

Review Article

Residual Risk of Hepatitis-B-Infected Blood Donations: Estimation Methods and Perspectives

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Despite a considerable reduction of the risk of HBV-infected blood donation entering blood supply (residual risk) due to improved screening by HBV NAT in the developed countries, the bulk of the people with HBV living in the developing countries still needs to be screened by serologic tests such as HBsAg and anti-HBc. Many of these countries lack resources for implementing NAT and are likely to remain so in the next decade or longer, thus depending on the HBV residual risk monitoring based on serologic testing and corresponding estimation methods. This paper reviews main HBV residual risk findings worldwide and the methods based on serology used for their calculation with repeat donors, as well as their extension to the first-time donors. Two artificial datasets with high (4.36%) and low (0.48%) HBV prevalence were generated to test the performance of five methods: the original incidence/window-period model based solely on HBsAg, its modification by Soldan in 2003, the Müller-Breitkreutz model, the HBsAg yield model, and its extension to include anti-HBc seroconversions within a year. The last model was closest to the true values of residual risk and had smallest variation of the estimates in both high and low prevalence data. It may be used for residual risk evaluation in relatively small samples, such as regional blood banks data.

1. Introduction

The consequences of infection by Hepatitis B virus (HBV) remain among the most devastating ones for an immunopreventable disease, particularly in the developing countries. The World Health Organization (WHO) estimates of the disease burden worldwide are widely cited in the literature. A decade ago, three quarters of the world population lived in the areas of high HBV prevalence [1]. Even the countries with universal child vaccination against HBV and advanced blood screening technology such as the USA still report a sizable HBV burden [2]. However, partitioning of this burden within countries and their regions is less well known as many of the high-incidence countries lack adequate epidemiological surveillance and systematic evaluation of the HBV impact on the health of the population. For example, even a simplified calculation of HBV morbidity and mortality burden developed by Goldstein and colleagues in 2005 [3] and available via the Centre for Disease Control and Prevention (CDC) website has been rarely used for a systematic country-specific evaluation of the yield of the public health policies. HBV

vaccine coverage and incidence reduction over time are most frequently used instead. Although these are important intermediate measures in so-called process evaluation [4], their impact on quality of life and mortality, often delayed for decades due to rather slow progression towards severe diseases such as liver cancer or cirrhosis, may be easily missed by the health policy makers. The underestimation of the HBV impact is exacerbated by perceiving other diseases with more immediate adverse effects as more serious by general public and health authorities alike, leading to prioritizing the latter.

The above situation has led to a paradoxical situation where the disease burden of HBV infection which can be prevented by affordable vaccine remains grossly underestimated, even when HBV is one of the principal causes of mortality among infectious diseases. Apart from the relatively low incidence (<1%) of fulminant hepatitis B with high mortality rates, most of the HBV-related deaths are attributed to the end-point chronic diseases, mainly liver cancer and cirrhosis. In the beginning of this century, the HBV residual risk in Europe was estimated to be the cause of almost 1% of posttransfusion deaths due to a liver disease, mostly because

of a fulminant form of the hepatitis B [5]. The shift in the emphasis from infectious to chronic diseases has been largely due to demographic and epidemiologic transition over the past decades, thus contributing to the widespread public perception of HBV as a low-level threat to individual and public health. While this may be reasonable for the developed countries, it is highly unlikely to hold for the developing countries for two reasons. First, many of the latter have started their HBV immunization programs relatively recently, so that large sections of the population remain exposed to HBV. This problem is obviously more serious in the countries where no universal child immunization has yet taken place. Second, high endemicity of HBV is largely concentrated in the developing countries, so its impact is likely to persist for longer time given the high HBV burden accumulated over time.

It is against this general background of the public health policies to combat HBV that the measures to reduce its transmission by blood transfusion and organ transplantation need to be evaluated. Although serologic screening for HBV had been introduced before HIV pandemic took place, it was the latter that increased the general public perception of the pressing need to improve blood safety. During the decade of 1990, all developed and the majority of the developing countries have improved HIV screening with p24 component added to the enzyme immunoassays. The second half of the decade was marked by the development of nucleic acid testing (NAT) technology in blood bank setting, mainly for HIV and hepatitis C virus (HCV), but also for HBV in the developed countries [6, 7]. As public risk perception of transfusional risk sets high standards for the HIV, it eventually elevated blood safety standards for other diseases transmissible by blood transfusion, including HBV. The latter was highly motivated by the concern about occult hepatitis B infection (OBI) and its impact on blood transfusion safety. As detection of OBI requires very sensitive NAT, this research agenda has attracted much interest in the recent years in the technologically advanced countries. Other countries, many of them with high HBV prevalence, mainly rely on serologic HBV markers to deal with the OBI threat to blood safety.

NAT era has opened the possibility to directly verify the number of NAT-positive and serology-negative blood donors, denominated as “NAT yield”, and to calculate its cost-utility with greater precision [7, 8]. On the other hand, this important diagnostic advance has furthered the sharp divide in blood safety standards between the developed and the developing nations. The purpose of this work is to review the methods for residual risk estimation based on serologic HBV markers, making these methods easier to implement in large parts of the world where the HBV NAT is unlikely to be used in the near future. As this estimation includes HBV incidence, it is also of great importance to evaluate its burden and health policies to reduce it more realistically.

The text that follows reviews some major issues in the so-called residual risk estimation for HBV, which refers to the risk of HBV-infected donation entering the blood supply, trying to show geographical diversity and common grounds of worldwide experiences in dealing with this issue. It also provides an example of how to calculate the risk estimates

with a variety of methods and shows their performance using two artificial data sets: one with high and the other with low HBV prevalence. Particular attention is given to the methods suitable for relatively small samples (of the order of 100,000) in low versus high HBV prevalence settings, in order to encourage their use for systematic risk monitoring in regional blood banks.

2. An Overview of the HBV Residual Risk Reports Worldwide

This section reviews the reports on the HBV residual risk from all over the world. As the majority of the reports referred to the developed countries, a separate review was made regarding the level of economic development. By and large, this division also corresponds to the levels of HBV prevalence; important exceptions to the rule are also reviewed. An effort was made to organize the major results by continents, countries, and sometimes even by regions within a country when such data were available. The testing algorithms for HBV prevalence were specified in most cases.

2.1. Developed Countries. The USA have been leading the residual risk research since the REDS study provided its initial impulse [9]. In the beginning of the 2000 decade, residual risk and NAT yield for HIV, HCV, and HBV were mainly estimated by the incidence/window-period models (see Section 3 of the paper for a review of this and other models). For the period 1995–2001, the repeat donors HBV incidence was estimated by HBsAg (surface HBV antigen) alone at 1.27 per 100,000, with this figure twice as high for the first-time donors [10]. Another study found that a sudden influx of the first-time donors almost tripled the proportion of HBsAg reactive tests from 0.1% to 0.3%, thus increasing the HBV residual risk from 1:170,000 to 1:140,000 [11]. In 2001, cost-effectiveness of the triplex NAT (HIV, HCV, and HBV) was thought poor, with the cost varying in the range of US\$ 3.5–4.3 million to prevent one transfusion-transmitted HBV infection [12]. Although the HBV residual risk was relatively high (1:205,000) in the beginning of the 2000 decade, other infections transmissible by blood transfusion, such as variant Creutzfeldt-Jacobs disease, West Nile encephalitis, malaria, Chagas, severe acute respiratory syndrome, and babesiosis, were pointed out as targets for the residual risk research [9, 13, 14]. For example, about 100 West-Nile-infected donations were estimated removed from the USA blood supply in 2003 [15]. Using revised HBV window period of 30–38 days, a marked reduction in the HBV residual risk was calculated from 1:86,000–1:110,000 in 1997–99 to 1:280,000–1:355,000 in 2006–8 [16]. The most recent estimates of the HBV residual risk in the USA were approximately 1:300,000 [17].

In Canada, HBV incidence and residual risk were estimated at 12.4 and 1.4 per 100,000 donors, respectively [18]. In 2005, a study showed that anti-HBc (core HBV antibody) screening yielded between 1:17,800 and 1:69,300 HBV infections among HBsAg-negative and HBV-DNA-positive donors [19]. The HBV residual risk was estimated at 1:153,000 for the first half of the 2000 decade [20]. A case-control

study covering the period between 1997 and 2006 showed that immigration from highly endemic areas was a major risk factor for HBV infection in the first-time donors [21].

In Europe, a mathematical model of residual risk and NAT yield for HIV, HCV, and HBV projected the yield of 1.2 per million by ID (individual donation) NAT for the year 1997, considered a rather small gain [22]. Another mathematical modeling of the cost per life-year gained with enhanced sensitivity HBsAg tests and HBV ID NAT was evaluated at 0.73 and 5.8 million euros p/10 million donations, respectively, for Europe in year 2000 [5]. The former option was deemed acceptable and the latter too costly at the time. After the introduction of NAT screening for the EU countries, more precise cost-effectiveness measures such as ICER (incremental cost-effectiveness ratio) per quality adjusted life-year became available, showing a value of 303.000 euros and 519.000 euros for HBV MP (minipool) NAT and ID NAT, respectively, for the Netherlands by the end of the 2010 decade [8]. The former option was thought acceptable and the latter too expensive.

Other European countries produced their HBV residual risk estimates too. In Spain, NAT screening for HIV and HCV was introduced in 1999 and halved residual risk per million from 18.67 to 9.78 during the 1997–2002 period [23]. However, the risk of HBV transmission by transfusion was estimated at 1:17.316 in a cohort study of Spanish blood donor recipients [24].

In Italy, first estimates for the second half of the 1990 decade reported HBV incidence of 10 per 100.000 and associated residual risk of 1:62.500 [25]. The residual risk for the 1999–2001 period was estimated at 1:14.286 using incidence/window period and HBV incidence adjusted for the transient nature of HBsAg [26]. In North-Western Italy, the residual risk for OBI was estimated to be about hundred times lower than for the HBsAg preseroconversion window period due [27]. However, despite low infectivity of OBI blood donations, many of its recipients were immunocompromised and therefore more susceptible to HBV. For the whole country, HBV NAT yield between 2001 and 2006 was evaluated at 5.78 per 100.000 donors or 1:17.301, largely due to OBI which was detected in 96% of the yield cases [28]. In the Latium region, HBV NAT yield was 1:25.021 over HBsAg, mainly for early WP infections but also for the late phase of resolving HBV infection, for serologically silent chronic HBV, and for rare HBsAg mutants [29].

The Swiss blood bank estimates 1:115.000 for the HBV residual risk in the first years of the 2000 decade were relatively high [30]. Although adding anti-HBc to routine HBsAg testing was thought to be cost-effective, with low deferral (<2%) of noninfectious donors [31], HBV ID NAT screening was introduced and showed the yield of 1:200.000, with OBI yield of 1:61.000 and HBsAg preseroconversion window-period risk of 1:153.000 [32]. Over the period analyzed, a threefold reduction of the HBV residual risk was achieved by ID NAT from 1:95.000 to 1:296.000.

In Germany, minipool NAT with 96 samples was estimated to yield 1:600.000 over HBsAg in 1997, with perceived utility of anti-HBc testing in reducing the HBV residual risk [33]. Although NAT for HIV and HCV reduced the residual

risk markedly, it was still unclear what it would be for HBV because low viral load could escape MP NAT, with projected yields of 1:230.000 by improved serologic screening and 1:620.000 by MP NAT [34]. In the mid 2010 decade, some authors argued that improving the coverage of HBV vaccine for blood donors would be as effective as MP NAT [35]. At the same time, a marked reduction in HBV incidence per 100.000 was observed, from 1.0 to 0.4 [36]. With anti-HBc prevalence of 1.8% and the HBV residual risk of 1:500.000, the introduction of a more sensitive test for this marker (PRISM HBCore) was deemed a viable screening option [37]. The HBV MP NAT yield in Germany during the 1997–2005 period was estimated at 1:360.000 [38]. Adding anti-HBc in 2005 deferred 1.75% noninfectious donors, but this might have been reduced to 0.49% by using HBV ID NAT and anti-HBs titer of 100 IU/L or more as deferral criteria [39]. The same study showed that most commercial anti-HBc kits were shown to be sensitive and reasonably specific. Another study estimated the risk of HBV seroconversion of 0.6 per 100.000 or 1:166.667 in year 2007 [40].

In France, NAT for HIV and HCV was introduced in 2001 and yielded one infected case per 200.000 donations in the first decade of its implementation [41]. The HBV residual risk was estimated at 1:640.000 for the 1992–2003 period, and the cost-effectiveness of HIV/HCV NAT was thought poor [42]. Before introduction of HBV NAT screening in 2010, the HBV residual risk was calculated as 1:1,886.792, with a lookback research confirming only two cases of HBV transmitted by blood transfusion [43].

In England, the HBV residual risk was hugely reduced from 1:260.000 in 1993 to 1:8,000.000 in 2001 [44]. The study used an adapted incidence/window-period model and simulated various parameters to estimate the credible range of the estimates. Similar risk of 1:7,142.857 or 0.14 per million donors was reported for the 1996–2003 period for the whole of Great Britain [45]. HBV incidence based on HBsAg IgM was halved between 1996 and 2008, with the first-time donors comprising most of the cases [46].

In Japan, OBI has become a great concern for safety of the blood supply in the last decade. By analyzing repeat-donor repository samples for the 1997–2004 period, HBV ID NAT found 1.08% reactive samples, 60% of which had low anti-HBs titer and were considered potentially infectious [47]. A prospective study of blood recipients found a high risk of posttransfusion HBV with 1 in 2139 recipients seroconverting [48]. More recently, a study showed that the HBV residual risk per million donations was reduced from 15.2 with MP NAT for 20 samples to 3.9 with ID NAT, thus preventing 75% of the window period and 85% of OBI entering the blood supply [49]. In addition, confirmed OBI transmission rate was up from 0.67% to 1.94% among donors with low-titre anti-HBc or anti-HBs viremia.

Taiwan is a rare developed country with relatively high HBV prevalence. In 2000, a six-month followup of a cohort of blood recipients screened solely by HBsAg showed post-transfusion transmission rate of 20 per 100.000 confirmed by HBV-DNA-positive results, providing an argument for HBV NAT in highly endemic areas [50]. Another cohort study with the same duration of followup revealed 0.9% blood

recipients with acute posttransfusional HBV among those who had not been vaccinated against HBV [51]. This finding confirmed the significance of OBI risk in hyperendemic areas and a large proportion of anti-HBc deferrals among noninfectious donors, reinforcing the advantages of HBV NAT in such areas. HBV NAT yield was estimated at 0.11% or 1:909 and was evaluated as cost-effective in endemic areas [52]. A lookback study based on repository samples found 1.1% of them with OBI but none of the blood recipients with HBsAg seroconversion or clinical symptoms of posttransfusion HBV [53]. The author hypothesized that previous exposure to HBV, common in hyperendemic areas, might have reduced the seroconversion and posttransfusion risk.

In the Republic of Korea, the HBV residual risk remained stable during the 2000 decade, with 1:45,896 in the beginning and 1:43,666 by the end of the decade [54]. The first-time donors' HBV incidence was about 20 times higher than in the repeat donors.

The UAE introduced HBV NAT in 2008. Before its introduction, the HBV residual risk per million was estimated at 1.41 as compared to 0.92 during the HBV NAT era [55].

In Australia, the HBV residual risk models produced an estimate of 1:483,000 in the beginning of the 2000 decade, with predicted HBV NAT yield of one in million [56]. The data available at that time were deemed insufficient to decide whether introducing HBV NAT and/or anti-HBc would be cost-effective.

2.2. Developing Countries. Among developing countries, the African continent has shown the most dramatic situation regarding residual risk not only for HIV but also for HBV. In the Sub-Saharan Africa, about half of the blood donors were deferred because of HBsAg-reactive rapid test result [57]. The rapid tests widely used in Africa were shown to be sensitive for HIV and HCV but missed 3% of HBV-DNA-positive donors detected with 10-sample minipool testing. Mathematical modeling of the HBV residual risk in the same region used the WHO and published incidence and prevalence data to arrive at HBV infection risk by transfusion of 4.3% [58]. In Senegal, the HBV residual risk was estimated at 1:1000 in the first half of the 2010 decade [59]. In Abidjan, the capital of the Ivory Coast, the HBV residual risk was estimated as 1:383 [60], and in Conakry, the capital of Guinée, it reached staggeringly 1:121 [61]. More recently, a pooled analysis of the data from 51 blood banks in 17 African countries showed low sensitivity (75.6%) of serological HBV testing by HBsAg and anti-HBc due to widespread use of rapid tests [62]. The specificity of the tests was also lower (94.5%) compared to the developed countries.

South Africa was the first African country to introduce HBV ID NAT screening, thus being able to observe in the first year of its implementation a yield of 1:36,612 for HBV and 1:5,200 for OBI among HBsAg-positive donors [6]. More recently, the HBV ID NAT yield was estimated more precisely at 1:19,608, of which 1:25,627 in pre-anti-HBc and 1:83,473 in post-anti-HBc window period [7].

In the Middle East, an analysis from Egypt showed that, in highly endemic region with anti-HBc prevalence of 7.8%, adding this marker to routine HBsAg screening of blood

donors yielded 0.5% HBV-DNA-positive test results [67]. Another research showing the utility of this HBV marker for routine screening in hyperendemic areas was realized in Shiraz, Iran, where the anti-HBc yield reached 6.55% and that of HBV DNA testing 12.2% among HBsAg-negative blood donors [68]. On the other hand, this yield was shown to generate a very high discard of likely noninfectious blood donors in Turkey as 99% of the yield cases were HBV DNA negative [69]. Similar concern was raised in New Delhi where almost 20% of HBsAg-negative donors were reactive to anti-HBc and 37% of these tested anti-HBs negative but 41.4% had anti-HBs titer exceeding 100 UI/L, considered protective against HBV infection [70].

In China, residual risk of 1:17,501 was calculated in Shenzhen, with predicted yield per million donors of 6.9 with more sensitive HBsAg tests, compared to 9.5 for MP NAT and 28.3 for ID NAT [71]. For the whole of China in 2008 and 2009, the HBV ID NAT yield was estimated via incidence/window period at 1:10,555 overall, 1:1,104 among blood donors with elevated levels of ALT and 1:1,509 for OBI [72]. Under these conditions, MP NAT with 4–16 samples would miss 43%–79% of the HBV ID NAT yield, confirming the effectiveness of the latter as opposed to low utility of elevated ALT for screening purposes in hyperendemic areas.

In Latin America, Brazil has been the leading country in residual risk research, including the HBV-related one. The first didactic introduction of the incidence/window-period model and the residual risk calculation appeared in 1998 [73], followed by a report on significant risk reduction in Santa Catarina state during the 1990 decade [74]. Nevertheless, the HBV incidence was approximately 300 per 100,000 person-years and corresponding residual risk close to 1:14,000, based on the standalone HBsAg method [63]. In addition, the HBV residual risk increased in the first two years of the 2000 decade before resuming a downward trend initiated in the previous decade [75]. This transient upsurge in residual risk was likely the result of HIV test seeking among blood donors, suggested by a significant increase of HIV residual risk over the same period [75]. Another Brazilian study from São Paulo also found evidence of HIV test seeking [76] which was likely to elevate the HBV residual risk as well, given that risky sexual behavior plays a role in the transmission of both viruses in the population. In a Brazilian state with high HBV prevalence areas, the HBV residual risk for the period 1998–2002 was estimated at 1:10,700 [77].

3. Methods for Estimating the HBV Residual Risk

The Retroviral Epidemiology Donor Study (REDS) has extensively used the incidence/window-period model [63, 78, 79] in the second half of the 1990 decade to estimate the risk of an infected donation entering the blood supply despite negative results of the serologic screening. The risk became known as “residual risk” and was calculated as a product of two independent probabilities: (a) the probability of a donor being infected during the study period, that is, the incidence of a viral infection in the donor population, and (b) the probability of detecting an infectious donation by available

serologic markers, which tends to zero in the early phase of infection when serologic screening cannot detect specific viral antigens or antibodies, known as immunologic window period [63, 78]. This approach has been widely applied to HIV, HCV, and HBV, with some adjustments in the latter case. In the beginning of the 2000 decade, it became an internationally accepted method, applied in various countries [80].

A synthesis of the methods for calculating the HBV residual risk based on routinely used serological markers HBsAg and/or anti-HBc (IgG + IgM) is presented (Table 1). Other methods using anti-HBc IgM [45, 81] or anti-HBe [81] are not considered here as these are mainly research driven and unlikely to be used for routine residual risk monitoring in blood bank setting in the near future.

The following section reviews main models proposed to estimate the HBV RR.

3.1. The Standalone HBsAg. This method is based solely on HBsAg screening and is restricted to repeat blood donors. It includes an adjustment proposed by Korelitz and colleagues [63] that takes into account the transient nature of the marker by dividing its average duration (63 days for the second generation EIA, 77 days for ChLIA|PRISM) [82–84] by the length of the average interdonation interval (IDI) among HBsAg seroconverting repeat donors. The seroconversion is defined as the first positive test result after the last negative result, and the time between the two makes the IDI in question. Over time, more stringent case definitions have been adopted, such as repeatedly positive serologic test results after the first one, sample to cutoff values greater than six, and confirmation of HBV DNA by NAT [65], but the core model remained the same. In addition, this model assumes that 5% of the repeat donors may be chronic HBV carriers whose antigens or antibodies are always detected by serologic screening and that 25% of the donors never produce detectable HBsAg levels due to the primary antibody response [63], thus leading to the following calculation of the probability (P) of detecting an incident HBV case by HBsAg testing:

$$P = 0.7 \left(\frac{\sum s1}{\text{Mdn}(\text{IDI}_{s1})} \right) + 0.05, \quad (1)$$

where $s1$ and $\text{Mdn}(\text{IDI}_{s1})$ are the number of HBsAg seroconverting repeat donors and their median IDI, respectively. Although most applications so far have used median IDI, mean IDI has been suggested more recently [7].

The adjustment factor for the incidence density (rate) is then $1/P$, and the incidence is the number of HBsAg seroconverting repeat donors ($s1$) divided by all the repeat donor person-time at risk (IDI_{ad}), assuming that the seroconversion occurred at the midpoint of the IDI. Finally, the HBV residual risk is given by multiplying the incidence by its adjustment factor and the WP duration:

$$\text{Residual risk} = \left(\frac{\sum s1}{P(\sum \text{IDI}_{\text{ad}} - 0.5 \sum \text{IDI}_{s1})} \right) \text{WP}. \quad (2)$$

It is worth noticing that various parameters of the above equation may be highly variable between the donor populations. IDI depends on the donation frequency; the larger the proportion of the repeat donors, the higher the precision of this parameter. Often the definition of repeat donors is restricted to those who donated within last 12 months, whereas those with larger time span between donations are considered “lapsed donors”. A variety of social, demographic, and cultural factors influence IDI. Some authors have argued that the assumptions about the incidence adjustment factor may not hold for some donor populations, although its overall impact on the residual risk is likely to be limited [56]. Modifications of the WP model should also include assumed duration of the HBsAg detectability, extended from 63 days for the second generation EIA to 77 days for ChLIA|PRISM [56].

3.2. Müller-Breitkreutz Model. The probability of an infected repeat donor may be estimated by cumulative incidence, that is, the proportion of incident cases among all repeat donors ($s1/n_{\text{rd}}$), and the probability of an infected WP donation may be estimated by dividing the window duration by the median IDI for HBsAg seroconverting donors (IDI_{s1}), thus leading to the following expression [64]:

$$\text{Residual risk} = \frac{\sum s1}{n_{\text{rd}}(\text{WP}/\text{Mdn}(\text{IDI}_{s1}))}. \quad (3)$$

Again, median is motivated by a small number of HBsAg seroconverting donors, and average preseroconversion interval depends on the test sensibility. The cumulative incidence estimate used here is a proportion which does not take into account a variable person-time denominator as opposed to the incidence density or rate.

3.3. HBsAg Yield. Another method for estimating HBV incidence and residual risk was named “HBsAg yield method” [16, 85, 86]. It requires both HbsAg and anti-HBc serologic markers. It modifies the case definition in the Müller-Breitkreutz model by considering as seroconverters only those HBsAg-positive repeat donors who were also anti-HBc negative ($s2$), thus excluding those who tested positive on both markers. Then the probability of an infected repeat donor is again estimated by cumulative incidence ($s2/n_{\text{rd}}$) and the probability of an infected WP donation by dividing the window duration by the median IDI for HBsAg seroconverting donors (IDI_{s2}), thus leading to the following expression for calculating the residual risk (RR):

$$\text{Residual risk} = \frac{\sum s2}{n_{\text{rd}}(\text{WP}/\text{Mdn}(\text{IDI}_{s2}))}. \quad (4)$$

The cumulative incidence is called the “yield rate” [65], although it is not a density-type incidence estimator to which the expression “rate” is normally applied in epidemiology. The HBsAg preseroconversion interval is restricted by the onset time for anti-HBc and is named “yield window”. The ratio of the cumulative incidence between the repeat and the first-time donors is denominated the “yield rate ratio”

TABLE 1: Principal methods for the calculation of HBV residual risk based on serological markers HBsAg and/or anti-HBc.

Method (reference)	Probability of HBV infection	Incidence type	Probability of window-period donation	WP (days)
Standalone HBsAg [63]	$\sum s1 / \sum \text{pyrs}$	Rate	$0.7 (\sum s1 / \text{Mdn}(\text{IDI}_{s1})) + 0.05$	59
Müller-Breitkreutz model [64]	$\sum s1 / n_{rd}$	Cumulative	$\text{WP} / \text{Mdn}(\text{IDI}_{s1})$	59
HBsAg yield [65]	$\sum s2 / n_{rd}$	Cumulative	$\text{WP} / \text{Mdn}(\text{IDI}_{s2})$	44
HBsAg and anti-HBc yield [66]	$\sum s3 / \sum \text{pyrs}$	Rate	1 if anti-HBc positive, $0.7 (\sum s1 / \sum \text{IDI}_{s1}) + 0.05$ if HBsAg+ and anti-HBc negative; ≈ 1	44
Modified standalone HBsAg [44]	$\sum s1 / \sum \text{pyrs}$	Rate	$\text{WP} / \text{Mean}(\text{IDI}_{s1})$	59

s1: number of HBsAg-seroconverting repeat donors (independent of anti-HBc result).

s2: number of HBsAg-seroconverting repeat donors who were anti-HBc negative on all testing occasions.

s3: number of HBsAg- or anti-HBc-seroconverting repeat donors (in the last 365 days).

n_{rd} : number of repeat donors.

WP: duration of immunologic window period.

IDI: interdonation interval (between last seronegative and first seropositive donation).

Pyrs: person-years at risk for HBV infection ($\sum \text{IDI}$ for all repeat donors $- 0.5 \sum \text{IDI}_{s1}$).

Mdn: median.

and is used as a risk ratio estimate for HBV seroconversion, that is, as a multiplying factor which allows to extrapolate the residual risk calculation to the first-time donors as well. This is an important gain over the methods restricted to repeat donors only whose residual risks are known to be significantly lower when compared to the first-time donors from the past research. However, it is worth noticing that the use of cumulative incidence ratio between the groups under comparison may be applied to any method willing to assume the accuracy of this approximation.

3.4. Extended Yield Method (HBsAg and Anti-HBc Yield).

Recently, an extension of the yield method was proposed to include anti-HBc (IgM and IgG) seroconverting donors within last year in addition to the HBsAg only seroconverters [66]. In other words, the repeat donor who had tested anti-HBc negative on previous donation not longer than a year ago and tested anti-HBc positive after that is considered an incident HBV case, despite negative HBsAg test results on both occasions. By analogy, such cases may be considered “anti-HBc yield”. These donors are most likely recently infected due to the relatively short IDI. As recrudescence HBV infection is a very rare event for repeat donors due to previous screening history and low HBV incidence in this group, the appeal of adding anti-HBc is twofold: (a) it reduces the probability of false negative screening result due to the transient nature of HBsAg marker and propensity to primary antibody response, and (b) it increases the precision of the incidence estimates by including more cases; typically, the anti-HBc yield is greater than the HBsAg one in a blood bank setting. This simply reflects the higher probability of finding a stable and often permanent marker of HBV infection such as core antibody compared to a transient marker such as surface antigen whose average duration is only 63 days [63].

3.5. Other Methodological Considerations. There are several additional methodological issues to be considered. First, the misclassification of seroconverting cases depends on their

confirmation algorithm. For a HBsAg reactive test, it may require the same result on subsequent independent blood samples or anti-HBc or HBV NAT positive results [65]. In addition, S/O values exceeding six may also be used to reduce false positive fraction for HBsAg. Some authors have proposed HBV confirmation criteria based on reactive anti-HBc and a variety of other markers of HBV infection, such as anti-HBc IgM, anti-HBe, anti-HBs without receiving the HBV vaccine, or HBV DNA [81]. However, many blood banks in the developing countries use, routinely only, only anti-HBc total (IgM + IgG) and HBsAg with subsequent testing for anti-HBs if any of the former were reactive. It is worth noticing that self-reported HBV immunization may be inaccurate, particularly regarding the number of doses received. In order to overcome these limitations, a simplified criterion of repeatedly reactive HBsAg or anti-HBc has been proposed for the confirmation of an incident HBV infection [66].

For the first-time donors, a variety of methods to calculate the HBV seroconversion risk ratio of these to repeat donors were reviewed by Soldan et al. [44]. First, the ratio of the HBsAg seroconverting fractions can be calculated between the two donor subpopulations. Second, the anti-HBc prevalence may be used as an estimate of cumulative HBV incidence because this marker is persistent in the vast majority of HBV-infected individuals since the sixth month after the infection. Third, the time at risk for the first-time donors may be estimated by assuming that they were exposed to HBV since birth and that the infection occurred at the mid-point of exposure time, so that it equals half their age at the time of HBV-seropositive test result. Fourth, it is possible to estimate probability of the HBV infection for the first-time donors during lifetime and their probability of donating blood during infectious window period, so that multiplying these probabilities (assuming that they are independent) gives an estimate of a window-period donation for this group. The next step is to multiply this estimate by the HBV-seropositive fraction among the first-time donors. The same

procedure can be applied to the repeat donors, so that the risk ratio between two donor subpopulations estimates the ratio of the window-period donation probabilities, that is, the HBV residual risk ratio.

Most of the above estimation methods have been developed for the HIV whose pandemic circulation could be estimated with reasonable precision for the purpose of these calculations. However, no such analogy exists for the HBV, thus assuming that the time of risk for HBV starting at birth is heavily dependent on the HBV vertical transmission rate which varies hugely between the countries and regions. For example, in the countries with low HBV prevalence and universal child vaccination, the risk of HBV infection in childhood is extremely low as compared to hyperendemic areas with high vertical transmission rate. Given all these uncertainties regarding the first-time donors time at risk for HBV infection, a simulation of various parameters seems a sensible approach [44].

4. Simulation Study

This section describes a simulation study to test the performance of the five incidence/window models based on routine serologic screening (Table 1). A description of the simulated data parameters and statistical methods is presented first, followed by the results of the data analysis, their interpretation, and brief discussion of the main findings.

4.1. Data. Two artificial datasets were created in order to test the accuracy of the selected incidence/window-period models based on serological markers HBsAg and anti-HBc (Table 1): one with high HBV prevalence of 4.36%, defined by reactivity to either or both of the markers, and another with approximately tenfold-lower prevalence of 0.48%. The choice of these values is somewhat arbitrary but still represents well the typical range of high-to-low HBV prevalence worldwide. A relatively small-size sample for this type of study was set to 100,000 donors for each prevalence level, with 23693 and 24646 person-years of followup between last seronegative and subsequent seropositive donation for the repeat donors (Table 2). The followup time is also known as interdonation interval (IDI), simulated by a beta distribution with long tails to the right to allow for a small fraction of donors with long IDI. Equal chance of HBV infection was assumed over the IDI by setting the date of infection within IDI at random for each donor. The time at risk for HBV infection was the difference between the randomly chosen date of infection and the date of previous seronegative donation for each infected donor. Mean IDI was set at about 100 days to reflect the magnitude of this parameter in various studies with observed data.

Since residual risk in the first-time donors has been found at a considerably higher level compared to the repeat donors in the vast majority of the studies, the former were set to approximately 16 times higher HBV (either marker) and about 4 times higher HBsAg prevalence than the latter (Table 2). A majority of HBV infection were HBsAg negative and anti-HBc positive to reflect the prevalence of this serologic profile in most blood bank settings, due to the

much longer duration of the latter and therefore much higher probability of producing a positive serological test result.

Total and person-years of interdonation interval (IDI) were 23693 for high and 24646 for low HBV prevalence, respectively. The largest parts of these totals were contributed by seronegative repeat donors (23587 and 24634 person-years), whereas rare HBsAg-positive and anti-HBc-negative donors contributed with 5.6 and 0.6 years for high versus low prevalence scenario. With anti-HBc-positive seroconversions in the last year counted in as incident HBV cases in the extended yield model, these figures increased to 94 and 11 person-years, in the same order. The median IDI were 100 and 110 days for the HBsAg seroconverting donors in low and high HBV prevalence groups, respectively.

As all HBV cases and their time at risk were true by definition, so was the HBV incidence calculated from these data, otherwise uncertain with real-life data. The discrepancy between the true and model-based incidence produced bias estimates for each incidence/window-period model (Table 3). Exact 95% confidence intervals (CI) were also calculated assuming Poisson distribution for the number of seroconverting HBV cases.

For the first-time donors, no assumption was made about their HBV infection date in this paper, so no true time with HBV was known and therefore no time at risk or incidence rate could be calculated. It is possible to speculate that the first-time donors may have the same distribution of time at risk as the repeat donors and extrapolate the average (mean or median) of the latter to the former. However, this assumption may be unrealistic for many blood bank settings. Therefore, only the ratio of HBsAg-seroconverting fractions and the so-called yield rate ratio [65] were employed to estimate the residual risk in the first-time donors. The difference between the two is that the former counts in HBsAg seroconversions independently of the anti-HBc test result, whereas the latter includes only HBsAg-positive and anti-HBc-negative cases. As HBV seroconversion is very rarely detected by the presence of positive test results on both markers, the two methods typically produce similar results.

For the first-time-to-repeat-donor risk ratio, the variation of the HBV residual risk estimate was calculated by substituting the central estimate by the extremes of the plausible HBV seroconversion window period (30–38 days) as in the source paper [65]. On the other hand, 95% CI of the HBV seroconversion risk ratio was used to multiply the HBV residual risk estimate of the repeat donors and to arrive at 95% CI for the first-time donors, based on the extended yield method.

Data simulation and all calculations were performed by Stata software [87].

4.2. Results. Main results of simulated residual risk for HBV according to the estimation methods and prevalence level are presented (Table 3).

For the high HBV prevalence (4.36%) data, both standalone [63] and its modified version based on cumulative incidence [44] underestimated the true residual risk by 50% and 56%, respectively (Table 3), whereas the HBsAg yield model [65] resulted in a more than tenfold underestimate. On

TABLE 2: Simulated data: serologic profile and followup for high versus low HBV prevalence datasets.

	First-time		Repeat		Total years at risk
	<i>n</i>	Prevalence (%)	<i>n</i>	Prevalence (%)	
High HBV prevalence: serologic profile					
HBsAg–, anti-HBc–	47820	NA	47820	NA	23586.63
HBsAg–, anti-HBc+	4000	7.70	200	0.42	50.43
HBsAg+, anti-HBc–	100	0.19	20	0.04	3.29
HBsAg+, anti-HBc+	30	0.06	10	0.02	1.38
All	51950	7.95	48050	0.48	23641.73
Low HBV prevalence: serologic profile					
HBsAg–, anti-HBc–	49587	NA	49977	NA	24634.49
HBsAg–, anti-HBc+	400	0.800	20	0.040	4.38
HBsAg+, anti-HBc–	10	0.020	2	0.004	0.47
HBsAg+, anti-HBc+	3	0.006	1	0.001	0.14
All	50000	0.826	50000	0.046	24639.48

n: number of cases, “+”: positive test result, and “–”: negative test result.

the other hand, the Müller-Breitkreutz model overestimated the risk by more than 80%. None of these models covered the true residual risk within its 95% CI. However, the HBsAg and anti-HBc yield model [66] produced only a slight underestimate of less than 5% and covered the true value of residual risk within their 95% confidence intervals.

For the low prevalence (0.48%) scenario, the standalone HBsAg model [63], its modification by Soldan et al. [44], and the Müller -Breitkreutz model all overestimated the true RR, whereas the HBsAg yield model underestimated it (Table 3). The yield and Müller -Breitkreutz models did not include the true residual risk value within their 95% confidence intervals, but the other models analyzed did. Again, the extended yield model including both HBsAg- and anti-HBc-seroconverting donors within last year [66] was the closest to the true residual risk with a slight underestimate of less than 6%.

For the first-time donors, the ratio of HBsAg-seroconverting fractions and the so-called yield rate ratio [65] were employed to estimate the residual risk in the first-time donors (Table 4). Although in principle it would be possible to calculate the first-time donor residual risk estimates for all of the methods analyzed here (Table 3), only two of them were selected for this exercise because their proponents defined the formulas for the extrapolation from the repeat to the first donor. The other methods have not specified in exact terms how to deal with various sources of variation relevant for this calculation.

The incidence ratio estimates for the first-time to repeat donors were similar for both methods, but corresponding residual risk estimates remained much further apart (Table 4). In the simulated data, the HBV prevalence ratio between the first-time and repeat donors was set to 16.56 (7.95% versus 0.48%) for the high prevalence and 17.96 (0.826% versus 0.046%) for the low prevalence scenario (Table 2). Residual risk ratio between two donor subpopulations should follow the true prevalence ratio, assuming that

other risk factors for HBV infection are equally distributed between them. A comparison of the true and estimated residual risk ratios is presented in Table 5.

Both methods grossly underestimated the “true” estimate, thus illustrating the difficulties in extrapolating the residual risk from repeat to first-time donors solely on the basis of their HBV prevalence ratio. Better estimates remain a challenge for the researchers in this area.

5. Discussion

The utility of anti-HBc marker in HBV screening of blood donors has been pointed out in various publications [33, 88–90]. It was argued that HBV MP NAT would not detect most anti-HBc-positive donors with low viral load, whereas more sensitive assays such as PRISM HBCore would provide a yield of 1 : 49.000 [88]. Although HBsAg assays are more sensitive in detecting HBV window-period infections, anti-HBc test can detect chronic carriers with low-level viremia without detectable HBsAg. The first few years of adding HBV NAT to routine screening of blood donations in the USA and Germany showed only a small yield [12, 36], and other studies pointed out that 3% of HBV-infected donations would remain undetected even by ID NAT, thus reinforcing the need to maintain the HBsAg marker for routine blood screening [91]. More recently, PRISM CLIA claimed a 60% reduction of the HBV residual risk over MP NAT, from 1 : 385.555 to 1 : 610.488 [92]. These findings provide strong arguments that improved sensitivity of serologic screening for HBV is a viable option for some blood bank settings.

Although by the first half of the 2000 decade NAT screening for HIV and HCV showed poor yield in many countries which had implemented it for routine blood screening [12, 41–44, 46, 55, 56], the extension of this method to HBV topped the agenda of new strategies for blood donor screening [90]. The observed NAT yield was reasonably close

TABLE 3: HBV incidence adjusted for the probability of detecting transient HBsAg marker (PWP) and residual risk (RR) for repeat donors.

HBV prevalence	Method (reference)	Probability of HBV infected ¹	PWP	RR (95% CI)
High	True values	0.0097286	1.0000	1: 636
	Standalone HBsAg [63]	0.0012664 (0.003286, 0.001808)	0.2600	1: 1270 (1: 890, 1: 1883)
	Müller-Breitkreutz [64]	0.0047867 (0.00419, 0.005447)	0.5906	1: 354 (1: 311, 1: 404)
	Modified standalone HBsAg [44]	0.0012664 (0.00085, 0.00181)	0.5506	1: 1434 (1: 1005, 1: 2126)
	HBsAg yield ² [65]	0.000416	0.2991, 0.3789	1: 7092 (1: 6345, 1: 8037)
	HBsAg and anti-HBc yield [66]	0.0092818 (0.0081, 0.0106)	0.99	1: 667 (1: 95, 1: 765)
	True values	0.0009438	1.0000	1: 6555
Low	Standalone HBsAg [63]	0.0001217 (0.0000251, 0.000357)	0.19856	1: 1632 (1: 556, 1: 7911)
	Müller-Breitkreutz [64]	0.000600 (0.0000124, 0.0001753)	0.5444	1: 30615 (1: 10479, 1: 148136)
	Modified standalone HBsAg [44]	0.0001217 (0.0000251, 0.000357)	0.5444	1: 15093 (1: 5145, 1: 73183)
	HBsAg yield ² [65]	0.000400 (0.0000048, 0.0001445)	0.2731, 0.3460	1: 8052 (1: 7225, 1: 9152)
	HBsAg and anti-HBc yield [66]	0.000893 (0.00056, 0.00135)	0.99	1: 6929 (1: 4577, 1: 11057)
	True values	0.0009438	1.0000	1: 6555
	Standalone HBsAg [63]	0.0001217 (0.0000251, 0.000357)	0.19856	1: 1632 (1: 556, 1: 7911)

¹Probability of HBV-infected donation (HBV incidence).²Instead of 95% CI, a range between the extremes of the window period (30–38 days) is given.

TABLE 4: HBV residual risk (RR) estimates for the first-time donors.

Method	HBV prevalence	First-time donors			Repeat donors			IR (variation) ^c	RR for the first-time donors (variation) ^d
		s ^a	n	(%) ^b	s ^a	n	(%) ^b		
HBsAg yield	High	100	51950	0.1925	20	48050	0.0416	4.62	1: 1533 (1: 888, 1: 2843)
	Low	10	50000	0.0200	2	50000	0.0040	5.00	1: 1610 (1: 4000, 1: 151280)
HBsAg and anti-HBc yield	High	130	51950	0.2500	30	48050	0.0624	4.01 (2.69, 5.96)	1: 166 (1: 112, 1: 247)
	Low	13	50000	0.0260	3	50000	0.0060	4.33 (1.23, 15.20)	1: 1599 (1: 456, 1: 5610)

^aNumber of HBV-seroconverting donors.^bPercentage of HBV-seroconverting donors.^cIC: Incidence ratio for the first-time to repeat donor; no variation was calculated for the yield method whereas 95% CI of the risk ratio was used for the HBsAg and anti-HBc yield method.^dMultiplies of the plausible range for the yield method versus 95% CI of the risk ratio for the HBsAg and anti-HBc yield method.

to the values predicted by incidence/window model. A 24-sample minipool NAT for HBV showed a yield of 1:352.451 over routine serologic screening, thus of a similar magnitude as HIV and HCV yield observed [93]. The downside of HBV NAT was small yield and cost-effectiveness in low prevalence areas, especially with minipool NAT, as well as the lack of sensitivity of even ID NAT to detect extremely sparse HBV DNA particles involved in transmission by transfusion. Under most circumstances, serologic screening with HBsAg and anti-HBc should be maintained, thus adding to the cost of HBV NAT. As epidemiologic parameters and financial aspects vary immensely across countries worldwide, the

cost-effectiveness of HBV NAT should be a country-specific decision [90, 94].

A range of methodological improvements for estimating the HBV residual risk deserves to be mentioned. The shift to probabilistic modeling of residual risk parameters [95] based on HBV viral load allowed a distinction between early versus late window-period seroconversions. Sensitive tests of the viral load such as HBV ID NAT and serologic profile (HBsAg, anti-HBc, and anti-HBs; rarely anti-HBe) provide clues to identify OBI and/or chronic carriers with low viremia [7, 96]. New animal models for HBV transmission have been developed, such as inoculating chimeric mice

TABLE 5: Comparison of HBV residual risk (RR) estimates for the first-time and repeat donors.

Residual risk estimation method	HBsAg yield		HBsAg and anti-HBc yield	
	High	Low	High	Low
HBV prevalence				
Repeat donor RR	1:7092	1:8052	1:667	1:6929
First-time donor RR	1:1533	1:1610	1:1599	1:1610
Estimated RRR ^a	12.82	5.00	4.08	4.33
True RRR ^b	16.56	17.96	16.56	17.96

^a Residual risk ratio of first-time to repeat donors.

^b Best estimate based on HBV prevalence ratio of first-time to repeat donor.

with human hepatocytes by human HBV [97]. In addition, a recent study claimed great diagnostic accuracy of the differential expression of HBV microRNA profile in serum for identifying OBI [98].

However, for the vast majority of HBV infections located in the developing countries, routine serologic screening with HBsAg and anti-HBc remains the best affordable strategy for the time being and probably for at least a decade ahead. As the countries that have initiated universal child vaccination against HBV did so a decade or two ago, the influx of the vaccinated blood donors has only started to reduce the HBV residual risk very slowly due to the vast majority of unvaccinated donors. Targeting blood donors with HBV vaccine has been recommended to increase the blood safety in such situation [74, 99], and a study showed that its cost-effectiveness may be as high as introducing HBV ID NAT in a low-prevalence country such as Germany (Ringwald 2005) [35]. In moderate-to-high prevalence countries, the cost-effectiveness is bound to lean even more towards enhancing the targeted vaccination strategy.

Whatever the national strategy to increase the blood safety is, it is essential to base it on sound epidemiological data and systematic monitoring of the residual risk. To that end, extended yield model including both HBsAg and recent anti-HBc seroconversions in repeat donors provides a simple, accurate, and affordable method. It is suitable for smaller blood bank settings of the order of hundred thousand donors as opposed to huge samples of the order of several million donors employed by the other methods; all of which were developed in the developed countries with low HBV prevalence. The extended yield method was shown to both reduce the bias and improve the HBV residual risk precision, so it may be sensitive enough for monitoring the residual risk time trend in a particular setting.

Although the criterion for the definition of HBV prevalence as high, intermediate, or low in the general population (WHO) are often extended to the blood donor population, it should be avoided for two reasons. First, the latter population should have a considerably lower risk for a variety of blood-borne diseases, with HBV at the top of this list, as it is predominantly sexually transmitted and therefore a marker of risky sexual behavior. Second, HBV infection is preventable by immunization affordable to virtually every country, so the criterion of what is high or low prevalence should be set against the real opportunity to reduce its prevalence to

the order of few cases per 100,000 in the adult population and perhaps even per million in the blood donor population. Some developed countries like Great Britain have achieved this level of HBV risk reduction [46], while many other are on their way. However, immigration from higher-prevalence countries has been observed as an important factor in reducing the HBV RR, particularly among the first-time donors (O'Brien et al. 2008; Brant et al. 2011) [21, 46]. Global health policy for reducing HBV prevalence should therefore give a special place to offering a cost-free HBV immunization to these donors in the country of immigration if it was not successive in the country of origin.

6. Residual Risk Estimation: Limitations and Perspectives

There are several limitations of this work which should be borne in mind. First, it is beyond its scope to address the question of HBV infectivity regarding either the phase of HBV infection or the host factors. Residual risk is limited to the probability of an infected blood unit being erroneously considered noninfectious and thus transfusable, so it fell short of taking into account other factors related to post-transfusion HBV infection, let alone its severity and clinical evolution.

Second, many incidence/window-period model parameters are pretty variable both between regions and between blood donors but their variation is typically underestimated in the calculation. For example, the repeat donors vary considerably regarding their IDI and consequently the time at risk of HBV infection. However, only average IDI is normally used for calculations, so this work followed the same tradition. IDI distribution is often heavy tailed to the right because of a small number of large values, thus adding the choice of the distribution to the uncertainties of the model. Again, this issue was ignored here to make the results comparable to those published in the literature.

Third, as the host response to HBV infection is highly variable, so is the time for HBsAg to reach the threshold of detectability for a given sensibility of a screening test, as well as the duration of the so-called eclipse phase [100] before HBV starts circulating in peripheral blood. In addition to the onset, the duration of HBsAg detectability is also variable between individuals and correlated with the onset of producing neutralizing antibodies. The eclipse period is by definition noninfectious and therefore should be excluded from the incidence/window-period model calculation, resulting in its reduction for approximately a week [100].

Fourth, the extrapolation of the HBV residual risk from the repeat to the first-time donors is based on a number of simplifying assumptions mentioned earlier, whose impact on the estimate variation has not been quantified except in a very simple way by applying the 95% CI of the relative risk of HBV seroconversion in the extended yield model. The inference about incidence rate of a viral disease based on its prevalence is prone to considerable amount of error [101] and so is any extrapolation from the repeat to the first-time donors using these premises.

All of these limitations result in a considerable underestimation of the residual risk variation by traditional methods of calculation. This may seem paradoxical as many published results already present wide confidence intervals even in the samples of the order of hundred thousands due to the very low frequency of seroconversion among repeat donors. However, virtually all of them account only for the random variation in the number of seroconversions and leave out other sources of variation discussed above. Simulation of a joint impact of various sources of variation was used a decade ago [44] but remained an exception instead of becoming a rule. With the advance of stochastic simulation software, Bayesian analysis has much to offer to this research area.

The underestimation of the HBV residual risk variation may have different impact for low versus high prevalence area. Most of the research has been done in the developed countries with low HBV prevalence, where the number of HBV seroconversions among repeat donors is very rare. On the other hand, with mean being equal to the variance in Poisson distribution used to model the variation in the number of seroconversions, high HBV prevalence makes larger means of seroconverting donors per unit time more likely, as well as their variance.

Although artificial data are the only way to guarantee certainty of a residual risk model parameters, eventually the utility of any model has to be tested with real data. It is important to monitor the HBV residual risk on a regular basis and look for its regional and sociodemographic variations in order to better understand the blood donor behavior and to direct preventive actions accordingly. Routine gathering of relevant epidemiologic data is necessary for both the blood donor and the general population to provide a solid basis for the incidence/window-period models. The knowledge of hepatitis B viral dynamics gathered with evermore sensitive NAT can be used to further improve the incidence/window-period model calculations and validate its robustness and precision.

Despite its limitations compared to the HBV DNA testing, the incidence/window-period model continues to play an important role in blood screening. It is the only affordable method for many developing countries which contain vast majority of the people with HBV in the world. Even for the countries with resources for the HBV DNA blood screening, serologic testing with HBsAg and anti-HBc still prevents some posttransfusion hepatitis B caused by OBI and chronic HBV carriers, although deferral of the donors with transfusable blood may be high. More sensitive serologic tests and targeting HBV vaccination of blood donors could be cost-effective alternatives in some cases [35]. The latter may also be a half-way to extend the vaccination to potential donors as well. Although it is not a typical task for a blood bank, it may be part of its strategy to recruit new donors and rise awareness of the importance of HBV prevention. In the countries where access to health services is limited, offering the vaccine within a blood bank may be an important logistic facilitator of such policy.

In conclusion, the incidence/window-period model for HBV has been around for 15 years and remains relevant for evaluating the HBV residual risk in vast majority of

the developing countries which concentrate the bulk of the people with HBV worldwide. The model has been improved over the years, benefiting from the insights on viral dynamics based on the research with highly sensitive HBV NAT. An adaptation of the incidence/window-period model termed “extended yield model”, which considers both HBsAg and recently (within last year) seroconverting anti-HBc repeat donors, seems particularly suitable for evaluating the HBV residual risk in smaller blood bank settings due to its robustness against bias and increased precision. Systematic monitoring of this risk and corresponding incidence are indispensable for improving the blood safety regarding HBV, still being the most common posttransfusional infection.

Abbreviations

Anti-HBc:	Hepatitis B core antibody
Anti-HBe:	Hepatitis B e antibody
Anti-HBs:	Antibody to hepatitis B surface antigen
HBsAg:	Hepatitis B surface antigen
HBV:	Hepatitis B virus
HCV:	Hepatitis C virus
ID NAT:	Individual donation nucleic acid testing
MP NAT:	Minipool nucleic acid testing
NAT:	Nucleic acid testing
OBI:	Occult hepatitis B infection.

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