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Assessing the Residual Risk for Transfusion-Transmitted Infections in the Philippine Blood Supply

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Due to a USAID-funded study on blood banks, a national policy was instituted in 1994 that set standards for Philippine blood services, promoted voluntary donation, and led to a ban on commercial blood banks. In this follow-up study, we assess the safety of the supply by determining the residual risk for transfusion-transmitted infections (syphilis, hepatitis B and C, HIV). We also identified unsafe facility practices and generated policy recommendations. A 1992 study found that transfusion-ready blood was not safe using the LQAS method ($P > 0.05$). We found that the 2012 residual risk became 0 to 0.9 percent attributable to the national policy. We noted poor to fair adherence to this policy. We identified unsafe practices such as use of rapid tests and lack of random blood retesting. Training and use of regional networks may improve safety. Despite improvement in safety, facilities complain of funding and logistical issues regarding compliance with the policy.

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†Abbreviations: AIDS, Acquired Immunodeficiency Syndrome; CBB, commercial blood banks; BSF, Blood Service Facility; DOH, Department of Health; EIA, enzyme immune-assay; HIV, Human Immunodeficiency Virus; ID, identification; LQAS, Lot Quality Assurance Sampling; NVBSP, National Voluntary Blood Services Program; PCR, polymerase chain reaction; RR, residual risk; TTI, Transfusion Transmitted Infection; USAID, United States Agency for International Development; WHO, World Health Organization.

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INTRODUCTION

According to the World Health Organization (WHO†), the provision of safe blood is primarily the responsibility of the State. It encourages members to have a national program and updated policies regarding blood and blood-related services [1].

Great strides have been made in making the blood supply safer for patients. Mandatory screening of donated blood for transfusion-transmitted infections has greatly reduced the risk of getting infected via transfusions. The increasing use of nucleic acid amplification tests also contributed to further reduction in risk of infection. This is more often seen in developed countries such as the United States and Germany, where residual risk for hepatitis B, one of the more commonly screened for transfusion-transmitted infections, is at 1 per 300,000 donations [2] and 1.51 per 10^6 donations [3], respectively.

In the Philippines during the early 1990s, a USAID-funded study by Paraan et al. showed the residual risk for infection in the supply of transfusion-ready blood to be greater than 5 percent [4]. Paraan et al. attributed this risk to the presence of commercial blood banks wherein donors were remunerated for the blood they donated. This study, together with the call from WHO for more involvement of the State, led to the creation of a National Blood Services Act of 1994 (Republic Act 7719). With the aim to "promote public health," the act enumerated 12 objectives as State mandates, including to promote voluntary blood donations; to lay down the principle that blood for transfusion is not a commodity for sale; to mandate the Department of Health to establish a National Blood Transfusion Service Network; to establish scientific and professional standards for the operation of blood collection units and blood banks; and to regulate the safety of all blood donation-related activities, among others. The Blood Services Act of 1994 therefore created standards for blood services facilities, abolished commercial blood banks (CBB), and promoted voluntary non-remunerated donations. Two decades have passed since the implementation of the Act, but its effect on safety has not been studied.

This study is a follow-up to the study of Paraan et al. to document the effect of the implementation of the national policy on blood safety. We assessed the safety of the Philippine blood supply by determining the residual risk from transfusion-ready blood. We also assessed the adherence of blood service facilities to the national guidelines.

Residual risk (RR) is the risk of transfusion-transmitted infection despite the application of safety measures in the blood collection, testing, processing, and storage processes during blood donations. Residual risk exists in donated blood products that have been tested because of limitation of testing procedures, such that infections may not have been detectable during the testing process. To test for RR, more sensitive confirmatory tests are done on already tested or transfusion-ready blood.

METHODS

Study Population and Sampling

We utilized a cross-sectional study design and obtained a random sample of blood service facilities (BSF) for inclusion in the study. We first obtained a list of all blood services facilities registered with the national government. Facilities that do not collect blood donations and those that collect only during emergencies were excluded. The exclusion of the latter type of facility is due to the difficulty of obtaining blood samples due to quick turnaround time from donation to transfusion and unpredictable donation schedules. The remaining blood service facilities were then classified into one of four categories based on the type of processes and services they offered (Table 1). Information regarding services was obtained through review of government registration reports and through phone interviews of BSF staff.

In determining residual risk, we utilized lot quality assurance sampling method (LQAS). This method tests a hypothesis rel-

Table 1. Blood Service Facilities in the Philippines Classified According to Processes Performed.

Blood Service Facility Type	Processes			
	Collect	Test	Store	Distribute
A	√	√	√	√
B	√	√	√	
C	√		√	
D	√		√	√

ative to a threshold prevalence level. We tested the hypothesis that "the contamination rate of the sample will be less than the population contamination rate of unscreened blood determined from the past study" [5].

> Null hypothesis: The contamination rate is greater than or equal to 4 percent ($P \geq 0.04$) (based on the 1994 study led by Asuncion Paraan entitled "Project to Evaluate the Safety of the Philippine Blood Banking System," in which the reported contamination rate was 5 percent).
>
> Alternative hypothesis: The contamination rate is less than 4 percent ($P < 0.04$).

In LQAS, we defined the lots as the five categories of blood banks. In each lot, we performed simple random sampling. The defined critical value (contamination rate) in each lot was set at 4 percent. Referring to Lemeshow and Taber's article on LQAS [5], allowing one "defective sample" in a lot and the contamination rate of 4 percent with 95 percent confidence level, a sample size of 109 per lot was required.

The Paraan et al. study concluded that the supply of transfusion-ready blood in the Philippines in 1992 was not safe, using a prevalence cut off of 5 percent. This led to the abolishment of commercial blood banks (CBB) and more stringent collecting, testing, storage, and distribution procedures in the blood donation process. Therefore, in the post-1992 era with an improved setting, we decided to use a more stringent cut off of 4 percent.

In the case of the five transfusion-transmitted infections (hepatitis B, hepatitis C, human immunodeficiency virus, syphilis, malaria) being screened by the National Voluntary Blood Services Program (the implementing agency for the national blood policy), the fact that human immunodeficiency virus (HIV) has a very low prevalence in the Philippines (less than 1 percent of total population [6] and donated blood [7]) does not affect the sample size significantly as the process of the screening is a "one equals all" method, such that if any one of the five transfusion-transmitted infections (TTI) is present, then the blood is considered tainted. As such, the low prevalence of one of the TTI is masked because of the higher prevalence of the other TTIs.

Due to limitations in funding, it should be noted we only tested for four of the TTI. Testing for malaria was not done. Testing for malaria was considered during the proposal preparation, however, two major factors were considered in our decision to eventually not test for malaria. In 2012, the WHO statistic for the prevalence of malaria in the Philippines was 9,552 out of a total of 93.3 million population [8]. Further, because we were testing for residual risk, we could not use the standard testing procedure for malaria being used in the BSFs (i.e., thick and thin blood smears). The cost of ordering PCR test for residual testing for all study samples was not possible with the limited research budget that we had. In that actual process of blood donation, BSF staff were trained on assessing "deferrals" by specifically asking donors if they had received treatment for malaria in the last 3 years, had traveled to malaria endemic areas within the

Table 2. Number of Blood Services Facilities and their production in 2011.

Blood Service Facility Type	Number of facilities in 2012	Units produced in 2011		Blood samples
		n	%	
A	167	779,774	84%	126
B	60	70,095	8%	109
C	5	5,200	1%	106
D	44	70,735	8%	108
Emergency Only	32	3,459	0.4%	n/a
TOTAL	308	929,263	100%	449

last 6 months, and if the donor was a former resident of malaria-endemic areas in the last 12 months. As such, given the low prevalence and the explicit "deferral conditions" for malaria, we felt that in order to keep within budget, we omitted testing for malaria with minimal fear of grossly mitigating our results.

Therefore, to compare the quality of the four types of existing blood service facilities in the Philippines, which are listed above, we needed a sample of size of 109*4 = 436. Allowing for a 3 percent allowance for breakages and other laboratory incidents, we came up with a required sample size of 436*1.03 = 449.08, therefore, 449 random samples. The sample size for this study was 449 randomly selected blood units.

To determine the number of samples to be collected per facility, we assigned identification (ID) numbers to each facility depending on their production the previous year. Higher production would mean greater number of ID numbers assigned to a facility. Each sampled ID number is equivalent to one blood sample from a donor in a blood service facility. For example, if a blood facility is assigned 10 ID numbers and five of those numbers were sampled, five blood samples were obtained from that facility. The random sequence was generated using RANDOM.ORG.

Blood Collection and Testing

Blood samples were drawn either from randomly selected donors or blood bags in the different blood service facilities included in the sampling. Preference for collection from donors is due to the fact that the use of a sterile connecting device for collection from blood bags is considerably more expensive and is sometimes not allowed by local BSF policies. Samples were centrifuged, and serum was stored in cryovials at a temperature between -30 to -20°C. It is a standard laboratory requirement that blood samples need to be centrifuged and frozen to at least -20ºC within 6 hours after collection from the donor. Samples that were older than 6 hours were therefore not included. If blood samples were collected from a donor, testing results from local BSF screening were obtained, and those that tested positive for any TTI were excluded in the final dataset.

The samples were sent in one batch to an independent, non-NVBSP related testing facility (Thailand Ministry of Public Health — US CDC Collaboration (TUC) HIV/STD Laboratory, Building 2, Tivanon Road, Nonthaburi 1100, Bangkok, Thailand) for testing. Testing for HIV, hepatitis B, and hepatitis C was done using both serological and nuclear amplification tests. Syphilis testing was also done using treponema pallidum heme-agglutination assay.

Self Assessment on Adherence

We asked blood service facility managers where samples were obtained to answer a self-assessment tool on national guidelines and standards. Adherence was rated using a scale of 0 to 5, with 0 described as "never done" and 5 as "always done or complied with." The tool lists standards stated in the national guidelines created by the national agency that manages the national blood program. The principal investigator also conducted visits to selected blood service facilities and conducted validation interviews.

Table 3. Risk of Transfusion-Transmitted Infections of the Philippine Blood Supply, 2012.

BSF* Type	Blood Samples	Reactive as per US-CDC laboratory tests	Estimated point prevalence	95% Confidence Interval
A	126	1	0.8%	0.02% to 4.3%
B	109	0	0.0%	0.00% to 3.3%
C	106	1	0.9%	0.02% to 5%
D	108	0	0.0%	0.00% to 3.3%
Total	449	2	0.4%	0.05% to 1.6%

*Blood Service Facility

Ethics

This study was granted approval by the University of the Philippines Research Ethics Board (UPMREB-2012-031-NIH) on August 3, 2012.

RESULTS

Government records showed that there were a total of 308 blood service facilities, 32 of which were excluded from the study because they only collected blood for emergencies (Table 2). Type A facilities were the most numerous and contributed the most to the 2011 blood supply. The type A facilities included both free-standing blood collecting units and blood banks attached to a hospital. Type B and C were mostly blood banks attached to hospitals. Type D facilities were mostly free-standing blood collecting units. Type A was found to be usually located in the cities. The other types were more often found in rural areas.

We obtained 449 blood samples from all four types of blood service facilities. The blood samples came from 83 different separate facilities across the country. Among these samples, two samples were reactive to at least one of the five TTIs: one from a type A facility and the other from a type C facility (Table 3). The sample from type A was reactive for hepatitis B infection using both the serological (enzyme-immunoassay/EIA) and nuclear amplification (polymerase chain reaction/PCR) tests. The sample from type C was reactive for HIV using serology, non-reactive using nuclear amplification and tested indeterminate using Western blot. Given that we used the LQAS method, we estimated the overall risk of infection from any blood from any facility type was less than 3.5 percent with a post-hoc point estimate of 0.4 percent (95% CI 0.05% - 1.6%). Post-hoc computation using Paraan et al.'s data showed that residual risk in 1994 was 5.2 percent, with a range from 3.1 percent to 8.2 percent.

We also asked blood service facilities to answer a self-assessment questionnaire on national guidelines. The 83 BSFs participated in the survey. We see that only type B facilities reported relatively higher compliance to national standards and guidelines. Looking at individual components, there is a different picture with facilities having notably low scores in personnel, audits, and testing and preparation (Table 4).

Looking into certain specific items that affect testing capability of BSF, we noted good adherence with updating their licenses to operate (81.2 percent), use of accredited suppliers of reagents (76.5 percent), and performance of control tests (79.2 percent), but poor compliance in terms of having adequately trained personnel (36.7 percent) and participating in audits both internal (42.8 percent) and external in the form of the National External Quality Assurance Scheme (25.9 percent). There is also no system in place that re-tests non-reactive blood, and facilities do not actively seek out donors who had positive results. Facilities also failed to send their samples for confirmatory testing to the national reference laboratory.

We surveyed the facilities regarding how they screened for TTI. All facilities reported that they tested all of their donated blood, but the tests that they use differed. Fa-

Table 4. Mean Adherence of Blood Service to National Policies and Guidelines.

Quality Assurance Framework Component	Blood Service Facility Type				Average
	A n = 47	B n = 15	C n = 5	D n =16	
1. Physical Plant	82%	90%	66%	86%	81%
2. Equipment	70%	78%	58%	65%	68%
3. Reagent	81%	79%	71%	63%	74%
4. Personnel	68%	68%	53%	60%	62%
5. Quality Assurance System	69%	68%	46%	62%	61%
6. Technical Procedure Manual	72%	66%	20%	60%	55%
7. Quality Control	83%	83%	33%	60%	65%
a. Audits	54%	37%	26%	50%	42%
b. Handling of Donors	87%	75%	71%	79%	78%
c. Collection	89%	89%	63%	83%	81%
d. Information System	0%	0%	0%	0%	0%
e. Labelling	87%	88%	72%	81%	82%
f. Testing and Preparation	55%	56%	NA	NA	56%
g. Release	82%	86%	45%	76%	72%
h. Environmental Management	77%	83%	64%	66%	72%
i. Records	76%	88%	64%	67%	74%
AVERAGE	74%	77%	59%	67%	69%

cilities used enzyme immunoassays (EIA), rapid tests (which often uses immunochromatography), or both. In facilities that used both tests, they either used rapid tests as a substitute for EIA when stocks for EIA ran out or used them to pre-screen donors prior to blood donation then tested the donated blood using EIA (Table 5).

DISCUSSION

A 92 percent reduction in the residual risk of TTI from 5.2 to 0.4 percent was noted since the enactment of the National Blood Services Program Act. However, BSFs reported minimal compliance with regard to national standards and guidelines. The improvement in safety strengthens the evidence for having a national policy on blood and blood banking. A similar effect of a national policy on safety was observed in South Africa. There was a documented decrease in HIV-1 prevalence in the donated supply of around 53 percent, from 0.17 percent to 0.08 percent, after a structured blood policy was implemented [9].

Possible key policy changes that contributed to the reduced residual risk were the promotion of voluntary non-remunerated blood donors only and prohibition of commercial donors and blood banks. Commercial blood supply has often been viewed as unsafe as seen in Paraan et al.'s study. In China, it was reported that HIV infection is alarmingly high among commercial plasma blood donors [10]. AIDS from transfusion in Mexico is also attributed to commercial donors and plasmapheresis centers [11].

Despite improvements in blood safety, there was still room for improvement, especially when one considers that the current residual risk translates to a potential of at least four infections per every 1,000 transfusions. In the case of the Philippines, every blood donation is in a multiple blood bag system (i.e., triple or quadruple blood bags), wherein the whole blood collected from the donor can be fractionated into one unit pack red blood cell, one unit platelet concentrate, one unit cryosupernate, and one unit cryoprecipitate. One whole blood donation is processed into four units that can be prepared and transfused to up to four adults. In addition, children generally need less amounts of blood; for example, one unit of packed red cell can be transfused to up to four children.

The failure of the blood service facility to detect the reactive samples reflects a fail-

Table 5. Types of Transfusion-Transmitted Infection testing procedures among Blood Service Facilities in the Philippines.

TTI[a]	Tests	A (n=47)	B (n=15)	D (n=16)
Malaria	Any	100%	100%	69%
Syphilis	Rapid test only	21%	47%	19%
	EIA[b] test only	34%	20%	0%
	Rapid, then EIA tests	11%	7%	6%
Hepatitis B	Rapid test only	4%	13%	0%
	EIA test only	51%	47%	25%
	Rapid, then EIA tests	9%	13%	0%
Hepatitis C	Rapid test only	4%	13%	0%
	EIA test only	51%	40%	18%
	Rapid, then EIA tests	11%	20%	6%
HIV 1 Antibody	Rapid test only	6%	13%	0%
	EIA test only	49%	40%	19%
	Rapid, then EIA tests	13%	20%	6%
HIV 2 Antigen	Rapid test only	2%	0%	0%
	EIA test only	47%	20%	13%
	Rapid, then EIA tests	6%	7%	6%

[a]Transfusion-transmitted infection; [b]enzyme immunoassay

ure of the Philippines' screening system. It was possible that the false negative results were due to chance as no test is perfect. Another possibility is that the facility was not a using a test with enough sensitivity. Reactive samples were obtained from two facilities, which reported using both enzyme immunoassays and rapid (immunochromatographic) tests for their screening of donors. The technical committee of the NVBSP, during the time of study, required that screening reagents for HIV and hepatitis C should have sensitivity of 100 percent and greater than 98 percent specificity. For hepatitis B and syphilis, the reagent was required to have greater than 97 percent sensitivity and greater than 98 percent specificity. In general, rapid tests for HIV, according to a study by Gray et al., had sensitivities averaging 97.7 percent, specificities averaging 90.7 percent only [12]. Therefore, the technical committee of the NVBSP does not allow the use of rapid tests.

Despite the clear guideline by the national agency regarding the type of tests for screening, several facilities still utilized rapid tests. These facilities reported that they often have limited funds that only allowed them to use enzyme immunoassays year-round. As such, instead of not performing screening, they opted to use cheaper alternatives such as the rapid test. Increased availability of tests in facilities and increased support by the national government should help the situation.

Aside from using the required tests, system safeguards could be put in place to improve safety, such as improving capacity of personnel and the implementation of the audit system. We noted that employed personnel were licensed medical technologists; however, training specifically for blood banks appeared inadequate. Poorly trained personnel can introduce errors in testing that may lead to misclassification of tested blood. The lack of training may be due to limited funding allocated by BSF for training and the relative inaccessibility of training due to geographical constraints.

Another safeguard is conduct of audits. These would ensure that facilities utilize testing methods or kits that have acceptable performance in terms of screening for TTIs.

Currently, the national program implements a National External Quality Assurance Scheme, in which the BSF test samples are sent by the reference laboratory. However, there are BSF that reported they have not participated in it. Few facilities have also reported having a quality assurance officer. Since the audits were poorly implemented, the government loses a tool that will catch BSF with poor performance and screening capabilities. Limited funding and geographical challenges were possible reasons for poor compliance with this policy. Licensing agencies may also be blamed as participation in this was a requirement for being allowed to operate.

Our study utilized lot quality assurance scheme for determination of residual risk. This method allowed us to show whether a certain critical level of risk is present or not. However, a study design utilizing bigger samples could be used to precisely determine residual risk. We also utilized self-assessment tools to enable participating BSFs to identify their own strengths and weaknesses as well as areas of improvement. This was done with the view of providing them opportunities for improving their own performance (if they wished to do so). The possibility of respondent-related sources of errors or biases such as the Hawthorne effect and social desirability bias may have affected the center's self-assessment. To mitigate the possible effects of such biases, the rationale for the study and the use of self-assessment tools were carefully explained to the participating centers during the process of obtaining informed consent. It was further explained that the research team was independent of the Department of Health (DOH), which is the regulatory body in charge of blood centers. They were informed that their responses would be kept confidential and anonymous. The main regulatory agency, DOH, would have no way of tracing which BSFs responded in a particular way. We saw that even if we assumed all BSFs gave an overestimation of their adherence to standards, there were still critical items that they admitted to having failed to adhere to.

The enactment and implementation of a national program and policy on blood transfusion has led to improved safety as seen in the reduction in residual risk from 5.2 in 1994 to 0.4 percent in 2011. Policy implementation and provision of support to blood service facilities may lead to further improvement in blood safety.

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