusion-transmissible infections such as hepatitis B virus (HBV) remain a major concern for the safety of blood transfusion. This cross-sectional study aimed to assess the trend of HBV prevalence and associated risk factors among a first-time donor population in a low endemic country.

Study design and methods: Between 2010 and 2018, blood samples were collected from first-time donors presented at donor collection sites of Belgian Red Cross-Flanders. They were tested for hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (anti-HBc) and HBV DNA, HIV and hepatitis virus C (HCV) antibodies and RNA, and syphilis antibodies.

Results: A total of 211,331 first-time blood donors (43.7% males, median age 25 years) were analyzed. HBsAg prevalence decreased from 0.06% in 2010 to 0.05% in 2018 (P=0.004) and this declining trend was accompanied by an increased number of donors in the HBV vaccinated birth cohort (P<0.001). HBsAg prevalence was 0.33% in foreign-born donors and 0.02% in Belgian natives (P<0.001). Multivariate risk profiling showed that anti-HBc positivity was significantly associated with mainly foreign-born donors (odds ratio, OR=9.24) but also with older age (OR=1.06), male gender (OR=1.32), year of blood donation (OR=0.94) and co-infections with HCV (OR=4.31) or syphilis (OR=4.91).

Discussion: The decreasing trend in HBV prevalence could mainly be explained by the introduction of the universal HBV vaccination. Being born in endemic areas was the most important predictor for HBV infection while the co-infections with syphilis suggest unreported sexual risk contacts.

Keywords: Blood donation, Hepatitis B, Migration, Sexual risk behavior, Vaccination

Introduction

Worldwide hepatitis B virus (HBV) infection is the main cause of life-threatening liver diseases such as cirrhosis and hepatocellular carcinoma.[1,2] The World Health Organization (WHO) estimated that HBV infection results in 887,000 deaths globally in 2015.[3,4] The prevalence of HBV infection varies widely across countries.[5,6] Approximately 45% of the world's population lives in high-prevalence areas (≥8% hepatitis B surface antigen (HBsAg) positive), 43% lives in intermediate-prevalence areas (2-7% HBsAg positive) and 12% lives in low-prevalence areas (<2% HBsAg positive).[7] The HBV infection prevalence rates are generally low in most countries in Western Europe, the Americas, Japan and Australia, while there is a high burden of disease in sub-Saharan Africa and some countries in the Western Pacific region.[6,7] The HBsAg prevalence in the general population of Belgium has been estimated at 0.7 to 1.0%.[8-10] These results were obtained more than a decade ago or in a population with relatively many immigrants. Even in low endemic countries such as Belgium, HBV prevention and control is a public health priority.[11]

To prevent transfer of transfusion-transmissible infections (TTIs), such as HBV, to the patient during blood transfusion, the donor health questionnaire is one of the important safety measures to identify risk behavior and defer people from donation.[12] Deferral policies for persons whose sexual behavior puts them at risk of acquiring HBV infections or who were born in HBV endemic regions, are commonly applied by blood transfusion services in Western countries.[12-14] Among the blood donor population, the available evidence suggests a link between HIV-1 infection and men who have sex with men (MSM). Currently, these candidate donors are excluded for at least one year after the last MSM contact.[15] Recent meta-analyses could demonstrate that having sexual risk contacts (e.g. sex with an intravenous drug user or receiving money for sex) or having a tattoo or body piercing are probably associated with an increased risk of HBV infection.[16,17] To date, there is only indirect evidence from the general population available to support the reasons for donor deferral based on migration from HBV endemic countries.[6] Nonetheless, since the presence of red blood cell antigens is related to ethnicity, it is crucial to recruit blood donors in certain ethnic groups for saving the lives of patients who share

their blood group.[18,19] When reducing the deferral period, especially the presence of occult HBV infections is of concern regarding blood safety. Occult HBV infection corresponds to blood donors negative for HBsAg but reactive for HBV DNA.[20] HBV transmission by these donors may occur through transfusion.[21,22]

This cross-sectional study aimed to assess the trend of prevalence of HBV infection and associated risk factors in blood donors in Flanders (Belgium) between 2010 and 2018. The results of this study can be used as a scientific basis for policy-makers to further underpin the current approach on donor deferrals and for updating the current burden of HBV infection in Flanders.

Materials and methods

Donor population and risk factors

This study included all first-time blood donors in Flanders, recruited at 11 donor centers and mobile blood collections, in the period 2010–2018. Before each donation, donors completed a standardized donor health questionnaire and a written informed consent. The content of the questionnaire was discussed with a medical doctor in a face-to-face interview.

When a risk factor was identified, the donors were deferred and not tested for HBV or other TTIs such as HIV, hepatitis C virus (HCV) and syphilis. Risk factors related to (i) health or medical treatments including amongst others dental care, surgery, injection of drugs and needle treatment, (ii) sexual risk contacts and (iii) stay abroad directly result in at least a temporary exclusion from blood donation. Since these candidates were not tested for HBV, the identified risk factors could not be taken into account in the data analysis. During the course of the study, candidate donors were deferred from blood donation for five (2010-2016) and three years (2016-2018) when they were born in HBV endemic countries based on the prevalence estimates reported by Schweitzer et al.[6] It is hence important to note that these donors were only temporary deferred and not permanently excluded from blood donation.

Donors with confirmed HBV infection were invited to the blood bank for medical counseling and for repeat testing to exclude laboratory errors. A trained medical counselor conducted a face-to-face

interview using a standardized posttest questionnaire dealing with potential non-reported risk factors.[23]

The following donor characteristics were recorded and included in the analysis as potential risk factor for current or past HBV infections: gender, age, country of birth and other TTIs (HIV, HCV and syphilis). The year of blood donation was studied to analyze trends in HBV infection among donor (sub)populations. The donor ages were grouped from mid-decade to mid-decade. Based on their country of birth, donors were stratified into (i) Belgian natives and foreign-born donors (FBD), into (ii) low (<2% HBsAg positive), intermediate (2-7% HBsAg positive) or high (>8% HBsAg positive) endemic HBV countries and into (iii) the six WHO regions (Africa, Americas, Eastern Mediterranean, Europe, Southeast Asia and Western Pacific)[6]. The characteristics derived from the donor's country of birth were used for evaluating the impact of migration as a risk factor on current or past HBV infection. For assessing the effect of the universal HBV vaccination in Belgium, the native Belgian first-time donors were divided in two birth cohorts (< 1987 and $\geq$ 1987). The universal infant vaccination program began in September 1999 and infants have been vaccinated against HBV at the ages of 8, 12 and 16 weeks and 15 months while adolescents with the age range of 10-13 years received catch-up vaccination. The vaccination program hence covers persons born in 1987 or later.[11] Posttest self-reported risk factors were categorized as blood-related (e.g. intravenous drug use, transfusion, tattoo/piercing, medical procedures), sexual (e.g. number of (new) sexual partners, context and nature of sexual encounters and potential risk factors present among sexual partners) or endemic (country of birth). Although blood-related, having an HBV infected household member (parent or sibling) was categorized as a separate risk factor.

Donor screening and confirmation testing

All first blood donations were tested for HBsAg (Prism/Architect HBsAg, Abbott Diagnostics, Abbott Park, IL, USA), anti-HBc (Architect anti-HBc, Abbott) and HBV DNA (COBAS MPX, Roche Molecular Diagnostics, Pleasanton, CA, USA). The limits of detection (LOD) for analysis of HBsAg and anti-HBc were <0.1 PEI U/ml and <1 PEI U/ml, respectively. For these serological tests, a single blood sample

was first screened and, when reactive, the sample was retested in duplicate. HBV DNA screening was performed in pools of six donations and HBV DNA positive pools were resolved to identify the individual HBV DNA positive donation. The LOD for HBV DNA in minipools of six was 22.8 IU/ml between 2010-2016 and 8.4 IU/ml between 2017-2018.

Similarly, all blood donations were also routinely tested for HIV, HCV and syphilis antibodies using commercial assays: Abbott Prism HIV O plus/Architect AG/Ab combo assays, Abbott Prism/Architect HCV assays and Microtrak Syphilis TPHA PK (2010-2016) or NewBio PK TPHA (2017-2018) assays (Newmarket Biomedical Ltd. Kentford, UK), respectively. A triplex nucleotide amplification testing (NAT) was also performed for measuring HIV RNA and HCV RNA together with HBV DNA.

HBsAg, HIV, HCV and syphilis confirmation testing was done on all serologically repeat-reactive samples. For HBsAg, the confirmation test was performed with a neutralization assay (Architect HBsAg neutralisation, Abbott). Confirmation testing on positive HBV DNA, HIV RNA and HCV RNA samples with an alternative real time PCR assay with similar LOD was only performed on serologically negative blood donors. No confirmatory analyses were used for repeat-reactive anti-HBc donations. Moreover, in the absence of HBV DNA reactivity, these positive anti-HBc donations were not individually retested for HBV DNA for confirming occult HBV infections during the course of the study. Our blood service established this retesting procedure in February 2019.

Taken together, HBsAg and HIV, HCV and syphilis antibody positivity here involves that the analyses were reactive during the screening, repeat and confirmatory procedure. Anti-HBc positivity is only based on the screening and repeat testing. Lastly, reactive NAT tests rely on positivity of minipool and individual testing (confirmed or not). The blood testing procedures for HBsAg, anti-HBc and HBV DNA are schematically presented in Fig. S1 (see Supporting Information).

Outcomes

The primary outcome variables are (i) the prevalence of current infection with HBV (HBsAg positivity) and (ii) current or past HBV infection (anti-HBc positivity) in the blood donor population. Moreover, we aimed to identify occult HBV infections (HBsAg negative, HBV DNA and anti-HBc positive). We were

not able to identify window-period infections since anti-HBc IgM positivity was not analyzed in the collected blood samples. Since the antibodies against HBsAg (anti-HBs) were not analyzed in all blood donations, it should be stressed that universal vaccination was assumed based on the use of birth cohorts.

Statistical analysis

Donor characteristics were summarized by descriptive statistics using means, standard deviations and 95% confidence intervals for continuous variables, median and inter-quartile ranges (IQR) for non-normal continuous data and percentages for categorical data. The Shapiro-Wilk test was used to test the continuous data for normality. Logistic regression models were used to analyze the trends in donor characteristics between 2010 and 2018.

For relating various risk factors to HBsAg (current HBV infection) and anti-HBc positivity (current or past infection), the odds ratios were estimated by the chi-squared or Fisher's exact test. For anti-HBc prevalence, all variables that had a P value of <0.10 in univariate analysis were included in a multivariate logistic regression model to estimate adjusted odds ratios (aOR). The final model was created, by using a backward stepwise procedure with a P value of <0.05 considered statistically significant. The independent variables were assessed for multicollinearity by evaluating the variance inflation factors. Due to the expected small number of events, no logistic regression analysis was performed for HBsAg prevalence. Multivariate logistic regression models were used to analyze the trends in current (or past) HBV infection as a function of time. Regarding the latter, the dependent variable was diagnosed HBsAg or anti-HBc positivity and the term of the risk factor variable (age, gender, country of birth or vaccinated birth cohort) multiplied by the time variable was added as covariate to examine the effects of the interaction between risk factor and time, as well as to investigate whether the rates of change over time in prevalence differed across groups. A statistically significant interaction between time and a given group indicated that the rate of change in prevalence differed over time compared with the reference group.[24] Data analysis was conducted in RStudio: Integrated Development Environment for R (RStudio, Inc., Boston, MA.).

Ethical approval

The study was approved by the Medical Ethics Committee of UHasselt (18/0086R), and was conducted in accordance with the provisions of the Declaration of Helsinki and its amendments.

Results

Characteristics of blood donors

Between January 2010 and December 2018, 211,331 first-time blood donors, including 92,366 (43.7%) men, were tested for HBV infection and gave their written informed consent. An additional 3,117 first-time donors did not agree with their coded personal data being used for scientific research. The median age of the first-time donors was 25 years (IQR 20). The donor characteristics are listed in Table 1.

Data on the country of birth were missing for 1.0% (2,126/211,331) of the blood donations of which 54.2% (1,153/2,126) in 2010. As a consequence, we excluded all the blood donations in 2010 from the subgroup analyses based on country of birth. FBD comprised 7.5% (13,742/183,071) of the donor population and 25.4% (3,491/13,742) of these FBD donors originated from HBV intermediate or high endemic countries (see Supporting Information, Fig. S2). In total, the FBD originated from 158 different countries. Among the FBD, 73.1% (10,047/13,742) had their roots in WHO European region with more than 50% (5,310/10,047) from the neighboring countries the Netherlands, Germany, France and Luxembourg. Furthermore, 21.5% (2,156/10,047) of the European FBD were born in intermediate or high endemic countries with 34.7% (748/2,156) born in Turkey, 15.1% (326/2,156) in Italy, 14.3% (310/2,156) in Russia, 10.8% (233/2,156) in Romania and 25.0% (539/2,156) in 12 other countries. A total of 3,614/13,742 FBD (26.3%) were born outside the WHO European region and originated mostly from Morocco (21.1%, 763/3,614), Iran (7.6%, 273/3,614), India (6.2%, 223/3,614), USA (5.9%, 214/3,614) and Democratic Republic of the Congo (5.5%, 200/3,614). The number of FBD admitted to blood centres in Flanders relatively increased ($p<0.001$) with about 5% for every study year. Finally, based on the universal vaccination program in Belgium, the number of Belgian donors born after 1987 (vaccinated birth cohort) relatively increased with 11.6% per year ($p<0.001$).

Prevalence of HBsAg and anti-HBc positivity

Of the 210,419/211,331 (99.6%) first-time donors successfully tested for HBsAg, HBsAg was detected in 109 of them. Since 9 of the 109 HBsAg positive donors (8.3%) had no detectable HBV DNA and core antibodies, the overall positivity rate for current HBV infection was 0.05% (95% CI 0.04-0.06; 100/210,419). These other 9 donors were presumably vaccinated just before blood donation. The recent vaccination status was confirmed in seven of these donors based on a posttest interview and an additional blood sample. HBsAg was not detected anymore in these samples after two weeks. Of the 100 blood donors with current HBV infection, 93 had detectable HBV DNA and seven had unknown or no detectable levels of HBV DNA (Fig. 1).

The overall anti-HBc positivity was 0.86% (95% CI 0.82-0.90; 1,802/209,193). Of note, potential occult HBV infections were detected in two male donors (0.11%; 2/1,802) who were older than 35 years, one born in Syria and one in Turkey.

Trend and risk factors of HBsAg positivity

Table 2 shows the prevalence of current HBV infection by different risk factors. The HBsAg prevalence decreased from 0.06% (17/26,994) in 2010 to 0.05% (9/19,998) in 2018. Overall, the HBsAg prevalence among the blood donor population declined with 11% per year between 2010 and 2018 (P=0.004). Out of the 100 HBsAg positive persons, 65 were males (0.07% HBsAg positivity rate) and 35 females (0.03% HBsAg positivity rate) (P<0.001, OR=2.39 for male vs female donors). The higher hepatitis B prevalence rates among males compared to females did not change over time (data not shown). The positivity rates in 18-24 year-olds (0.02%, 17/103,161) were significantly (P<0.001) lower than in donors older than 25 years. In the 2010-2018 period, the trend in HBsAg prevalence rate decreased for all age groups (Fig. 2) but no significant interaction effect could be demonstrated between age and time (P=0.680).

The prevalence for HBsAg during the period 2010-2018 was substantially higher (P<0.001) among FBD (0.33%, 45/13,690) compared with Belgian natives (0.02%, 37/168,773). About 55% (45/82) of the donors who tested positive for HBsAg were FBD of which 56% (25/45) were immigrants from HBV

intermediate or high endemic countries. The prevalence rates were significantly (P<0.001) higher for donors born in HBV intermediate or high endemic countries compared to those born in low endemic regions. Fig. S3 (see Supporting Information) illustrates the country of birth distribution of the HBsAg positive cases with eight HBsAg positive donors born in Morocco, six in Turkey, four in Romania and three in Bulgaria. Fig. 2 shows a downward trend in HBsAg prevalence among FBD as well as in donors born in Belgium over the period 2010-2018. We could not demonstrate a significant difference in this decline between migrants and Belgian natives (P=0.375). Among the Belgian native donors born $\geq$ 1987, the prevalence rate (0.01%, 7/97,732) was significantly lower (P<0.001) than among those who were born before 1987 (0.04%, 30/71,041).

The prevalence of HIV, syphilis and HCV in the study population was 0.003% (95% CI 0.001-0.007; 6/210,416), 0.04% (95% CI 0.03-0.05; 83/210,400) and 0.02% (95% CI 0.01-0.03; 41/210,340), respectively. Among the HBsAg positive donors, only one donor had a HCV co-infection and one other donor had a co-infection with syphilis.

Standardized posttest survey data were available from 73/100 candidate donors with current HBV infection (Table 3). Heterosexual risk contacts (14%) and having an HBV-infected household member (16%) were the greatest posttest self-reported risk factors. There were no significant differences between these risk factors reported by Belgian natives or FBD. No unreported MSM contacts were identified among the persons with current HBV infection.

Trend and risk factors of anti-HBc positivity

Table 4 shows the prevalence of anti-HBc by different risk factors. The anti-HBc positivity decreased from about 1.0% in 2010 to 0.8% in 2018 (P<0.001). No significant interactions in the annual prevalence rates were observed between time and groups based on age, gender, country of birth or vaccinated birth cohort (data not shown). Prevalence rates for males and females were 1.06% (972/91,501) and 0.71% (830/117,692), respectively. The anti-HBc positivity was lower (P<0.001) in 18-24 years old (0.26%, 270/103,119) compared with donors older than 25 years.

The anti-HBc prevalence among Belgian native donors (0.51%, 849/167,690) was lower than in FBD. Current or past HBV infection in FBD was apparent in 668 of 13,667 (4.89%) with differences (P<0.001) between those born in low endemic countries (2.78%, 272/9,795) and HBV intermediate or high endemic countries (10.83%, 376/3,473). Twenty positive donors could not be assigned to a country with known endemicity.[6] Taken together, 44% (668/1,517) of the positive anti-HBc were among FBD of which 56% (376/668) originate from an HBV intermediate or high endemic country. About 33% (219/668) of the anti-HBc positive FBD were from Turkey (positivity rate 15.75%, 117/743) and Morocco (positivity rate 13.42%, 102/760). Furthermore, about 6% (39/668) of the anti-HBc positive FBD were born in Poland (positivity rate 5.19%, 39/751), 5% (36/668) in Romania (positivity rate 15.52%, 36/232), 4% (24/668) in India (positivity rate 10.96%, 24/219) and 52% (347/668) in 79 other countries. The exact country of birth of three anti-HBc positive FBD was unknown. In Fig. 3, we stratified the countries of birth based on anti-HBc positivity (low: <2%; intermediate: 2-7%; high: >8%). Anti-HBc prevalence in Belgian natives born after 1987 was 0.21% (205/97,701) and was significantly (P<0.001) lower compared with those born before 1987 (0.92%, 644/69,989).

Univariate analyses showed that HIV (P=0.001), HCV (P<0.001) and syphilis (P<0.001) infection were significantly associated with anti-HBc positivity. About 20% of the positive syphilis donors had a current or past HBV infection. Male donors had significantly (P=0.048) higher syphilis co-prevalence rates (27.1%, 13/48) than females (8.6%, 3/35).

The multivariate analysis confirmed that FBDs were more likely to have current or past HBV infection (aOR = 9.24; 95% CI 8.31-10.25) compared with Belgian natives and this risk factor accounted for about 60% of the variation in the model (Table 4). Furthermore, the age of the donor (aOR = 1.06; 95% CI 1.06-1.07) explained a substantial amount of the remaining variation (about 36%). Finally, donors with syphilis or HCV infection had increased odds of being infected with hepatitis B (in the past) but these parameters explained together less than 1% of the total variation. HIV infection did not statistically contribute to the model.

Discussion

Among the first-time blood donor population, about 0.05% were currently infected with the HBV and 0.86% showed evidence of HBV exposure, i.e. anti-HBc positive. Even with HBV DNA screening, the detection of occult HBV infections remains problematic due to very low HBV viral loads and anti-HBc testing is used to intercept potentially infectious HBsAg negative donations.[25,26] Although the predictive value of universal anti-HBc donor screening for occult HBV infections is low, the anti-HBc positive donations will not be used for blood transfusion for eliminating the residual risk of infectious donations based on the precautionary principle.[27,28]

The main finding of this study is that being born in an HBV intermediate or high endemic country is by far the most important risk factor for HBsAg and anti-HBc positivity among first-time blood donors in Flanders. The FBD account for about 55% or 44% of the HBsAg or anti-HBc positive cases, respectively. When controlled for confounders in a multivariate analyses for anti-HBc positivity, FBD explained about 60% of the model. Second, the results clearly show that young adults are less prone to HBV infection probably due to the universal vaccination program. As a potential result, a decreasing trend in HBsAg (11% per year) and anti-HBc (6% per year) prevalence was detected between 2010 and 2018. Lastly, co-infections between HBV and HCV or syphilis provided indirect evidence that unreported sexual risk behavior may be an important risk factor for HBV infections.

Previous prevalence studies in Belgium reported that 0.7% to 1.0% of the general population is positive for HBsAg and 6.4% to 8.4% is positive for anti-HBc.[8-10] It is important to note that blood donors are generally not a representative sample for the general population due to the strict and selective deferral criteria used by the blood banks.[13,14] Between 2017 and 2018, on average 13,500 persons were annually deferred from blood donation because of identified risk situations. About 18% of these potential donors were temporarily excluded based on sexual risk behavior, 37% based on risks related to stay abroad and 45% based on risks associated to needle treatments or medical interventions. More specifically, being born in HIV/HBV/HCV endemic countries accounted for 1.8% all risk-based deferrals. This selection bias explains the discrepancy between the prevalence of current (and past) HBV

infection in first-time blood donors and the general population. Indeed, the facts that candidate donors with identified risk behaviors based on the donor health questionnaire were not enrolled in the study and that blood donors generally exhibit a healthy lifestyle, directly result in an underestimation of the prevalence of HBV infection when one aims to extrapolate the infection rates to the general population.[29] Nevertheless, the prevalence of current HBV infection is in line with those reported in first-time blood donors in 2011 in most of the West-European countries: 0.12% in Germany, 0.07% in France, and 0.03% in The Netherlands.[30]

Immigration from HBV intermediate or high endemic areas has a pronounced effect on HBV prevalence among Flemish blood donors which is in line with prior studies conducted in the general population.[10,31,32] While immigrants from HBV intermediate or high endemic countries (mainly China, Romania and Turkey) represent only about 10% of the total European Union, they account for 25% of all chronic HBV infections.[31] Furthermore, based on genotyping, van de Laar et al.[23] showed that genotype D predominates in Flemish blood donors with a chronic HBV infection as a direct result of the migration from mainly Turkey and Syria (D1), Morocco (D7) and Eastern Europe (D2). This high genetic diversity suggests that the majority of chronic HBV infections in low endemic countries can be explained by population migration.[6,33,34]

Interestingly, having an HBV infected household member is one of the most reported posttest risk factors among the HBsAg positive blood donors born in Belgium. This could potentially be explained by transmission of HBV infection from first generation immigrants (i.e. foreign-born) to their children (second-generation immigrants, i.e. born in Belgium with a foreign-born parent) at birth or in childhood. To provide direct evidence, future studies should also ask blood donors for their ethnicity and parents' country of birth. Slot et al.[33] indeed found that second-generation immigrants from intermediate or high endemic countries still accounted for 6-10% of acute HBV infections in blood donors in the Netherlands.

In the general population in Flanders, Koc et al.[35] found that the acute hepatitis B notification rates decreased from 1.56 per 100 000 population in 2009 to 0.66 in 2017, possibly due to the

implementation of universal HBV vaccination in Belgium since 1999 with catch-up vaccination in one age cohort (11-13 years). Likewise, both HBsAg and anti-HBc positivity prevalence estimates were decreasing between 2010 and 2018 among our first-time blood donors in Flanders. The decrease in current or past HBV infection went hand in hand with an increase in number of donors who are assumed to be vaccinated against HBV. The HBV prevalence rate was lowest among the 18-24 year-olds covered by universal infant vaccination. The proportional increase in FBD throughout the study years could be an important confounding factor but we were not able to demonstrate a significant different trend in HBV prevalence between Belgian natives and FBD. The implementation of HBV vaccination into national routine immunization programs has globally resulted in a marked decrease in the disease burden.[36] One can assume that young FBD are increasingly being vaccinated during childhood in the country of origin. Although blood donors born in 1987 or later exhibited lower prevalence rates of current HBV infection in this study, seven (0.01%) of them were still identified as HBsAg positive. Among vaccinated 18- to 21-year old blood donors in China, the prevalence of HBsAg accounted for 3.4% suggesting exposure to HBV not prevented by vaccination.[37] Both Koc et al.[38] and Theeten et al.[39] indicated that the vaccinated serostatus in Belgium was more prevalent in vaccinated birth cohorts targeted in infancy (more than 80%) than in those targeted in adolescence (about 40-60%). Moreover, the self-reported coverage of vaccination against HBV between 1999 and 2017 in Flanders, Belgium, exceeded 90% of the infants from 2005 onwards while it was below 90% for adolescents up to 2017.[40] In line with these results, the majority of the HBsAg positive donors born $\geq$ 1987 in our analysis were expected to be vaccinated at ages between 10-13 years. Lastly, we cannot confirm whether correct measures were taken to prevent perinatal HBV transmission (e.g. HBsAg screening of pregnant women).[41,42]

Sexual transmission of HBV is predominant in low endemic areas and the risk of infection is especially high among people having e.g. multiple partners and MSM.[35,43,44] Given that syphilis is one of the most common sexually transmitted diseases in Western countries,[45] one can hypothesize that its co-infection with HBV potentially rise from sexual risk contacts. This hypothesis was supported by the fact

that the co-infection between HBV and syphilis was mainly among males and, more general, that male donors were more likely than females being infected with HBV. Higher rates of HBV infections among males have been described in several European countries with sexual contact as the most reported route of transmission.[46,47] However, it cannot be ruled out that these co-infections were due to vertical transmission since they were especially high in FBD from intermediate or high endemic countries.

This study has some limitations. Besides the fact that the results cannot be extrapolated to the general population, the major limitation of the current analysis is that no causal relationships can be extracted from this cross-sectional study. This study could not detect significant interaction effects in the trend analyses and associations between HBsAg and other TTIs such as HIV, HCV and syphilis due to low number of events (imprecise results). We also recognize that we could not differentiate between acute and chronic HBV infection because we had HBsAg results from only one time point. Further, based on the universal vaccination program in Flanders, we used cohorts based on year of birth (born before or after 1987) to assess the protective impact of assumed HBV vaccination.

The strength of this study is that it directly reveals that population migration is the most discriminant factor for current or past HBV infection among blood donors. The blood bank is always seeking for possibilities to shorten, or even lift, any deferral periods but a residual risk for HBV persists, and, based on the precautionary principle, it is essential that we identify high-risk donor groups for maintaining and improving the safety of blood transfusion. Indeed, despite a considerable reduction of the risk of HBV-infected blood donation entering blood supply due to improved screening by HBV NAT tests,[27,48,49] the residual risk of transfusing a blood unit infected with HBV still amounts 1 in 300,000 to 1,000,000 donations while it was estimated for HIV and HCV at about 1 in 4,000,000 to 6,000,000 and 1 in 700,000 respectively (unpublished results). When further reducing the deferral window for this donors born in HBV intermediate or high endemic countries, especially the detection of window-period and occult HBV infection remains a major point of concern regarding blood safety.

In conclusion, our study showed that 0.86% of the first-time donors were deferred from blood donation in Flanders between 2010 and 2018 based on serological evidence of current or past HBV

infection. Although the prevalence estimates decreased during the course of the study probably due to the introduction of the universal vaccination program, subpopulations of higher HBV prevalence exist among the blood donors. We identified FBDs as the most important high-risk group accounting for about 55 or 44% of the total HBsAg and anti-HBc positivity, respectively. There was also indirect evidence that donors having sexual risk contacts were more likely to be infected with HBV. To reduce or even eliminate HBV infections among the blood donor population, targeted effort is needed to improve screening and disease awareness among these high-risk groups.

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Tables

Table 1: Characteristics of first-time blood donors in Flanders, Belgium, 2010-2018 (n=211,331)

	Number (N)	Percentage (%)
Overall	211,331	-
Demographics		
Gender		
Female	118,965	56.3
Male	92,366	43.7
Age		
18-24 years	103,661	49.0
25-34 years	39,946	18.9
35-44 years	32,867	15.6
>45 years	34,857	16.5
Geographics		
Country of birth		
Belgian donors	169,329	92.5
FBD	13,742	7.5
Endemicity of FBD		
Low	9,850	71.7
Intermediate/High	3,491	25.4
Unknown	401	2.9
WHO region of FBD		
Africa	565	4.1
Americas	556	4.0
South-East Asia	507	3.7
Europe	10,047	73.1
Eastern Mediterranean	1,645	12.0
Western Pacific	341	2.5
Unknown	81	0.6
Vaccinated birth cohort †		
No	71,249	42.1
Yes	98,080	57.9

Definitions: † Assumed vaccination based on birth cohorts (Belgian donors born < 1987 or $\geq$ 1987)
Abbreviation: FBD, foreign-born donor; WHO: World Health Organization

Table 2: Prevalence of hepatitis B surface antigen among first-time blood donors and associated risk factors in Flanders, Belgium, 2010-2018 (n=210,419)

	Positive donors (n)	Total donors (N)	Prevalence (95% CI)	Unadjusted OR (95% CI)	P value
Overall (trend)	100	210,419	0.05% (0.04;0.06)	0.89 (0.82;0.96) †	0.004
Demographics					
Gender					
Female	35	118,344	0.03% (0.02;0.04)	*(ref)*	
Male	65	92,075	0.07% (0.05;0.09)	2.39 (1.58;3.60)	<0.001
Age					
18-24 years	17	103,161	0.02% (0.01;0.03)	*(ref)*	
25-34 years	18	39,790	0.05% (0.03;0.07)	2.75 (1.42;5.33)	<0.001
35-44 years	27	32,735	0.08% (0.06;0.12)	5.01 (2.73;9.19)	<0.001
>45 years	38	34,733	0.11% (0.08;0.15)	6.65 (3.75;11.77)	<0.001
Conitunous				1.05 (1.03;1.07)	<0.001
Geographics					
Country of birth					
Belgian donors	37	168,773	0.02% (0.02;0.03)	*(ref)*	
FBD	45	13,690	0.33% (0.24;0.44)	15.03 (9.73;23.24)	<0.001
Endemicity					
Low	56	178,585	0.03% (0.02;0.04)	*(ref)*	
Intermediate/High	25	3,478	0.72% (0.48;1.08)	23.08 (14.39;37.03)	<0.001
Vaccinated birth cohort ‡					
No	30	71,041	0.04% (0.03;0.06)	*(ref)*	
Yes	7	97,732	0.01% (0.01;0.02)	0.17 (0.07;0.39)	<0.001

Definitions: † Results of trend analyses between 2010 and 2018; ‡ Assumed vaccination based on birth cohorts (Belgian donors born < 1987 or $\geq$ 1987).
Abbreviations: OR, odds ratio; CI, confidence interval; FBD, foreign-born donor.

Table 3: Posttest self-reported risk factors of donors with current hepatitis B virus (HBV) infection.

Risk factor	Donors with HBV infection			P value
	Belgian donors (n=34)	FBD (n=39)	Total (n=73)	
Heterosexual risk contacts (%)	5 (15%)	5 (13%)	10 (14%)	1.0
Blood-related risk factors (%)	3 (9%)	3 (8%)	6 (8%)	1.0
Infected household members (%)	7 (21%)	5 (13%)	12 (16%)	0.528
Recent travel to intermediate or high endemic country (%)	1 (3%)	0 (0%)	1 (1%)	0.466
No/unknown risk factors (%)	18 (53%)	26 (67%)	44 (60%)	0.338

Abbreviation: FBD, foreign-born donor

Table 4: Prevalence of hepatitis B core antibodies among first-time blood donors and associated risk factors in Flanders, Belgium, 2010-2018 (n=209,193)

	Positive donors (n)	Total donors (N)	Prevalence (95% CI)	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Contribution to model (%)
Overall (trend)	1802	209,193	0.86% (0.82;0.90)	0.96 (0.95;0.98) †	<0.001	0.94 (0.92;0.96)	<0.001	1.2%
Demographics								
Gender								
Female	830	117,692	0.71% (0.66;0.76)	*(ref)*		*(ref)*		
Male	972	91,501	1.06% (1.00;1.13)	1.51 (1.38;1.66)	<0.001	1.32 (1.19;1.46)	<0.001	2.2%
Age								
18-24 years	270	103,119	0.26% (0.23;0.30)	*(ref)*				
25-34 years	289	39,683	0.73% (0.65;0.82)	2.79 (2.37;3.30)	<0.001			
35-44 years	477	32,159	1.48% (1.36;1.62)	5.74 (4.94;6.66)	<0.001			
>45 years	766	34,232	2.24% (2.09;2.40)	8.72 (7.59;10.02)	<0.001			
Continuous				1.06 (1.06;1.07)	<0.001	1.06 (1.06;1.07)	<0.001	36.1%
Geographics								
Country of birth								
Belgian donors	849	167,690	0.51% (0.47;0.54)	*(ref)*		*(ref)*		
FBD	668	13,667	4.89% (4.54;5.27)	10.10 (9.11;11.19)	<0.001	9.24 (8.31;10.25)	<0.001	59.6%
Endemicity §								
Low	1121	177,485	0.63% (0.60;0.67)	*(ref)*				
Intermediate/High	376	3,473	10.83% (9.82;11.92)	19.10 (16.91;21.58)	<0.001			
Vaccinated birth cohort ‡								
No	644	69,989	0.92% (0.85;0.99)	*(ref)*				
Yes	205	97,701	0.21% (0.18;0.24)	0.23 (0.19;0.27)	<0.001			
Other TTIs								
HIV *								
Negative	1800	209,170	0.86% (0.82;0.90)	*(ref)*				
Positive	2	6	33.33% (4.33;77.72)	57.60 (10.54;314.69)	0.001			
HCV								
Negative	1796	209,060	0.86% (0.82;0.90)	*(ref)*		*(ref)*		
Positive	5	41	12.20% (4.58;27.00)	16.03 (6.28;40.89)	<0.001	4.31 (1.16;12.55)	0.014	0.2%
Syphilis								
Negative	1786	209,077	0.85% (0.82;0.89)	*(ref)*		*(ref)*		
Positive	16	83	19.28% (11.75;29.71)	27.72 (16.03;47.91)	<0.001	4.91 (2.42;9.34)	<0.001	0.7%

Definitions: † Results of trend analyses between 2010 and 2018; ‡ Assumed vaccination based on birth cohorts (Belgian donors born < 1987 or ≥ 1987). Since only Belgian native donors were included in the birth cohorts, this variable was not included in the multivariate logistic regression analysis; § Due to concerns on multicollinearity between the variables country of birth and endemicity, endemicity was not included in the multivariate logistic regression analysis; * HIV infection did not statistically contribute to the multivariate logistic regression model and was excluded from the model using a backward stepwise procedure.
Abbreviations: OR, odds ratio; CI, confidence interval; FBD, foreign-born donor; TTI, transfusion-transmissible infections; HIV, human immune-deficiency virus; HCV, hepatitis C virus

Figure legends

Fig. 1: Positive hepatitis B virus (HBV) test results for first-time donors in Flanders, Belgium, between 2010-2018. Positive test results include hepatitis B core antibody (anti-HBc) reactive, hepatitis B surface antigen (HBsAg) reactive (confirmed by neutralization), and/or detection of HBV DNA donations (confirmed by single-unit triplex nucleotide amplification testing). Donors with current hepatitis B virus infection are highlighted in bold. Concept based on van de Laar et al.[27]

Fig. 2: Prevalence of hepatitis B surface antigen (HBsAg) (%) among first-time donors in Flanders, Belgium, 2010-2018, by (A) age group (n=210,419) (dashed black line: 18-24 years, solid black line: 25-34 years, solid dark grey line: 35-44 years, solid light grey line: 45+ years) and (B) country of birth (n=182,463) (solid black line: Belgian natives, solid grey line: foreign-born donors).

Fig. 3: Prevalence of hepatitis B core antibodies (anti-HBc) among first-time blood donors in Flanders between 2010-2018 based on country of birth (total number of donors per country >30).

Supporting Information

Fig. S1: Blood screening procedure for hepatitis B virus markers. (1) Retesting at next blood donation; no confirmatory analyses were used for repeat-reactive anti-HBc donations. (2) Confirmatory testing was only performed on serologically non-reactive blood samples.

Fig. S2: Country of birth of first-time blood donors in Flanders, Belgium, 2010-2018.

Fig. S3: Prevalence of hepatitis B surface antigen (HBsAg) among first-time blood donors in Flanders, Belgium, 2010-2018, based on country of birth.

Fig. 1

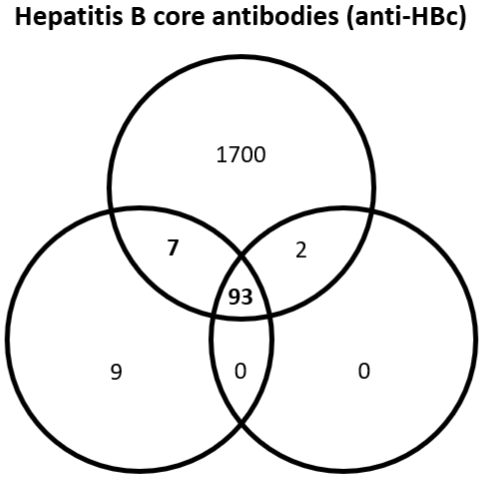
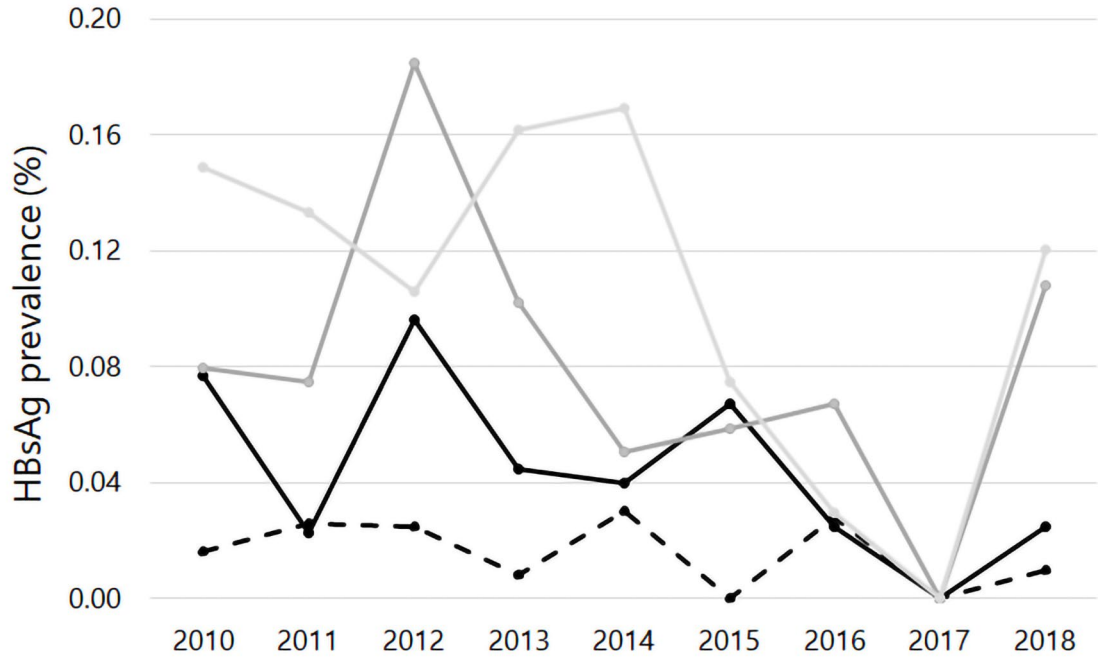

Hepatitis B core antibodies (anti-HBc)
1700
7
2
93
9
0
0
Hepatitis B surface antigen (HBsAg)
Hepatitis B virus DNA (HBV DNA)

Fig. 2

A.


0.20
0.16
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HBsAg prevalence (%)
2010
2011
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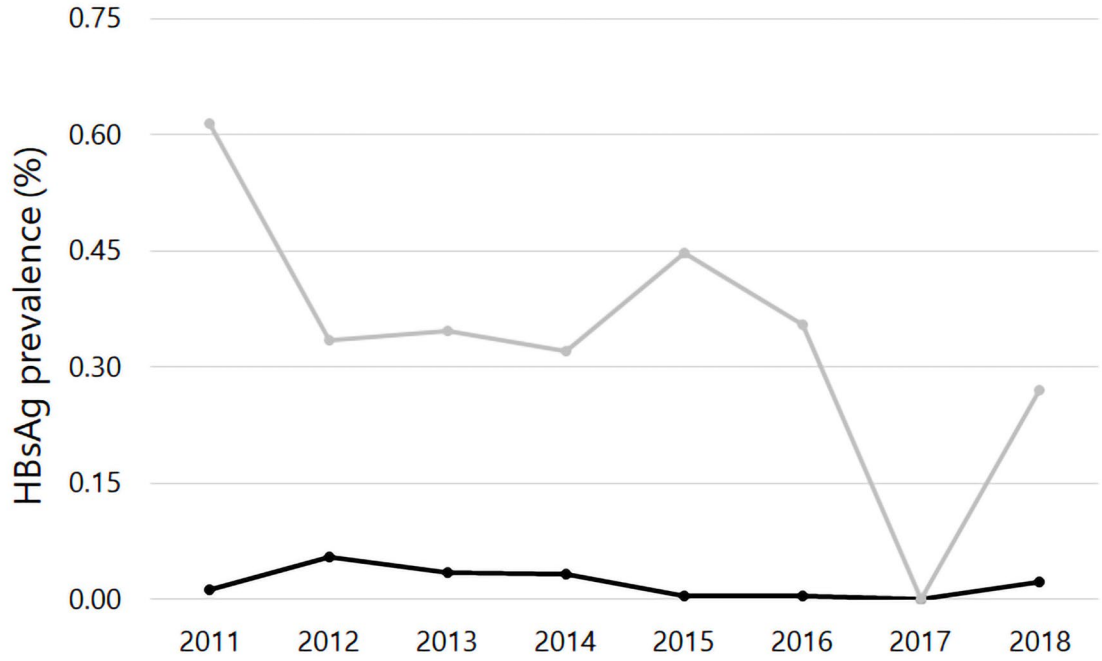
2018

B.


0.75
0.60
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0.15
0.00
HBsAg prevalence (%)
2011
2012
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2014
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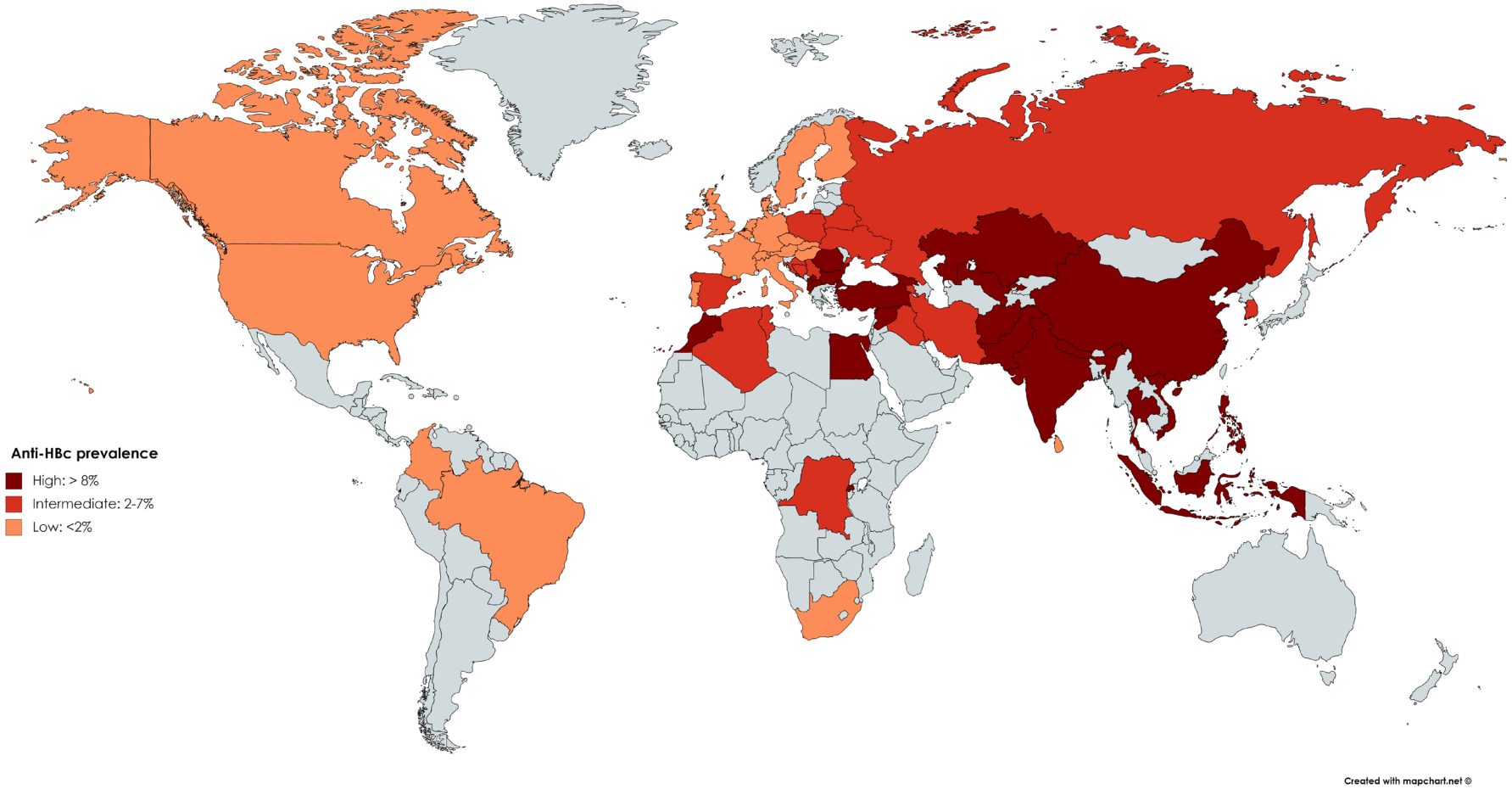
2016
2017
2018

Fig. 3


Anti-HBc prevalence
High: > 8%
Intermediate: 2-7%
Low: <2%
Created with mapchart.net ©

Supporting Information

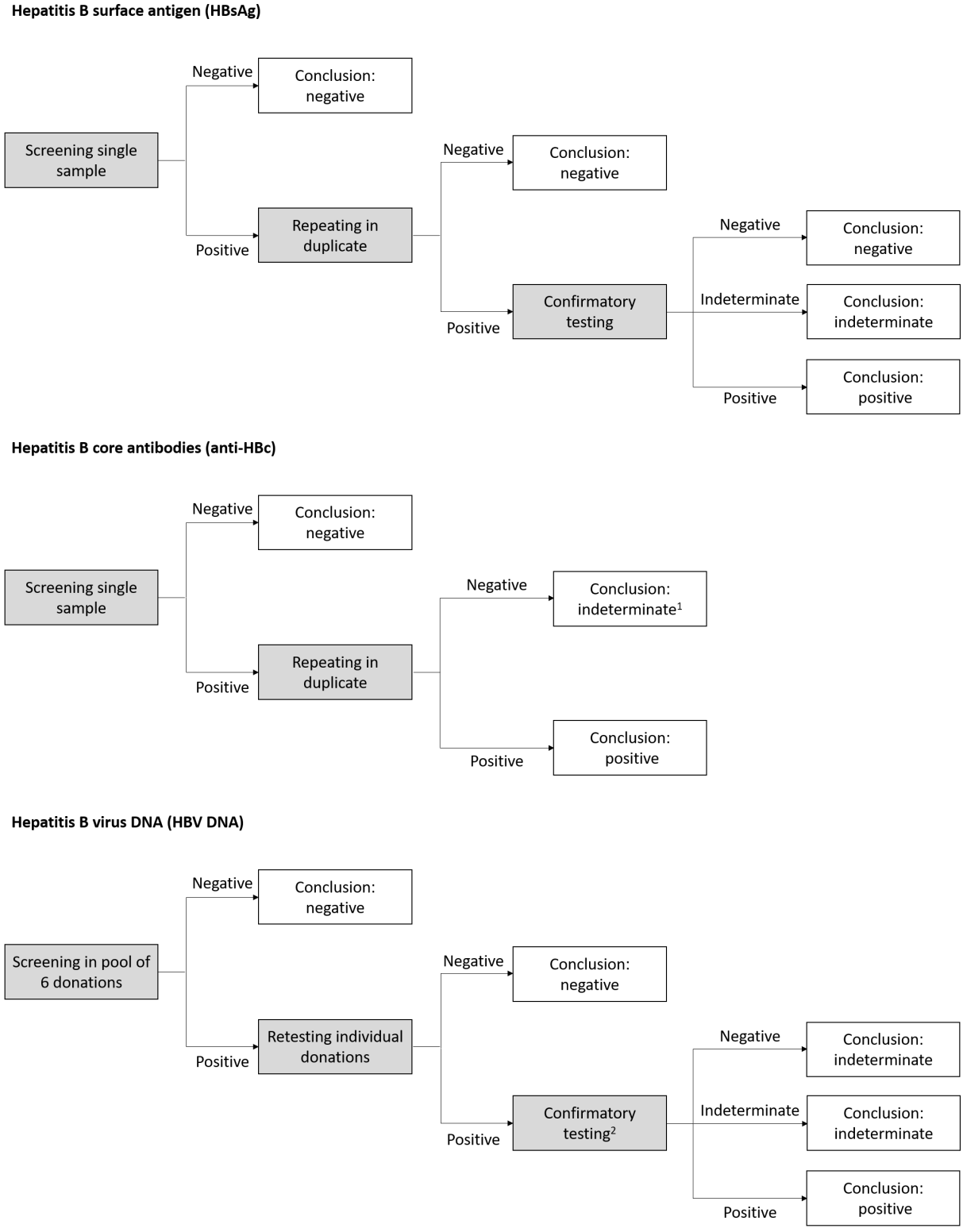


Fig. S1: Blood screening procedure for hepatitis B virus markers. (1) Retesting at next blood donation; no confirmatory analyses were used for repeat-reactive anti-HBc donations. (2) Confirmatory testing was only performed on serologically non-reactive blood samples.

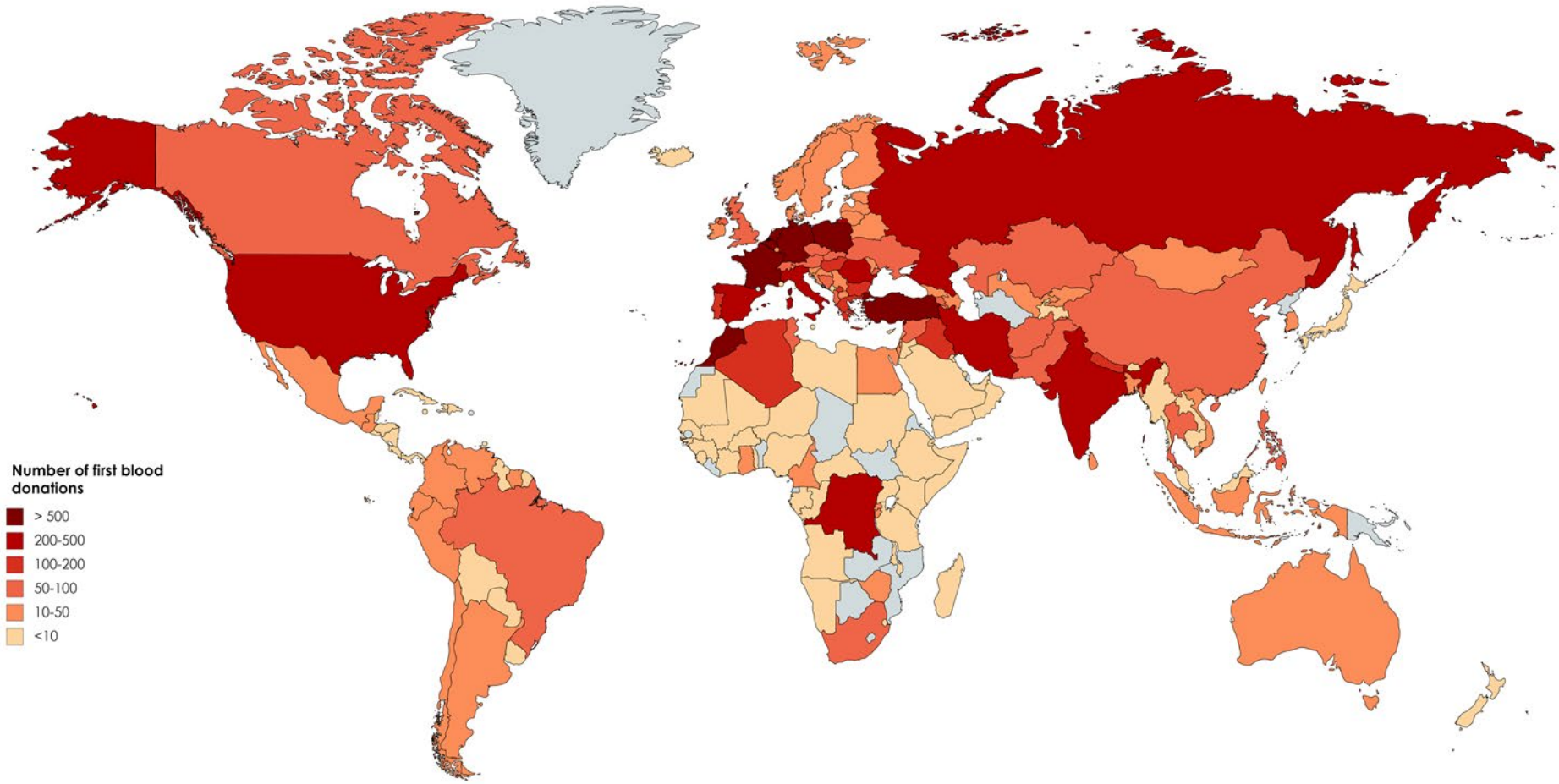


Fig. S2: Country of birth of first-time blood donors in Flanders, Belgium, 2010-2018.

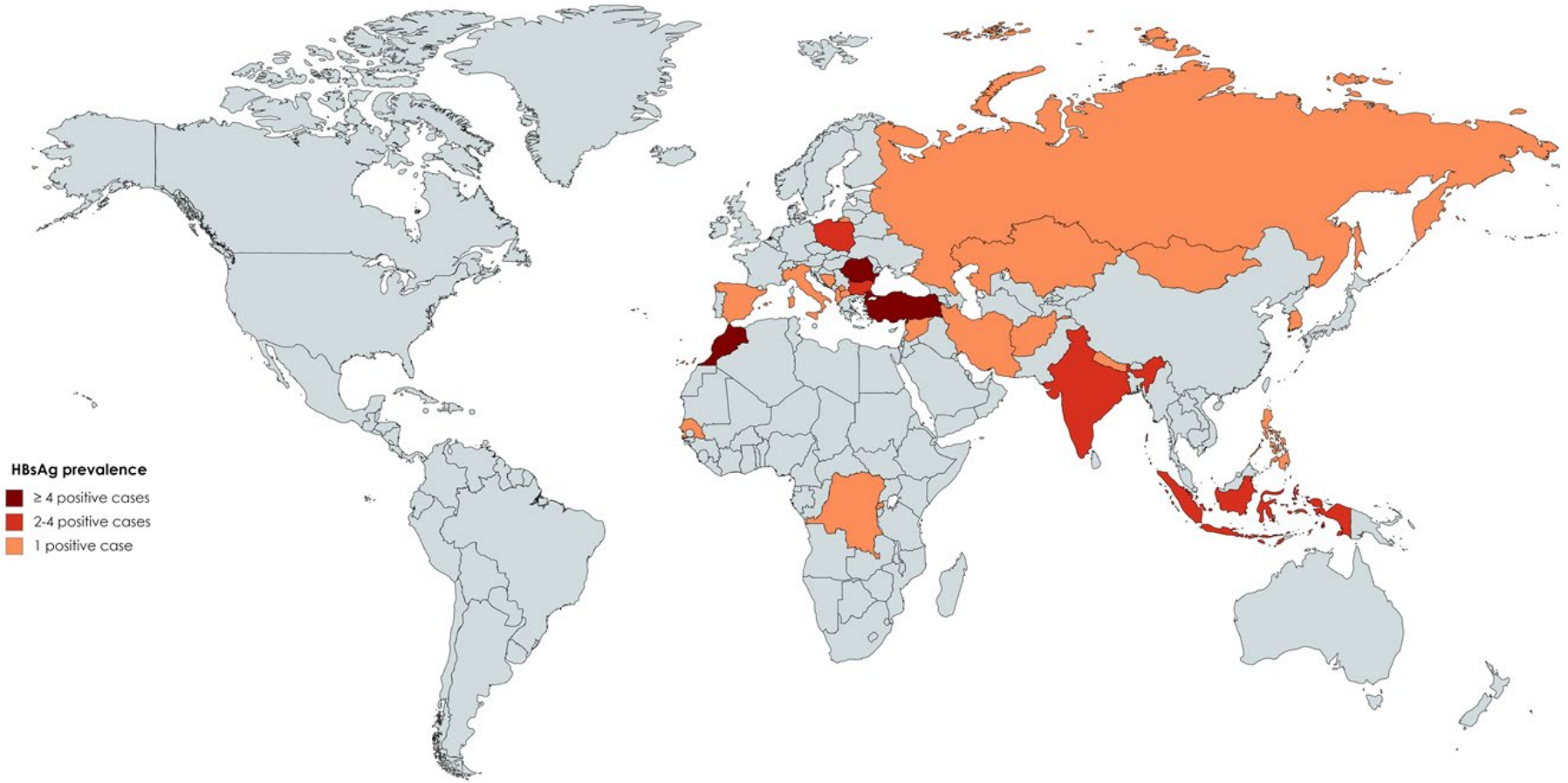


Fig. S3: Prevalence of hepatitis B surface antigen (HBsAg) among first-time blood donors in Flanders, Belgium, 2010-2018, based on country of birth.