Residual risk of transfusion-transmitted viral infections in Shenzhen, China, 2001 through 2004

Guifang Shang, Clive R. Seed, Fei Wang, Dongmei Nie, and Albert Farrugia

BACKGROUND: There are no current estimates of the residual risks of transmission by blood of hepatitis B virus (HBV) or hepatitis C virus (HCV) and human immunodeficiency virus (HIV) in China. Such estimates are an essential prerequisite to monitoring and improving transfusion safety as well as supporting evidence based assessment of the value of implementing new screening interventions.

STUDY DESIGN AND METHODS: Viral screening data for donors from Shenzhen, China, for the period 2001 to 2004, were retrospectively analyzed. The data were applied to a published model to estimate the residual risk of transmitting HIV, HBV, and HCV by blood transfusion in Shenzhen, as well as to assess the residual risk reduction value of various new tests.

RESULTS: The point estimates for the combined 2003 and 2004 period calculate as 1 in 17,501 for HBV, 1 in 59,588 for HCV, and 1 in 903,498 for HIV. The predicted yield for improved hepatitis B surface antigen (HBsAg) assays, minipool (MP) nucleic acid testing (NAT), and individual-donation (ID) NAT was 6.9, 9.5, and 28.3 per million donations, respectively. The predicted yield for implementing a fourth-generation HCV (antigen-antibody) or MP NAT assay was 13.4 or 14.7 per million donations, respectively. For HIV, the predicted yield for implementing a fourth-generation HIV (antigen-antibody) or MP NAT assay was markedly smaller, 0.25 or 0.65 per million donations, respectively.

CONCLUSIONS: Relative to that reported for Western blood systems, the prevalence and the residual risk of HBV and HCV are high, whereas HIV is comparable. Pending a formal cost-effectiveness study for NAT, implementing improved HBsAg and combination HCV antibody-antigen assays in Shenzhen would markedly reduce the residual risk.

Estimating the residual risk (RR) of transfusion-transmitted viral infections with risk modeling is now common practice in many countries, however, there are no current estimates for mainland China. Such data are important because they support effective monitoring for transfusion safety as well as evidence based assessment of the value of implementing new screening interventions like Nucleic Acid Testing (NAT). Further, in respect of hepatitis B virus (HBV) where the prevalence in China is known to be high compared to that of the US and Europe, RR estimation can also inform public health policy development.

Although Shenzhen has a population contributed to by the majority of provinces of China the demographics of the population are somewhat atypical among Chinese cities. Donors are drawn from a mobile, relatively young and proportionally well educated population making the epidemiology of the blood donor population only somewhat reflective of that of China as a whole. In contrast to donor populations assessed in previous RR studies the proportion of first-time donors (FTDs) in Shenzhen is

ABBREVIATIONS:

ChLIA = chemiluminescent immunoassay; FTD(s) = first-time donor(s); I = median preseroconversion interval; ID = individual donation; LTR(s) = mean lifetime risk(s); MP = minipool; p(FTD) = prevalence of first-time donations; P(FTD) = residual risk for the first-time donations; p(RD) = prevalence repeat donations; P(RD) = residual risk for the repeat donations; RD(s) = repeat donor(s); WP(s) = window period(s).

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markedly higher, around 60 percent. Since the most widely applied risk model (incidence-window period [WP]) is based on estimating the rate of incident (new) infection in repeat donors (RDs) which make up only 40 percent of the Shenzhen donor population, its application here is problematic. In light of this an alternate published model was selected which individually calculates the risk in FTD and RD populations. Although the accuracy of this model has been retrospectively validated with the yield of NAT-positive, antibody-negative donations for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in Australia, it has not been previously applied to a donor population with high viral prevalence as is the case for HBV and HCV in Shenzhen. In recognition of this, the model assumptions were modified to account for the differing epidemiology in China as well as the comparatively young donor population. By use of the modified model and applying viral screening data from Shenzhen for the most recent 2-year period (2003-2004), RR estimates for transfusion-transmitted HIV, HCV, and HBV were derived. In addition, an assessment of the relative value of implementing various new screening interventions including a hepatitis B surface antigen (HBsAg) assay with improved sensitivity, combination fourth-generation HCV and HIV antigen-antibody screening assays, and nucleic acid testing (NAT) was performed.

MATERIALS AND METHODS

Study population and data collection

Shenzhen is located in southern China very close to Hong Kong. From a population during the study period numbering some 3 million, the Shenzhen Blood Center collects approximately 50,000 donations per annum. All FTDs and RDs are administered the same risk-based donor questionnaire before acceptance for donation. Since 1998, voluntary blood donation has been the sole contributor to the blood supply. Chinese blood donation law allows whole-blood donations of either 200 or 400 mL with the donation interval of at least 90 or 180 days, respectively. Increasing the proportion of 400-mL donations will therefore lengthen the median interdonation interval among RDs. The Shenzhen Blood Center is equipped with state-of-the-art sample handling, testing, and data management systems. Donor demographics and donation information are captured as electronic data files with information including donor identification number, donation date, number and types of donations, and results of serologic screening and confirmatory tests, allowing accurate retrieval of information for the calculation of viral prevalence and assessment for seroconversion in the RD population.

Mandatory screening

Before acceptance, all donors were prescreened for HBsAg with a rapid dipstick assay (AiKang Biotechnology, Hangzhou, China) and deferred if positive. Screening for HBsAg, anti-HCV, and anti-HIV was performed on all donations in parallel with one domestic and one imported commercial assay as defined in Table 1. All donations were also screened for Treponema pallidum antibody and alanine aminotransferase (ALT). Importantly, ALT testing was performed as a postdonation screening test (kinetics method, Taiwan Unison, Xinzu Biotech, Taiwan) in 2001 and 2002; however, from 2003 on, donors were screened before donation (Reflotron Plus, Roche Diagnostics, Mannheim, Germany) and deferred from donation if their ALT was abnormal. If the prescreen ALT was normal, they were retested after donation with the screening test and deferred in the event their ALT was above the normal range (40 IU/L). Because a raised ALT often correlates with acute (incident) HCV infection, this policy change may have resulted in the selective exclusion of these donors before donation in 2003 and 2004. This has implications on the interpretation of the RR estimates calculated on the basis of incident infections (discussed later).

Viral confirmatory testing

Seropositive status for HCV and HBsAg was assigned with the confirmatory tests specified in Table 1 performed by the Shenzhen Blood Center and for HIV performed by the Shenzhen Center for Disease Control reference laboratory.

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<tr>
<th>Screening and confirmatory assays</th>
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<tr>
<td>Viral marker</td>
<td>Domestic assay</td>
<td>Screening</td>
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<tr>
<td>Anti-HCV</td>
<td>Sino-America Huamei*</td>
<td>Ortho†</td>
<td>Chiron RIBA 3.0‡</td>
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<td>HBsAg</td>
<td>Xiamen Xinchuang§</td>
<td>Abbott‖</td>
<td>Ortho neutralization¶</td>
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<td>Anti-HIV</td>
<td>Zhuhai Lizhu**</td>
<td>Melia††</td>
<td>Melia Western blot‡‡</td>
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* Sino-America Huamei anti-HCV EIA (Sino-America Huamei Biotechnology Ltd, Luoyang, People’s Republic of China).  
† Ortho anti-HCV third-generation EIA (Ortho-Clinical Diagnostics, Inc., Raritan, NJ).  
‡ RIBA third-generation anti-HCV immunoblot (Chiron Corp., Emeryville, CA).  
§ Xiamen Xinchuang HBsAg EIA (Xiamen Xinchuang Scientific Ltd., Xianmen, People’s Republic of China).  
‖ Abbott Auszyme HBsAg (Abbott Laboratories, Abbott Park, IL).  
¶ Ortho HBsAg neutralization EIA (Ortho-Clinical Diagnostics, Inc., Raritan, NJ).  
** Zhuhai Lizhu anti-HIV EIA (Zhuhai Lizhu Biotechnology Ltd., Zhuhai, People’s Republic of China).  
†† Melia anti-HIV-1 and -2 EIA (Organon Teknika, Bioxel, the Netherlands).  
‡‡ Melia HIV-1 and -2 Western Blot (Organon Teknika, Bioxel, the Netherlands).
Seropositive status was assigned consistently across all donations in the study and based on the requirements of the test manufacturer for HCV and HBsAg or the recommendation of the Shenzhen Center for Disease Control for HIV. To minimize the possibility of incorrectly assigning a “seroconverter” status (e.g., potential false-positive results or incorrect test interpretation), we reviewed the dates and results of screening and confirmatory tests, as well as any available follow-up information for cases of seroconversion.

Estimation of RR of infection

Results for serologic testing of blood donations were obtained from Shenzhen Blood Center for all donations tested during 2001 to 2004 (Table 2). By use of these data, the RR of infection was estimated for each virus with a published risk model which assumes that the RR is proportional to the probability of an undetected WP donation within the study period. The model separately calculates the RR component for FTDs and RDs. The population risk is derived by summing these adjusted by the proportion of each in the population.

Model definitions

First-time donor. A first-time donor is a donor who has not previously attended according to Shenzhen Blood Center records.

Repeat donor. A repeat donor is a donor who has a previously recorded attendance as a donor.

Window period. The window period is time between infection and first detection of the viral marker (unique to each test).

Seroconverter. A donor was considered to have “seroconverted” for an agent if before their seropositive donation they had made a previous “negative” donation with a test of comparable sensitivity.

Prevalence of first-time donations. The prevalence of first-time donations (p(FTD)) is the rate of confirmed seropositive donations per million first-time donations.

Prevalence of repeat donations. The prevalence of repeat donations (p(RD)) is the rate of confirmed seropositive donations per million repeat donations.

Median preseroconversion interval. Median interval in days between the seropositive and seronegative donations for all seroconverters. Median preseroconversion interval (I) is inversely proportional to the RR in RD, that

| TABLE 2. Shenzhen donation, prevalence, and seroconversion data for HBsAg, HCV, and HIV 2001 to 2004 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| First-time donations            | 28,751          | 26,140          | 27,182          | 26,346          | 53,528          |
| Repeat donations                | 15,691          | 17,175          | 17,238          | 17,972          | 35,210          |
| Percent RDs                     | 35.3            | 39.6            | 38.8            | 40.5            | 39.7            |
| Donation age (years) distribution (%) |                 |                 |                 |                 |                 |
| 18-25                           | 55.8            | 53.3            | 53.3            | 55.8            | 54.5            |
| 26-35                           | 33.3            | 34.3            | 34.7            | 33.3            | 34.1            |
| 36-45                           | 8.6             | 9.3             | 7.5             | 9.1             | 8.3             |
| 46-55                           | 2.3             | 3.1             | 4.5             | 1.8             | 3.2             |
| Proportion (%) of the           |                 |                 |                 |                 |                 |
| 400-mL donation                 | 46.9            | 47.2            | 67.3            | 65.6            | 57.1            |
| 200-mL donation                 | 53.1            | 52.8            | 32.7            | 34.4            | 42.9            |
| HBsAg                           |                 |                 |                 |                 |                 |
| Number confirmed positive FTDs  | 400             | 306             | 297             | 256             | 553             |
| p(FTD) (per 100,000 FTDs)       | 1,391           | 1,170           | 1,092           | 972             | 1,033           |
| Number of confirmed positive RDs| 47              | 46              | 30              | 27              | 57              |
| p(RD) (per 100,000 RDs)         | 299.5           | 267.8           | 174.0           | 150.2           | 162             |
| Number of seroconverters        | 47              | 46              | 30              | 27              | 57              |
| I                               | 820             | 836.5           | 873.5           | 839             | 867             |
| HCV                             |                 |                 |                 |                 |                 |
| Number of confirmed positive FTDs| 18              | 21              | 11              | 16              | 27              |
| p(FTD) (per 100,000 FTDs)       | 62.6            | 80.3            | 40.5            | 60.7            | 50.4            |
| Number of confirmed positive RDs| 17              | 17              | 10              | 8               | 18              |
| p(RD) (per 100,000 RDs)         | 108.3           | 99.0            | 58.0            | 44.5            | 51.1            |
| Number of seroconverters        | 17              | 17              | 10              | 8               | 18              |
| I                               | 498             | 488             | 823             | 918             | 895.5           |
| HIV                             |                 |                 |                 |                 |                 |
| Number of confirmed positive FTDs| 3               | 2               | 1               | 2               | 3               |
| p(FTD) (per 100,000 FTDs)       | 10.4            | 7.6             | 3.7             | 7.6             | 5.6             |
| Number of confirmed positive RDs| 0               | 0               | 2               | 0               | 2               |
| p(RD) (per 100,000 RDs)         | 0               | 0               | 11.6            | 0               | 5.7             |
| Number of seroconverters        | 0               | 0               | 2               | 0               | 2               |
| I                               | NA*             | NA              | 549             | NA              | 549             |

* NA = not applicable.
is, the longer the median interdonation interval the lower the RR.

**Mean lifetime risk.** The mean lifetime risk (LTR) is the mean lifetime infection duration in days. Based on a review of the viral epidemiology and primary modes of transmission in Australia, LTRs were originally assigned as HCV 9125 days (25 years), HBV 3650 days (10 years), and HIV 3650 days (10 years). To ensure that the LTRs were appropriate for the Shenzhen blood donor population, we undertook a review of the published literature (Table 3). As a consequence, we have maintained the HIV LTR at 10 years because despite the different principal transmission route (male-to-male sexual contact in Australia and intravenous drug use in Shenzhen) survival after HIV infection is directly impacted by access to antiretroviral therapy. Because patients diagnosed with HIV infection in Shenzhen have similar access to free treatment as patients in Australia, it is appropriate to use the same LTR. In respect of HBV, to account for the high prevalence of vertically transmitted chronic HBV infection in Shenzhen and proportionally younger age of first-time Shenzhen donors, we extended the HBV LTR from 10 to 30 years. This is based on the approximate median Shenzhen donation age of 25 and the maximum allowable donation age of 55 in China.

**RD risk calculation.** The RR for the repeat donations (P(RD)) was calculated as the prevalence (p(RD)) in RDs (per million donations) multiplied by the WP and then divided by the I for all seroconverters:

\[
P(RD) = \frac{WP}{I \times p(RD)}.
\]

**FTD risk calculation.** The RR for the first-time donations (P(FTD)) was calculated separately as the prevalence (p(FTD)) in FTDs (per million donations) multiplied by the ratio of the WP and the LTR in days:

\[
P(FTD) = \frac{WP}{LTR \times p(FTD)}
\]

**Total donor population risk.** The total RR is then derived by adjusting for the relative proportion of first-time and repeat donations with the formula

\[
P(\text{total donor population}) = FTD \text{ proportion} \times P(\text{FTD}) + RD \text{ proportion} \times P(RD)
\]

**Example calculation: HIV (2003-2004).**

RD calculation (WP = 22 days, I = 549 days, p(RD) = 57 per million donations)

\[
P(RD) = \frac{22 \times 57}{549} \approx 2.28 \text{ per million donations}
\]

FTD calculation (WP = 22 days, LTR = 3650 days (10 years), p(FTD) = 56 per million donations)

\[
P(FTD) = \frac{22 \times 56}{3650} \approx 0.34 \text{ per million donations}
\]

**Total population risk.**

\[
P(\text{total donor population}) = FTD \text{ proportion} \times P(\text{FTD}) + RD \text{ proportion} \times P(RD)
\]

\[
P(\text{total donor population}) = 0.603 \times 0.34 + 0.397 \times 2.28 = 1.11 \text{ per million donations}
\]

**Yield projections.** The projected yield for any new assay is proportional to the difference in the WPs for the two assays. It is derived by subtracting the two RR estimates (Table 5).

**Example calculation: HCV (2003-2004).** RR for current enzyme immunoassay (EIA; WP, 66 days) is 16.8 per million. RR for combination antigen-antibody EIA (WP, 12.5 days) is 3.4 per million; thus the projected yield for the antigen-antibody EIA is 16.8 - 3.4 = 13.4 per million.

**WP estimates**

The duration of the WPs was taken from the literature directly or derived to best approximate the current Shenzhen assays or the proposed alternatives as follows:

- HIV: for HIV antibody (current Shenzhen assays), 22 (range, 6-38) days; for fourth-generation HIV antigen-antibody assay, 17 days (5-day WP closure for HIV antigen compared to HIV Western blot from Busch and coworkers); and for HIV minipool (MP) NAT (16-member pools with Procleix HIV-1 and HCV assay, Chiron Corp., Emeryville, CA), 9 (range, 7.8-10.2) days.
• HCV: for HCV antibody (current Shenzhen assays), 66 (range, 38-94) days; for MP NAT (16-member pools with Procleix HIV-1 and HCV assay), 7.4 (range 6.1-8.7) days; and for HCV antigen-antibody assay, 12.5 days (derived by adding the mean 5.1 days MP NAT to antigen-antibody WP closure observed by Laperche and coworkers).

• HBV: for HBsAg (current Shenzhen EIAs), 43.6 (range, 37.4-49.7); for HBsAg (PRISM chemiluminescent immunoassay [ChLIA], Abbott, Abbott Park, IL), 38.3 (range, 33.0-43.7) days as derived by Kleinman and Busch, based on back-extrapolation modeling previously described for HIV and HCV RNA; for 16-member NAT, 36.3 days (mean, 2-day WP closure compared to PRISM ChLIA in studies by Biswas and coworkers [1 day] and Koppelman and coworkers [3 days]); and for individual-donation (ID) NAT, 21.8 days (mean, 16.5-day WP closure compared to PRISM ChLIA in studies by Biswas and coworkers [19 days] and Koppelman and coworkers [14 days]).

Statistical analysis
Confidence intervals (CIs) for individual model risk estimates were derived by direct calculation of the risk with the upper and lower CI for the WP. Comparison of RR estimates was performed with chi-square (HBV and HCV) or Fisher’s exact (HIV) and considered significant if p values were less than 0.05.

RESULTS
Repeat donor prevalence, I, and the RR point estimate per year are summarized in Table 4. Given the fact that the 2003 and 2004 estimates were not significantly different (p > 0.05 for HIV, HCV, and HBV), they were combined as the most appropriate measure of the “current risk” in Shenzhen. These estimates for HBV, HCV, and HIV calculate as 1 in 17,501, 1 in 59,588, and 1 in 903,498, respectively. Both the HBV and the HCV p(RD) showed a declining trend over the study period, HBV p(RD) declining from 2995 in 2001 to 1502 in 2004 and HCV p(RD) declining from 1083 to 445 per million donations in the same period. There was no discernible trend for HIV p(RD). The I for HBV was relatively constant (range, 820-873.5) during the study, whereas there was a marked lengthening for HCV from 488 days in 2002 to 823 days in 2003, coinciding with the change to ALT before screening and the increased proportion of 400-mL donations (47.2% in 2002 to 67.3% in 2003). Projected yields and RR estimates for various new testing options for HBV, HCV, and HIV are summarized in Table 5. The predicted yield in comparison to current HBsAg assays for an improved HBsAg assay (PRISM HBsAg ChLIA), MP NAT...
(16-member), and ID NAT was 6.9, 9.5, and 28.3 per million donations, respectively. The predicted yield for implementing a fourth-generation HCV (antigen-antibody) or MP NAT assay was 13.4 or 14.7 per million donations, respectively. For HIV, the predicted yield for implementing a fourth-generation HIV (antigen-antibody) or MP NAT assay was markedly smaller, 0.25 or 0.65, respectively, per million donations.

### DISCUSSION

This study presents novel HIV, HCV, and HBV RR estimates from Shenzhen, the first economic special zone in China. The median RR estimates for HBV, HCV, and HIV for the period 2003 to 2004 were selected as best representing the current risk in Shenzhen and calculated as approximately 1 in 17,501, 1 in 32,637, and 1 in 34,435, respectively, with a published risk model applied previously to Australian blood donors.\(^1,7\) This model is not the most widely applied but was selected as the “best fit” primarily because the high proportion of FTDs in the Shenzhen donor population required a direct method of estimating the risk in FTDs. Although the incidence-WP model has been used for this purpose,\(^14\) it requires NAT screening data unavailable here because NAT is not currently performed in Shenzhen.

The finding of a lower RR in FTD compared to RD is unexpected and contrasts with Western blood donor populations. We speculate that this reflects both the differing donor demographics and the motivations for donation in Shenzhen. First, in comparison to Australia, the Shenzhen donor population is markedly younger with the majority aged between 18 and 25 years, whereas the median donor age in Australia is 44 (ARCBS, unpublished). In general, older donors donate more frequently and are more conservative and comparably more averse to risk behavior. These donors are overrepresented in the RD population in Australia, resulting in a lower incidence and RR in RDs. In Shenzhen, they are replaced by younger donors less averse to continued risk behavior, which tends to equilibrate the FTD and RD risk profile. Second, although all donations in Shenzhen since 1998 have been sourced from volunteer blood donors, there are potential incentives for blood donors in Shenzhen. Despite medical insurance being provided free of charge by most employers,\(^20\) this does not cover the cost of blood for transfusion. A donor in Shenzhen who donates a unit that is issued for transfusion is entitled to receive blood free of charge for the rest of his or her life. In addition his or her direct relatives are eligible to receive an equivalent number of units to that donated by the donor. Further, unemployed donors are tested for free as part of the donation process but cannot access testing at no charge in the public health system unless they are covered by medical insurance. This potentially encourages “test-seeking” behavior, that is, donors who engage in high-risk behavior attending to donate to determine their infectious status. These factors may contribute to the comparably higher HBV and HCV RR observed in Shenzhen as well as the finding that RDs fail to deliver the premium of “lowered risk” invariably found in Western donor populations.\(^1,15\)
Direct comparison of the Shenzhen estimates with those from other published studies must be interpreted with caution because of the variability in the model(s) applied and/or underlying assumptions (e.g., WPs). This noted that the RR for HBV and HCV in Shenzhen is markedly higher, indicating the need to consider additional and/or improved safety measures including donor screening tests. In contrast, the RR estimate for HIV is comparable confirming the efficacy of the existing HIV antibody screening strategy.

HBV

The HBV RR estimate for the study period of approximately 1 in 18,000 is markedly higher than those from Europe, North America, and Australia, which range from approximately 1 in 70,000 (Italy, Spain, Canada) to 1 in 1.3 million (Australia). This differential reflects the higher prevalence of HBV in the Shenzhen FTDs: 1,161 compared to approximately 75 per 100,000 in US FTDs. Although it is encouraging that the RR estimate declined over the study period from approximately 1 in 11,000 in 2001 to 1 in 18,000 in 2004, this should be interpreted with caution given the coincident implementation in 2003 of predonation ALT testing and the increase in proportion of 400-mL donations.

In the model the RR in RD is directly proportional to the p(RD) and inversely proportional to the I. The HBV I remained relatively constant during the study period despite the increased proportion of 400-mL donations, which would have acted to increase the median interdonation interval among RDs (including seroconverters) because an increased proportion would have donated at the longer 180-day minimum interval. Perhaps because I for HBV was already markedly longer than 180 days (836.5 days in 2002), the impact of the proportional increase in 400-mL donations on I and consequently RR was negated. In contrast the RR decline did correlate directly with a decline in the HBV p(RD) subsequent to the ALT policy change to predonation screening of donors in 2003. It is unclear whether this change could by itself explain the decline in RR, although it seems unlikely because since 1998 Shenzhen has utilized a rapid HBsAg test, also performed before donation to exclude HBsAg-positive donors before collecting a donation. The test has a sensitivity of 80 to 90 percent; therefore, only 10 to 20 percent of HBsAg-positive donors are subsequently accepted and tested by EIA, these constituting the “donation” HBsAg prevalence. Whether the prescreening ALT test would identify any of the 10 to 20 percent of HBsAg rapid test-negative and/or EIA-positive RDs leading to a decline in RD prevalence is difficult to determine. There is one other potential reason for the decline in RD prevalence. Since January 2002, Shenzhen began to undertake a widespread HBV vaccination program. To be eligible individuals were required to demonstrate that they were HBsAg-negative. Therefore RDs were eligible, and once they were vaccinated and presumably protectively immune, they would be less likely to be infected, even in the face of overt risk behavior. This may have contributed to the observed decline in seroconverters (and RD prevalence) in 2003 and which continued in 2004.

Irrespective of whether the RR truly declined across the study period, the comparatively high 2004 RR estimate indicates the need to consider implementing further HBV safety initiatives in Shenzhen. In terms of donor screening and in the context of a high-prevalence population such as Shenzhen where hepatitis B core antigen (anti-HBC) is not a viable option because it would exclude approximately 40 percent of eligible donors, the alternatives are limited to either a more sensitive HBsAg assay or HBV NAT. In a US study to assess these two options, Biswas and colleagues demonstrated that highly sensitive HBsAg assays have almost equivalent performance to pooled NAT in reducing the WP relative to less sensitive assays. The authors of a recent European multisite evaluation comparing a highly sensitive HBsAg assay (PRISM HBsAg ChLIA) with a commercial triplex NAT assay (Procleix Ultrio, Chiron Corp.) for simultaneous detection of HIV-1, HCV, and HBV concluded similarly. Taken together these two studies indicate that relative to the most sensitive HBsAg assays available, HBV NAT in pools of 16, for instance, provides only a modest WP closure of between 1 and 3 days. By averaging the WP closure obtained in these two studies and applying the WPs for the existing HBsAg and PRISM HBsAg, from recent modeling by Kleinman and Busch, we projected yields and RR for various screening options in comparison to the existing Shenzhen HBsAg assays (Table 5). As would be predicted, the yield for ID NAT is highest (28.3 per million donations) followed by MP NAT (9.5) and PRISM ChLIA (6.9). Notably the yield differential between MP NAT and PRISM ChLIA HBsAg assay is comparatively small, only 2.6 per million donations, an important consideration given that NAT is undoubtedly the more expensive option to implement with questionable cost-effectiveness where this has been formally assessed.

The assessment of the significance of the comparatively high RR of approximately 1 in 18,000 for the combined 2003 to 2004 period bears discussion in itself. This figure seems at odds with the lack of a confirmed transfusion-transmitted HBV report in Shenzhen for more than 10 years. There are several possible reasons for this apparent discrepancy. First, HBV vaccination in China as a component of a concerted health-care initiative commencing in 1978 has resulted in most children being immunized, acute infectious diseases becoming a rarity, and the neonatal and maternal mortality rates declining to levels comparable to those of developed countries. Although no formal data are available in respect of the...
proportion of blood recipients in Shenzhen with existing HBV immunity (anti-HBs), on the basis of the high HBV prevalence, high anti-HBc-positive rate (approximately 40%), and widespread vaccination of the donor population, it would be predicted to be high. This is supported by a study from Taiwan, a population with comparably high HBV prevalence to China, in which only 39 of 909 recipients (4.3%) were HBV-“naive” defined by the lack of detectable HBsAg, anti-HBs, anti-HBc, and HBV DNA in pretransfusion samples.26 In immunocompetent recipients at least, this existing immunity will invariably prevent infection resulting from transfusion with an infectious WP unit. Second, the majority of HBV infections spontaneously resolve without symptoms and therefore go unreported.27 Third, the modeling assumes that the entire 43.6-day WP is infectious. As noted by Kleinman and Busch,17 this is a conservative assumption reflecting the lack of conclusive data on the minimum infectious dose in humans. Irrespective of the susceptibility of blood recipients in Shenzhen, implementation of an improved EIA would at minimal cost lead to a reduction in the RR of transfusion transmitted HBV.

HCV

Consistent with HBV, the HCV RR estimate for Shenzhen of approximately 1 in 60,000 is markedly higher than those from Europe, North America, and Australia, which range from a high of approximately 1 in 250,000 (Spain6) to a low of 1 in 20 million (UK2) with intermediate estimates of 1 in 1.8 million (United States15) and 1 in 3.6 million (Australia1).

Although there was an apparent decline in RR during the study period from approximately 1 in 18,000 in 2001 to 1 in 66,000 in 2004, as discussed previously this should be interpreted with caution given the coincident implementation in 2003 of predonation ALT testing and the increase in proportion of 400-mL donations. In contrast to HBV where I remained constant over the study period, I for HCV increased from 488 days in 2002 to 823 days in 2003. There are two possible reasons for this observed lengthening of I. First, it may be due to the selective exclusion of donors with incident HCV infections because ALT elevations in such donors generally correlate with early infection. Incident HCV donors will have shorter interdonation intervals and their removal will tend to lengthen I. Second, the increased proportion of 400-mL donations tends to lengthen the interdonation interval among all RDs including seroconverters. Irrespective of the reason for the lengthening of I, it directly contributes to a decline in RR. Notably though, it is not the only contributor to the RR decline because both the FTD and the RD HCV prevalence also declined markedly between 2002 and 2003, both of which contribute to a decline in the RR estimate. The decline in FTD prevalence may have been impacted by an increased public awareness of infectious disease transmission routes subsequent to the SARS outbreak in 2003.28 The decline in RD prevalence correlates with the decline in incident infections (number of seroconverters) possibly linked to the implementation of ALT before screening.

Despite the lack of a reported case of transfusion-transmitted HCV during the study period, the comparatively large RR in Shenzhen during the same period argues for the need to consider implementing additional safety measures for HCV. In terms of testing strategies, the addition of either HCV RNA or HCV antigen to the existing HCV antibody screening strategy are logical options. In respect to HCV RNA, MP NAT has been widely implemented since the late 1990s as a risk reduction strategy for HCV based on its ability to close the WP by almost 90 percent from approximately 66 days to 7 days.29 The comparatively high cost of implementing NAT as well as poor cost benefit where it has been formally assessed,8 however, has resulted in some countries deciding against introducing NAT. The cost benefit of NAT is further impacted by the requirement to maintain HCV antibody screening to detect HCV antibody-positive donors with intermittent low-level viremia below the detection limit of currently implemented NAT assays.30,31

Recently, assays for the simultaneous detection of HCV antibody and core antigen have been developed.16,32 Laperche and colleagues16 reported that 31 of 44 (70.5%) of MP NAT-positive samples were also positive on the MonoLisa HCV antigen-antibody Ultra EIA with a mean delay of 5.1 days in detecting HCV infection. Based on this WP closure, the projected yield after implementing this assay in Shenzhen would be 23.8 per million donations compared with 26 for MP NAT. The modest yield differential for this option in comparison to NAT warrants careful consideration given that it could be accomplished by simply replacing the existing antibody assay with the combination HCV antigen-antibody assay avoiding the expensive setup costs associated with implementing NAT.

HIV

In contrast to HBV and HCV, the HIV RR estimate for the study period of approximately 1 in 0.9 million is comparable to those from Europe, North America, and Australia, which range from a high of approximately 1 in 400,000 (Spain6) to a low of 1 in 10 million (France6) with intermediate estimates of 1 in 2 million (United States15) and 1 in 7.6 million (Australia1). The low RR compared to HBV and HCV reflects both the efficacy of the existing HIV antibody based testing strategy and the markedly lower prevalence of HIV infection in the donor population.

Assuming that additional measures are determined necessary then, there are two logical options, the addition of HIV antigen or HIV RNA to the existing HIV antibody
testing strategy. HIV RNA in the form of MP NAT has been implemented in some countries reducing the WP by almost 60 percent from 22 to 9 days.\textsuperscript{15,29} In comparison, fourth-generation HIV assays able to simultaneously detect HIV antibody and antigen reduce the WP by approximately 5 days, to 17 days. With these WP estimates, MP NAT and HIV antigen-antibody assays would be predicted to provide a very modest yield of 0.65 and 0.25 per million donations, respectively, in Shenzhen. The RR estimates would decline to approximately 1 in 2.2 million and 1.2 million for MP NAT and HIV antigen-antibody screening, respectively.

One further consideration to reduce the RR for all viruses relates to the recommended donation interval. Current Chinese blood donation law provides the option of a 200- or 400-mL donation at minimum intervals of 90 or 180 days, respectively. The modeling indicates that it would be beneficial to encourage donors to donate 400 mL at 180-day intervals because this increases the median donation interval among the RD population and specifically the preseroconversion interval (I) for seroconverting donors resulting in a decline in RR. Although inconclusive, the lengthening of I for HCV in 2003 coincident with the increase in proportion of 400-mL donations and a decline in RR provides evidence in support of the benefit of this strategy.

**Modeling limitations**

The predictive value of the risk estimates and yield projections are dependent on a number of assumptions. First, the estimate assumes that most of the risk per unit is due to the probability of WP donations and other sources of transfusion risk are insignificant (such as testing errors, viral variants, and chronic seronegative carriers). This appears to hold true for HIV and HCV but may be less applicable to HBV where chronic infection marked by transient HBsAg can confound the estimates.\textsuperscript{33} Unlike the incidence-WP model, which incorporates a correction factor to account for the estimated 42 percent of total incident infections due to the transient nature of HBsAg in acute self-limiting infections,\textsuperscript{33} the Australian model does not include a specific correction factor. Seed and associates,\textsuperscript{1} however, noted that the RR estimates calculated by the incidence-WP model incorporating a correction factor were not markedly different from those calculated with the Australian model, indicating that the Australian model is less affected by the failure to detect “HBsAg-negative,” recently infected individuals. The same observation applies to the comparative incidence-WP–derived RR estimate for Shenzhen, which for RDs calculates as approximately 1 in 3800 (data not shown). The second assumption is that the Australian model, previously applied only to a low HBV prevalence population, is equally appropriate to a high-prevalence population like Shenzhen with its proportionally higher risk of vertical transmission. The modification of the HBV LTR is designed to compensate for this and therefore improve the accuracy of the model. The third assumption is that previous negative donations made within the study period are truly negative and not WP donations. The net impact of missing true WP donations will be to lengthen the median preseroconversion interval (I) leading to an underestimate of the true RR. The fourth assumption is that the WP estimates applied in the current modeling accurately reflect those for the assays under consideration. If the duration of the assay WP is in fact longer than that applied in the modeling then this will lead to an underestimate of the true risk and vice versa. It is therefore essential to estimate WPs accurately and where possible use estimates derived for the specific assay. The WPs applied in the current study are derived where possible with a consistent approach based on back extrapolation of viral replication rates. This novel approach, which assumes infectivity begins at one viral copy per 20 mL of plasma, is consistent with both transfusion lookback and animal model inoculation studies and was applied initially to HIV and HCV then later extended to HBV.\textsuperscript{15,17} The WPs derived from this modeling assume that the beginning of the “ramp-up” phase of viremia is a discrete event. Two recent reports, one concerning HIV\textsuperscript{34} and a second in reference HCV,\textsuperscript{35} indicate the existence of intermittent low-level viremia below the limit of detection of current NAT assays several weeks before the commencement of the viral “ramp-up” stage presumed to coincide with the beginning of the infectious WP. Although this has the potential to extend the infectious WP for HIV and HCV and consequently impact the RR estimates, the HCV study authors have recommended awaiting the results of inoculation studies to determine the infectivity of such samples before making adjustments to the existing modeling process.\textsuperscript{35} The fifth assumption is that donors do not change their donation behavior as a result of acquiring an infection. Assuming that they were to deliberately delay their next donation then the I will be lengthened resulting in an overestimation of RR (as I is inversely proportional to risk). Alternatively, by deliberately attending earlier, perhaps in order to obtain a test (so-called “test seeking”), the preseroconversion interval will be shortened leading to an overestimation of the RR. As discussed, there is certainly the potential for this phenomenon to have occurred during the study period. The final assumption is that the sample size provides for an adequate number of seroconverters, from which to derive I accurately. In this regard combining 2003 and 2004 data provides sufficient for HBV and HCV where there are 57 and 18 seroconverters, respectively. For HIV though, there are only two seroconverters and therefore the RR estimate and yield predictions must be interpreted with due caution.
The cost-effectiveness of NAT is highly dependent on the clinical consequences of a transmission as well as the existing RR. In respect to HIV, the infection with the most severe clinical outcome, the projected yield for HIV MP NAT in the study is less than 1 additional infection identified per 1 million donations. This is similar to reported yields for MP NAT in the United States and suggests that the cost-effectiveness for HIV NAT in China would also be poor. In respect to HCV, the next most clinically important infection, the observed US yield of 4.25 per million donations is markedly less than the 14.7 projected for infection, the observed US yield of 4.25 per million donations. This is similar to reported yields for MP NAT in the United States and suggests that the cost-effectiveness for HIV NAT in China would also be poor. In respect to HCV, the next most clinically important infection, the observed US yield of 4.25 per million donations is markedly less than the 14.7 projected for Shenzhen. In a European HBV cost-effectiveness study, Pereira applied a RR range of 50,000 to 300,000. Consistent with HCV, the RR (and therefore the projected yield) in Shenzhen is markedly higher at approximately 1 in 18,000. Therefore, drawing conclusions from these studies in respect of the likely cost-effectiveness of NAT implementation in Shenzhen is not appropriate.

Pending formal cost-effectiveness studies in Shenzhen, what conclusions can be drawn from the current study? First, in respect to HBV there is a compelling case for replacing the existing Shenzhen assays with an improved assay capable of achieving sensitivity for HBsAg of better than 0.1 ng per mL. This would substantially reduce the RR without markedly increasing the cost of screening. Second, the continuation of universal HBV vaccination is strongly supported. Not only does it reduce the prevalence in the donor population directly thereby reducing the RR, but it also minimizes the impact of releasing infectious units as a result of increased immunity in the recipient population. Third, in respect to HCV, careful consideration should be given to implementing a fourth-generation combination HCV antibody-antigen EIA. The projected yield of such an assay approaches that of MP NAT at a fraction of the cost. Fourth, in respect to HIV, there appears little justification for additional measures to reduce the existing risk, which is comparable to Western blood services. In recognition of the public concern over HIV transmission though and subject to a rigorous evaluation to ensure that antibody sensitivity is maintained, implementing a fourth-generation combination HIV antibody-antigen EIA warrants consideration. Finally, Shenzhen donors should be encouraged to donate 400 mL at a minimum interval of 180 days because of the associated RR reduction for all viruses.

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