

85. dealing witjh tests

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Submission date: 27-Mar-2023 04:32PM (UTC+0800)

Submission ID: 2047863762

File name: 85._dealing_witjh_tests.pdf (348.31K)

Word count: 5823

Character count: 30686

Dealing with tests and treatments for HIV, syphilis, and hepatitis B infection to prevent mother-to-child transmission (MTCT) from a tertiary hospital in Indonesia



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Received: 2022-02-03

Accepted: 2022-04-10

Published: 2022-04-22

ABSTRACT

Background: Mother-to-child transmission (MTCT) of Human Immunodeficiency Virus (HIV), syphilis, and Hepatitis B can cause a health burden and lead to morbidity and mortality in children. An attempt to eliminate the transmission has been made worldwide. This study aimed to evaluate the triple elimination of MTCT for HIV, syphilis, and hepatitis B in a tertiary hospital in Indonesia.

Methods: We evaluated 690 medical records of new pregnant women seeking antenatal care (ANC) in a tertiary hospital in the east part of Indonesia from January to December 2018.

Results: HIV, syphilis, and hepatitis B testing were performed on 97 patients (14.1%). HIV and hepatitis B, HIV and syphilis, and syphilis and hepatitis B testing were performed on 149 (21.6%), 6 (0.9%), and 6 (0.9%) patients, respectively. The prevalence of HIV, syphilis and hepatitis B was 4.2%, 0.4%, and 3.8%, respectively. HIV treatment by administering antiretroviral therapy (ART) was done in 86.2% of patients. Injection of benzathine penicillin G as the treatment of syphilis was done in 66.7% of syphilis patients. HBV DNA examination followed by tenofovir administration was done in 3.8% of hepatitis B patients.

Conclusion: The testing rate of HIV, syphilis, and hepatitis B in pregnant women in a tertiary hospital in the east part of Indonesia in 2018 (14.1%) was below the target set by World Health Organization ($\geq 95\%$). Increasing access to antenatal screening as early detection is the key to preventing mother-to-child transmission (MTCT).

Keywords: hepatitis B, HIV, mother-to-child transmission, syphilis, triple elimination.

Cite This Article: Wardiana, M., Prakoeswa, C.R.S., Sawitri., Rahmadewi., Astari, L., Prasetyo, B., Budiono., Hidayati, A.N. 2022. Dealing with tests and treatments for HIV, syphilis, and hepatitis B infection to prevent mother-to-child transmission (MTCT) from a tertiary hospital in Indonesia. *Bali Medical Journal* 11(1): 334-340. DOI: 10.15562/bmj.v11i1.3376

INTRODUCTION

Human Immunodeficiency Virus (HIV), syphilis, and hepatitis B can be transmitted from an infected mother to her infant during pregnancy, upon delivery, or through breastfeeding and cause morbidity and mortality. The survival chances of children infected with HIV are low.¹ In 2005, 2.4 million children were living with HIV. According to World Health Organization (WHO) data, acquired immunodeficiency deficiency syndrome (AIDS) accounts for 3% of deaths in children under five years of age worldwide.² While syphilis transmission during pregnancy can adversely affect the fetus in the second and third trimesters. Syphilis during pregnancy is associated with premature delivery, spontaneous

abortion, stillbirth, nonimmune hydrops, perinatal death, and two characteristic syndromes of clinical disease, early and late congenital syphilis.³ In 2016, the WHO estimated 661,000 total cases of congenital syphilis that caused 200,000 stillbirths and perinatal deaths.⁴ On the other hand, hepatitis B virus (HBV) transmission from the mother to her child is still an essential source of hepatitis B cases. The risk for the development of chronic HBV infection is strongly associated with the age of exposure. The risk of chronic disease in infants exposed to HBV from their mother is 90%.⁵

In 2017, the WHO proposed an integrated approach to achieve triple elimination of mother-to-child transmission (MTCT) of HIV, syphilis, and hepatitis B. The Ministry of Health

of the Republic of Indonesia also adopted this regulation. It is done to ensure that even if the mother is infected with HIV, syphilis, and/or hepatitis B, it will not be transmitted to her child. However, there has not been enough data on the evaluation of the triple elimination program in Indonesia. In Indonesia, a tertiary hospital has a role in implementing the triple elimination of HIV, syphilis, and hepatitis B. Therefore, this study aimed to evaluate the implementation of triple elimination in a tertiary hospital in the east part of Indonesia in 2018.

METHODS

This study is a descriptive retrospective study based on medical records of pregnant women seeking antenatal care (ANC) in a tertiary hospital in the east part

69 of Indonesia from January to December 2018. This research has obtained ethical approval from the Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya (reference number: 1772/KEPK/I/2020). Total sampling was used in this study. The inclusion criteria were a newly pregnant woman seeking ANC whose first visit was in 2018. The exclusion criteria were missing medical records. Variable evaluated in this study were characteristics including age, educational level, occupation, admission source, parity status, detection, and treatment of HIV, syphilis, and hepatitis B among pregnant women. The detection status and results were assessed by the examination done either in this hospital or other health care recorded in the medical records. Treatment for positive cases involving another division, such as internal medicine and dermatology and venereology; including antiretroviral therapy (ART) administration for HIV, injection of Benzathine Penicillin G (BPG) intramuscularly for syphilis, and detection of hepatitis B envelope antigen (HBeAg) for hepatitis B. The data was then analyzed using the SPSS 16 program.

RESULTS

Six hundred and ninety medical records were evaluated. The participant characteristics are shown in Table 1. The majority, 362 (52.5%) of the women, were in the 26-35 age group, 415 (60.2%) had the educational status as middle or high school, and 391 (56.7%) of the women were housewives. Since this study was conducted in tertiary health care, most patients (314 or 45.5%) were transferred from another hospital. In addition, seven (1.0%) patients were transferred from the HIV outpatient clinic with known HIV status and had been treated with ART.

Triple testing of HIV, syphilis, and hepatitis B was done in 97 (14.1%) patients. Hepatitis B tests alone surpassed HIV tests alone (200 or 29.0% vs. 21 or 3.0%). Twenty-nine (4.2%) patients tested positive for HIV; among them, two patients also tested positive for hepatitis B. Syphilis was tested positive in 3 (0.4%) patients. No patient tested positive for HIV, syphilis, and hepatitis B (Table 2).

The most common testing method is

6 the Rapid Diagnostic Test (RDT) for HIV and syphilis. While in hepatitis B, the most common detection method is HBsAg testing. In HIV, 3 (0.4%) patients referred from HIV outpatient clinics were checked for a cluster of differentiation 4 (CD4) only because of the known HIV status. On the other hand, there was 1 (0.1%) patient tested using RDT followed by Venereal Disease Research Laboratory (VDRL) and *Treponema pallidum* haemagglutination assay (TPHA) examination for syphilis (Table 3).

Table 4 shows the results of CD4 counts from 12 HIV-positive patients. Of 29 patients who tested positive for HIV, 26 were known from RDT. Yet only nine patients followed by CD4 count. Of 12

patients checked for CD4 count, 6 (50.0%) patients had $CD4 \leq 350$ cell/mm³.

ART was given to 25 (86.2%) patients, while four (13.8%) patients underwent urgent cesarean section due to an emergency condition such as fetal distress or abnormal nonstress test (NST). All syphilis patients were referred to the dermatology and venereology department. However, 1 (33.3%) patient did not return for the injection. Thirteen (50.0%) patients who tested positive for hepatitis B were referred to the internal medicine department. Still, only 1 (3.8%) underwent a hepatitis B virus deoxyribonucleic acid (HBV DNA) test followed by administering antiviral, and 1 (3.8%) patient underwent an HBeAg test.

Table 1. Sociodemographic profile of study subjects.

Characteristics	n (N=690)	(%)
Age (years)		
12-16	1	(0.15)
17-25	159	(23.0)
26-35	362	(52.5)
36-45	166	(24.1)
46-55	2	(0.3)
Education level		
Primary school or under	61	(8.8)
Middle or high School	415	(60.2)
Bachelor or above	214	(31.0)
Occupation		
Housewives	391	(56.7)
Private employees	176	(25.5)
Teachers	40	(5.8)
Entrepreneurs	29	(4.2)
Civil servant	26	(3.7)
Medical workers	18	(2.6)
Farmers/fishers	6	(0.9)
Colleagues	4	(0.6)
Admission source		
Transferred from another hospital	314	(45.5)
Voluntarily	106	(15.4)
Transferred from another division	82	(11.9)
Transferred from primary health care	59	(8.6)
Transferred from doctor	38	(5.5)
Post inpatient	29	(4.2)
Transferred from midwives	11	(1.6)
Transferred from the private clinic	10	(1.4)
Transferred from HIV outpatient clinic	7	(1.0)
No information	34	(4.9)
Parity		
Primigravida	187	(27.1)
Multigravida	460	(66.7)
Grandemultipara	43	(6.2)

Abbreviations: HIV, Human Immunodeficiency Virus.

Table 2. The testing rate and results for HIV, syphilis, and hepatitis B.

Tested	N=690	(%)	Tested positive	N=690	(%)
HIV	21	3.0	HIV	27	3.9
Syphilis	0	0.0	Syphilis	3	0.4
Hepatitis B	200	29.0	Hepatitis B	24	3.5
HIV + Syphilis	6	0.9	HIV + Syphilis	0	0.0
HIV + Hepatitis B	149	21.6	HIV + Hepatitis B	2	0.3
Syphilis + Hepatitis B	6	0.9	Syphilis + Hepatitis B	0	0.0
HIV + Syphilis + Hepatitis B	97	14.1	HIV + Syphilis + Hepatitis B	0	0.0

Abbreviations: HIV, Human Immunodeficiency Virus.

Table 3. The testing methods for HIV, syphilis, and hepatitis B.

Method	n (N=690)	(%)
HIV	273	39.6
RDT only	261	37.8
CD4 only (known HIV status)	3	0.4
RDT and CD4	9	1.3
Syphilis	109	15.8
RDT	102	14.8
VDRL only	3	0.4
TPHA only	1	0.1
VDRL and TPHA	2	0.3
RDT and VDRL and TPHA	1	0.1
Hepatitis B	450	65.2
RDT	7	1.0
HBsAg	441	63.9
RDT and HBsAg	2	0.3

Abbreviations: CD4, a cluster of differentiation 4; HBsAg, hepatitis B surface antigen; HIV, Human Immunodeficiency Virus; RDT, rapid diagnostic test; TPHA, *Treponema pallidum* haemagglutination assay; VDRL, venereal disease research laboratory

Table 4. The results of CD4 count among HIV-positive patients.

CD4 count	n	(%)
≤ 350 cell/mm ³	6	50.0
> 350 cell/mm ³	6	50.0
Total	12	100.0

Abbreviations: CD4, a cluster of differentiation 4

Treatment of hepatitis B for the remaining thirteen (50.0%) patients was not recorded (Table 5).

DISCUSSION

This study aimed to evaluate the implementation of triple elimination in a tertiary hospital in the east part of Indonesia in 2018. Detection of HIV, syphilis, and hepatitis B altogether was done in 97 (14.1%) patients. This early antenatal examination rate was higher than the examination from 2004 to 2009 at the Guatemalan National Hospital, which was tested on 118 (0.76%) of 15,563 pregnant women in the prenatal clinic.⁶ The increase

in early detection may have been driven by WHO, which launched a program to eliminate mother-to-child transmission with catalyzed maternal and child health services in 2017 and led to a “triple elimination initiative,” further pushing the agenda for integrated service delivery into a global effort in health programs. Unfortunately, the information about HIV, syphilis, and hepatitis B coverage testing altogether in Indonesia, either hospital or national level, is unavailable. This is the first study that provides information evaluating the implementation of triple elimination in Indonesia.

Based on Indonesia's health profile

in 2020, there were 2,404,754 pregnant women who were tested for HIV. From the examination, 6,094 (0.25%) were tested positive.⁷ As for the syphilis examination, 753,669 pregnant women were tested, and 4,198 were found to test positive.⁸ In 2020, 51.37% out of 5,221,784 pregnant women carried out early detection of hepatitis B. From national screening in Indonesia compared to a study in Netherland, this is a much lower rate. The estimated coverage of screening programs for HIV, syphilis, and hepatitis B in the Netherland was > 99% in all years from 2009 to 2015.⁹

In the triple elimination program, the target coverage set by WHO for HIV, syphilis, and hepatitis B testing in pregnant women' is ≥ 95%. While the Ministry of Health of the Republic of Indonesia states that to achieve complete quality detection of ANC, coverage in 2018 is at least 60% of pregnant women tested for HIV, syphilis, and hepatitis B.¹ The low coverage in this study could be due to the newly established policies set in 2017, so the detection has not been done routinely yet. Another cause is the omission of registration. The majority of this study's subject was referral patients who might have been screened for HIV, syphilis, and hepatitis B in previous health care. However, the examination results were not recorded in the patient's medical record due to the manually registered process. This method makes the availability of the data rely on the provider.

The most common examination was for HIV and hepatitis B in combination, done in 149 (21.6%) patients. HIV detection was exceeded by hepatitis B detection alone (21 (3%) versus 200 (29%)). Among the 29 (4.2%) patients who tested positive for HIV, 26 (89.6%) were known from RDT, but only nine (31%) were followed by CD4 count, whereas CD4 count is important

Table 5. Treatment of patients who tested positive for HIV, syphilis, and hepatitis B.

Treatment	n	N	(%)
HIV			
Administering ART		25	(86.2)
Cesarean section		4	(13.8)
Fetal distress + pre-eclampsia	1		
Abnormal NST	1		
Inpartu	2		
Total		29	(100.0)
Syphilis			
Injection of BPG 2.4 million units, 3 times/week, intramuscularly		2	(66.7)
No injection		1	(33.3)
Total		3	(100.0)
Hepatitis B			
Examination of HBV DNA status and administering of antiviral (tenofovir)		1	(3.8)
HBeAg test		1	(3.8)
No HBeAg test		11	(42.4)
No data		13	(50.0)
Total		26	(100.0)

Abbreviations: ART, antiretroviral therapy; BPG, benzathine penicillin G; HBeAg, hepatitis B envelope antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; NST, nonstress test

to determine cotrimoxazole prophylaxis. Adult HIV patients, including pregnant women with WHO clinical stage 3 or 4 and/or CD4 count ≤ 350 cell/mm³, are recommended to have cotrimoxazole prophylaxis. Cotrimoxazole is a fixed-dose combination of two microbial agents used to cure various bacterial, fungal, and protozoal infections. Cotrimoxazole prophylaxis is a simple, well-tolerated, and inexpensive intervention to decrease the morbidity and mortality related to HIV.¹⁰

Syphilis became the least tested among other diseases. A study evaluating the coverage of maternal syphilis screening during ANC based on data reported by 81 countries in the UNAIDS Global AIDS Monitoring system in 2016-2017 stated that only four countries met the WHO target for coverage $\geq 95\%$, namely Bolivia (96.0%), Burkina Faso (100.0%), Eritrea (97.2%), and Tajikistan (100.0%). Indonesia reported that its coverage was 1.7%.⁹ While in this study, 109 (15.9%) were tested for syphilis. Barriers to the elimination of MTCT of syphilis could be in the setting of local communities, such as the problem is not seen as necessary, the stigma associated with STIs, costs associated with detection and treatment; among health care service providers

such as lack of awareness or training in the appropriate intervention, insufficient logistical support; among program managers such as syphilis accorded a low priority compared with other health problems, lack of resources for effective interventions; and among policy-makers and decision-makers such as lack of awareness of actual disease burden, lack of understanding of the cost-effectiveness of the intervention, little external pressure to adopt or implement policies, and few apparent political rewards for action.¹¹ In 2018, syphilis testing was not available at this tertiary hospital, so patients had to do this examination at their own expense. This problem depicts the barriers that have been mentioned before. The health insurance should have covered this testing; nevertheless, the hospital could not provide the logistics. The solution offered is to do the examination in a private laboratory, but not all patients are willing to do it due to the cost and stigma associated with it. A higher policy decision should be taken to guarantee that this issue is resolved in order to increase syphilis testing coverage.

A rapid diagnostic test (RDT) is an interesting option because it is easy to use, inexpensive, and quite accurate compared to conventional tests. It also

offers a clear advantage of enabling the implementation of timely interventions to prevent MTCT of HIV and increased linkage to ART and HIV care for HIV-infected women.^{12,13} WHO also proposes the use of dual HIV/syphilis RDT. In a study of dual HIV/syphilis tests on a single device, the accuracy of HIV diagnosis remained high regardless of the test manufacturer or whether evaluations were conducted in laboratory or field settings. From the evaluation of the Standard Q HIV/Syphilis Combo Test (SD Biosensor, South Korea), a dual rapid test using stored sera (N=400) in a laboratory setting in Lima, Peru, sensitivity and specificity for HIV antibody detection was 100.0% (95% CI: 98.2%–100.0%) and 99.5% (95% CI: 97.2%–100.0%), respectively.¹⁴ The sensitivity and specificity for treponemal antibody was 97.5% (95% CI: 94.3%–99.2%) and 100.0% (95% CI: 98.2%–100.0%), respectively.¹⁴ Between 2014 and 2016, at the Institute of Tropical Medicine Antwerp, Belgium, a total of 400 specimens were tested with four dual HIV-Syphilis rapid diagnostic tests (SD Bioline HIV/Syphilis Duo, DPP HIV-Syphilis Assay, Multiplo Rapid TP/HIV Antibody Test, and Insti Multiplex HIV-1/HIV-2/Syphilis Antibody Test) using a

well-characterized multiregional panel of stored sera specimens, showing excellent sensitivities and specificities results for HIV, ranging from 99.5 to 100% and from 93.5 to 99.5%, respectively.¹⁵ *Treponema pallidum* antibodies results were lower, with the highest of 87% for SD Bioline and the lowest sensitivity of 73.5% for Multiplo, the result of specificities ranged from 99.0 to 100%.¹⁵ The accuracy of syphilis testing was good (similar to single tests for syphilis), although not as high as HIV, in laboratory and field settings and regardless of the manufacturer.¹⁶ The use of technologies like these is certainly more practical and accessible because it reduces testing time, enhances syphilis and HIV test coverage, and speeds up the administration of medicine.

The prevalence of HIV among pregnant women in Indonesia in 2018 was 0.28%.¹⁷ The higher prevalence in this study (29 patients or 4.2%) can be caused by this tertiary hospital's status as a referral hospital, resulting in complications in pregnancy cases. Coinfection was found in HIV and hepatitis B. A study by Amsalu states that pregnant women infected with HIV were more likely to be HBsAg positive than those who were HIV negative.¹¹ It can be caused by a similar route of infection. Therefore, pregnant women with HIV should be suspected of having hepatitis B coinfection.

Three (0.4%) pregnant women tested with VDRL but not TPHA had nonreactive VDRL results. It is similar to a study by Ebenezer *et al.* in a tertiary hospital in India, where syphilis screening for pregnant women was done using the VDRL test. If the result is reactive, it will be followed by a confirmation test using TPHA.¹⁸ This algorithm is similar to the traditional algorithm by the Central for Disease Control and Prevention (CDC). However, the VDRL test has a high sensitivity with a high false-positive such as in pregnancy; therefore, in pregnant women, confirmation using TPHA is needed.¹⁹

Antiretroviral therapy (ART) was given to 25 (86.2%) pregnant women with HIV, while the remaining underwent cesarean section. ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of clinical

stage and at any CD4 cell count, and continued lifelong. Providing ART to all pregnant and breastfeeding women living with HIV serves three synergistic purposes: (i) improving the mother's health; (ii) preventing MTCT of HIV; and (iii) preventing the transmission of HIV from the mother to a sexual partner. ART should be initiated urgently in all pregnant women, even if they are identified late in pregnancy or postpartum. The most effective way to prevent mother-to-child HIV transmission is to reduce maternal viral load.¹⁰ The failure to reach 100% ART coverage for pregnant women in this study can be due to conditions requiring immediate surgery. It follows WHO recommendations for pregnant women whose HIV status is unknown. RDT checks should be carried out immediately. Cesarean section surgery can help protect against HIV transmission, especially in pregnant women who have not received ART. Vaginal delivery is appropriate for HIV-infected pregnant women who have been taking ART regularly for > 6 months, or it is known that viral load levels < 1000 copies/mm³ at week 36.¹⁰

Pregnant women with syphilis should be treated with benzathine penicillin G (BPG) because it is highly efficacious during pregnancy and remains the only recommended treatment for maternal syphilis and the prevention of congenital syphilis.²⁰ To get adequate treatment, the frequency of BPG injection should be adjusted to the disease stage. In this study, 2 (66.7%) patients received adequate treatment, the BPG 2.4 million units intramuscularly once a week for three consecutive weeks in the dermatology and venereology outpatient clinic. The remaining patients were referred to dermatology and venereology but did not return for treatment. A study in Hunan, China, stated that the barriers for pregnant women infected with syphilis to receive standard syphilis treatment are marital status, namely, unmarried/divorced/widowed (aOR = 0.81, 95% CI: 0.65–0.99); pluripara (aOR = 0.58, 95% CI: 0.46–0.74); number of children ≥ 2 (aOR = 0.45, 95% CI: 0.35–0.57); clinical stage of primary/secondary/tertiary syphilis (aOR = 0.72, 95% CI: 0.58–0.88); or unknown (aOR = 0.78, 95% CI: 0.70–0.86).²¹ The

stage of latent syphilis or syphilis of unknown duration that does not show symptoms and without complaints makes pregnant women unaware of the dangers of the condition to the unborn baby. This condition makes pregnant women reluctant to take medication. It involves good communication between doctors and patients, as well as adequate education for patients to comprehend the disease and its complications. Educating pregnant women and their partners about adequate treatment for syphilis based on its stage is crucial, especially in pregnant women with latent syphilis who do not show symptoms. The transmission from mother to child still occurs. Thus, it is expected that 100% of pregnant women with syphilis receive adequate treatment.

Pregnant women with positive HBsAg tests should be followed by HBeAg and HBV DNA tests. Antiviral treatment should be given to women with a high viral load.²² In this study, only 1 (3.8%) woman tested for HBeAg, and 1 (3.8%) tested for HBV DNA, followed by administering antiviral (tenofovir). Based on a systematic review, maternal HBV DNA of 200,000 IU/mL or more appears to be the optimal threshold for MTCT of HBV infection despite immunoprophylaxis. HBeAg assay accurately identifies women with HBV DNA levels above this threshold and high sensitivity for predicting immunoprophylactic failure cases. HBeAg can be used as an alternative to assess eligibility for antiviral prophylaxis in areas where HBV DNA testing is not available.²³ Antiviral prophylaxis is effective in preventing the transmission of HBV from mother to child. Based on a meta-analysis, administration of tenofovir 300 mg reduced the risk of transmission, with the pooled ORs for randomized controlled trials being 0.10 (95% CI 0.03–0.35).²⁴ In this study, the barrier to performing HBeAg and HBV DNA tests is the examination cost. Since those tests are not covered by insurance, people are reluctant to get them done. A study in the United States has concluded that HBeAg or HBV DNA testing in HBsAg-positive pregnant women, followed by antiviral administration to HBeAg-positive or high viral load mothers reduces mother-to-child transmission of hepatitis B and

is cost-effective. The cost of testing for HBeAg or HBV DNA is small compared with the cost of antiviral prophylaxis during pregnancy.²⁵ However, it also depends on the health care system in each country.

This study has some limitations, especially in the data collecting method. For example, we did not collect the data about what kind of device was used in the detection method. Besides that, since it is a multidisciplinary study, we faced some difficulties in gathering information from all divisions. Big sample size and time limitations also impact the data collection. To the best of our knowledge, this is the first study to evaluate the implementation of triple elimination of HIV, syphilis, and hepatitis B in pregnant women in Indonesia. Future research on a national scale may be needed to estimate program achievements and steps that can be taken to improve outcomes, specifically healthy children free from HIV, syphilis, and hepatitis B.²⁶

CONCLUSION

This study gives an insight into the implementation of the triple elimination of MTCT of HIV, syphilis, and hepatitis B in Indonesia's hospitals. Either the detection or management is still below the target set by WHO. Strategies to achieve success in the triple elimination program need collaboration between government and practitioners. Increasing access to antenatal screening as early detection is the key to preventing mother-to-child transmission (MTCT), along with the availability of prophylaxis and treatment as an antenatal care package. The use of rapid diagnostic tests (RDT), particularly dual HIV-syphilis test for early detection, has a fairly high level of accuracy and is accessible so that it can be used practically, but the coverage must be increased. In order to achieve this, all health workers from ANC services in the private sector (clinics, hospitals, and midwives) or the public sector must be empowered through training and logistical support. Screening, treatment, and prophylaxis for HIV, syphilis, and HBV should be a routine step in ANC with the government's capacity to make it a government-funded health program. To ensure diagnostic tests are of

fine quality and standard of interpretation, quality assurance is needed for point of care. Solid tracking systems are required for close follow-up of HBV, HIV, and syphilis-exposed infants. Computerized and electronic medical records could help build comprehensive patient data to obtain nationally integrated data. Collaboration between several divisions, such as obstetric and gynecologic, internal medicine, dermatology and venereology, and pediatric medicine, is needed. Medical coverage insurance and the hospital's facilities also have an essential role in supporting the triple elimination program. To ensure that this program is successful, efficient integration, joint commitment, and cooperation of stakeholders to set an integrated agenda, including jointly supported targets for healthy children free from HIV, syphilis, and hepatitis B, are needed.

ACKNOWLEDGMENTS

We acknowledge Dr. Soetomo General Academic Hospital staff, who participated in the data collection.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work. This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

ETHICS APPROVAL

This research has obtained ethical approval from the Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya (reference number: 1772/KEPK/I/2020).

AUTHOR CONTRIBUTION

MW: conception of the work, data collection, data analysis & interpretation, drafting of the article. 40
 CR, SS, RR, LA, BP: conception of the work, critical revision of the article 7
 BB: data analysis & interpretation, critical revision of the article
 AN: conception of the work, critical revision of the article, final approval of the version to be published.

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