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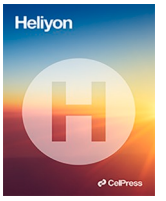

Research article

An insight into Indonesia's progress for newborn screening program: What is currently going on

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ABSTRACT

Objectives: In this literature review, we describe the progress of Indonesia's NBS program (which is heavily centered on CH screening), its current pilot projects, and what lies ahead for this program.
Setting: Since its conception began with congenital hypothyroidism (CH) screening, Indonesia has experienced plodding progress in NBS. There is a shortage of literature discussing the history, or the lack of, and journey of NBS in Indonesia.
Methods: We searched for literature in Pubmed and Google Scholar with keywords such as "Newborn Screening, "Neonatal Screening," "Indonesia," "Asia Pacific," "Congenital Hypothyroidism," "Congenital Adrenal Hyperplasia,""Critical Congenital Heart Disease," "Hearing Loss," and "Inborn Error of Metabolism."
Results: The only mandatory and regulated NBS program in Indonesia is congenital hypothyroid (CH) screening, with some pilot projects being conducted on screening for congenital adrenal hyperplasia (CAH), critical congenital heart disease (CCHD), hearing loss, and to a lesser extent, inborn error of metabolisms (IEMs).
Conclusion: Despite the evidence and benefits, the government does not mandate or regulate newborn diseases such as CHD, CAH, hearing loss, and IEMs. The lack of regulation exists despite multiple pilot projects and studies showing a benefit in at least trying to screen newborns for those conditions.

1. Introduction

The definition of newborn screening (NBS) varies but generally describes a practice of testing every single newborn for potentially critical conditions in the first few days of a newborn's life [1,2]. The goal of NBS is ideally a pre-symptomatic detection or at least to detect disorders that are life-threatening or cause long-term disabilities before the conditions cause death or irreversible damage [3,4]. Therefore, NBS saves thousands of newborns' lives by starting treatment as soon as possible to prevent or lessen the adverse effects of those conditions. In the past, NBS utilized laboratory-based blood tests and point-of-care functional tests, but nowadays includes functional testing such as hearing loss and critical congenital heart disease (CCHD) [5].

There are no doubts about the advantages of NBS. This program was even hailed as one of the last century's top ten public health initiatives [6]. The question, therefore, is, "Why do countries still not provide universal NBS for their newborns?" For example, until

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2020, Kosovo was the only country in Southeastern Europe that did not provide any NBS screening program [7]. The answer may partly be explained by the fact that NBS is beyond a regular and ordinary test. It has become a public health program that requires an integrated system consisting of choosing which conditions to screen, determination of timing and methods of sample collections, education, short-term follow-up (STFU), implementing screening and monitoring quality, confirmatory diagnoses for newborns with initial positive screens, and long-term follow-up (LTFU) which consists of referral and connection of the child for treatment, ongoing medical management, and program evaluation and feedback [8,9]. Looking at how intricate and delicate the system is, a country that has not started an NBS program may feel the daunting barrier entry to conducting it [10]. Table 1 provides a contextual background of Indonesia and some countries in the rest of the world regarding NBS.

The Asia Pacific region contributes to 68.5 million of the 136.7 million babies born worldwide. Five countries comprise 85 % of those 68.5 million, and one of those countries includes Indonesia [22]. In 2021, United Nations International Children's Emergency Fund (UNICEF) stated that Indonesia had an infant mortality rate (IMR) of 19 deaths per 1000 live births [23]. Using an IMR of below ten deaths per 1000 live births as a cut-off, Indonesia can significantly reduce its IMR by implementing an NBS program. However, since its conception began with congenital hypothyroidism (CH) screening, Indonesia has experienced plodding progress in NBS. There is a shortage of literature discussing the history, or the lack of, and journey of NBS in Indonesia. When literature discussed Indonesia's NBS, it was only mentioned in passing and sometimes contained inaccurate information [22,11]. Two different reviews could not agree on when Indonesia started its NBS [1,22]. This updated review is also timely since Indonesia is relaunching its congenital hypothyroidism (CH) screening in late 2022. Hence, this review aims to describe the progress of Indonesia's NBS program (which is heavily centered around CH screening), its current pilot projects, and what lies ahead for this program. The following paper will discuss the obstacles faced in implementing NBS in Indonesia.

2. Methods

We searched for literature in Pubmed and Google Scholar with keywords such as "Newborn Screening, "Neonatal Screening,"

Table 1
Demographics and characteristics of newborn screening in Indonesia and some countries in the world.

Country	Population (2022)[a]	Crude birth rate (per 1000 people) (2021)[a]	Infant mortality rate (per 1000 live births) (2021)[a]	Life expectancy at birth (2022)[a]	Gross domestic product per capita in 2022 (USD)[a]	Date NBS began [1,11]	Disease screened[a]
Australia	25,978,935	12	3	83	64,491.4	1967	CAH, CH, IEMs, and CF [12]
China	1.41 billion	11.2	5	78	12,720.2	1981	CH and PKU [1]
India	1.42 billion	17.4	26	67	2388.6	-(1980 [pilot project])	None [13]
Indonesia	275,501,339	16.4	19	68	4788	2014	CH[b]
Japan	125,124,989	7.2	2	84	33,815.3	1977	CH, CAH, and IEMs [14]
South Korea	51,628,117	7	10	84	32,254.6	1991	CH and PKU [15]
Laos	7,529,475	22	34	68	2088.4	-[2008 (pilot project) [16]]	None
Malaysia	33,938,221	13.5	7	75	11,971.9	1980	G6PD deficiency and CH [17]
Myanmar	54,179,306	17.2	34	66	1095.7	-(2000 [pilot project])	None [18]
Philippines	115,559,009	21.8	21	69	3498.5	1996	CH, CAH, PKU, GAL, G6PD deficiency, and MSUD [19]
Singapore	5,637,022	8.6	2	83	82,807.6	1965	G6PD deficiency, CH, hearing loss, IEMs [20]
Thailand	71,697,030	9.9	7	79	6908.8	1996	CH and PKU [21]
United States of America	333,287,557	11	5	76	76,398.6	1965	PKU, CH, GAL, Hbs, CAH, BIO, CF [1]
United Kingdom	66,971,411	10.1	4	81	45,850.4	1969	CH, PKU, SCD, CF, hearing loss, and some IEM panels [1]

NBS, Newborn screening; Hbs, Hemoglobinopathies; PKU, Phenylketonuria; CH, Congenital hypothyroidism; GAL, Galactosemia; CAH, Congenital Adrenal Hyperplasia; BIO, Biotinidase deficiency; CF, Cystic Fibrosis; SCD, Sickle Cell Diseases; G6PD, Glucose-6-phosphate dehydrogenase; MSUD, Maple Syrup Urine Disease.

[a] We are only including screening that is done universally in that country with a national mandate. Hence, this list does not include screening that is less than full populations screening, done in certain centers or populations, or only applicable to certain states.

[b] Although there is a national mandate to screen for CH with the intention of full coverage, the rate of CH NBS screening in Indonesia is still abysmal. Further information is available in the section "Congenital Hypothyroidism" in this manuscript.

aSource: The World Bank (IBRD + IDA). Data (Available at: https://www.worldbank.org/en/home)

"Indonesia," "Asia Pacific," "Congenital Hypothyroidism," "Congenital Adrenal Hyperplasia,""Critical Congenital Heart Disease," "Hearing Loss," and "Inborn Error of Metabolism." We also searched for relevant references in those published articles. Grey literature, such as state regulations, informative webinars on the topics by experts regarding current situations, and press release by the Indonesian Minister of Health (MoH), were also searched.

We only included the current mandatory NBS screening program in Indonesia and NBS screening programs with completed pilot projects. This review aims to provide an up-to-date NBS status in Indonesia and any studies published regarding the state of NBS in Indonesia. Screening for high-risk infants (e.g., head ultrasound to detect intraventricular hemorrhage in preterm infants), screening that only uses basic physical examination (e.g., tongue test to evaluate lingual frenulum [24]), or pre-natal screening (nuchal translucency for Down Syndrome) [25] would not be included in this review. We also do not discuss the challenges faced in implementing NBS, as that will be discussed in a separate article [10].

3. Indonesia's newborn screening program

3.1. Congenital Hypothyroidism

CH is defined as a deficiency of thyroid hormone from birth. Most commonly, it is caused by dysgenesis or dyshormogenesis. Prompt diagnosis and adequate treatment will lead to a grossly normal neurocognitive outcome in adulthood, which underlines the importance of CH screening in newborns. The concept of congenital hypothyroidism is beyond this review's scope and is well-presented elsewhere [26,27]. Currently, the incidence of CH worldwide is around 1:1400–1:1700 [28], almost twice as high as the previously cited number of 1:2000–1:4000 [29].

In May 1999, representatives from Korea, Indonesia, Malaysia, Vietnam, the Philippines, Myanmar, China, Mongolia, Pakistan, Thailand, and Bangladesh attended "Workshop on National Screening for Congenital Hypothyroidism" [22]. Indonesia first started its pilot project on NBS in collaboration with the International Atomic Energy Agency (IAEA) in June 2000 to March 2001 involving four hospitals and 6797 blood samples (3534 samples taken from cord blood serum and 3263 samples taken from dried blood spot [DBS]). At that time, the overall incidence of CH in East Asia was 1:3459, while the local incidence in an iodine-deficient district in Central Java was 1:1500 for permanent CH and 1:300 for transient CH. The recall rate was 3.28 % for samples obtained from cord blood tests and 0.64 % for heel stick samples, with 0.78 % of those samples were not analyzed due to incorrect collecting procedures [30]. Two of the largest tertiary hospitals in Indonesia, Hasan Sadikin Hospital and Cipto Mangunkusumo Hospital, screened 55,647 and 25,499 newborns for CH between 2000 and 2005, respectively, resulting in an incidence of 1:3528 cases. On September 27, 2006, a health technology assessment (HTA) was conducted, resulting in Ministry of Health approving mass CH screening [31]. After the HTA, eight provinces (West Sumatra, Jakarta, West Java, Central Java, Yogyakarta, East Java, Bali and South Sulawesi) were selected for pilot screening projects with two laboratories chosen as referral laboratories for congenital hypothyroid screening.

Due to the lack of integrated data and continuous CH screening, current data on the incidence of CH in Indonesia is fragmented. Between 2000 and 2013, 199,708 newborns were screened with 73 CH cases (1:2736) in 11 provinces (out of 33 provinces) [32]. In 2014, the Indonesian Ministry of Health passed a decree 2014 to mandate all states to conduct routine CH for all newborns. However, the cost was shifted towards states and individuals as this program was not yet funded by national health insurance or integrated into national health programs [33,34]. In 2014, the NBS coverage for CH was 0.6 % (28,421 out of 4,736,000 newborns). Later, when three more provinces were added to the data, the incidence became 1:2513 [35]. Between October 2015 and January 2016, five provinces

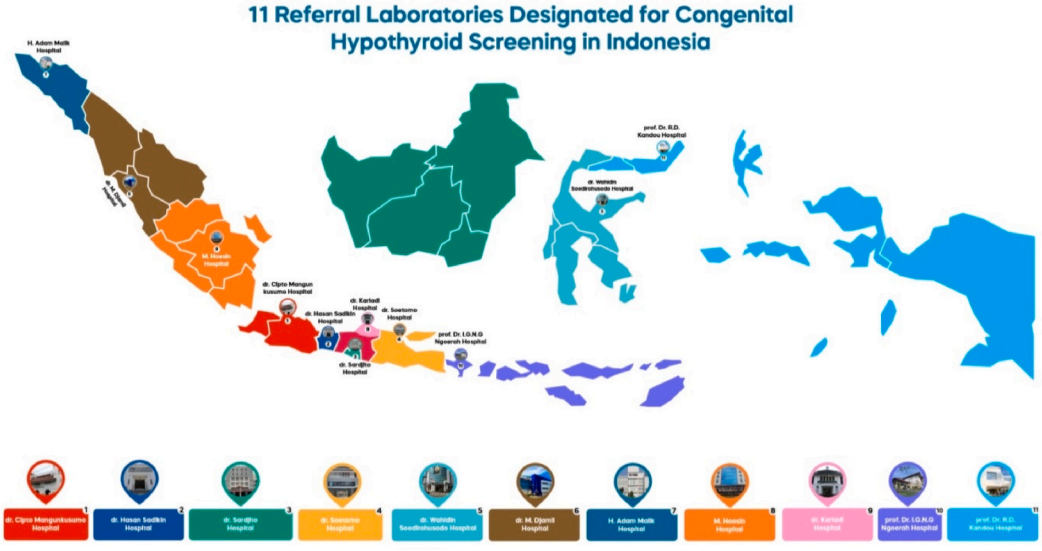

Fig. 1. Eleven referral hospitals designated for congenital hypothyroid screening in Indonesia.

(Jakarta, Cilegon, Semarang, Yogyakarta, and Denpasar) were screened, yielding an incidence rate of 1:226 [36]. In 2017, NBS screening was done in 32 provinces with funding from de-concentrated funds and non-physical special allocation funds designated to help regional public service operations. The following year saw an increase in NBS coverage for CH to 4.6 %, with three referral laboratories, which increased to five in 2019. Until 2020, the coverage of newborn CH screening is less than 2 % of all newborns. There was a revision in the Ministry of Health mandate to accelerate CH screening in newborns in 2020 and 2021. In 2022, the Ministry of Health accelerated the NBS program for CH with 11 referral laboratories (Fig. 1). They targeted 463,000 screened samples, or equal to 10 % of all newborns. Until the end of 2022, only 99,263 samples (21.4 %) were screened from the initial target (Fig. 2). Up to week three of August 2023, there were 369,552 collected samples or 8.26 % of the target. The breakdown of how many samples were collected in each laboratory is presented in Table 2.

One of the causes of CH that needs addressing here is iodine deficiency, mainly due to maternal iodine-deficient diets [27]. In Indonesia, there are several "hotspot" countries with iodine deficiency measured via total goiter rate (TGR) prevalence [37]. A country is classified as severely endemic for iodine deficiency if it has a TGR of ≥30 %, moderate (TGR 20–29.9 %), mild (TGR 5–19.9 %), and non-endemic if the TGR is <5 % [38]. The TGR prevalence decreased rapidly from 27.7 % in 1990 to 9.8 % in 1998 and increased slightly to 11.1 % in 2003. However, from 2003 onwards, Indonesia stopped counting the TGR prevalence and instead opted to use only urinary iodine excretion and intake of iodized salt from 2007 onwards, making comparisons difficult. The 2007 Basic Health Research (*Riskesdas*) results show that the median iodine excretion in urine obtained nationally is 224 μg/L. The proportion above 200 μg/L for urine iodine excretion seems to be increasing; in 2003, it was 35.4 %–37.2 %. The proportion of people with a median urine iodine of 300 μg/L or more is 21.9 % [38]. The results show that detected cases may be an iceberg phenomenon. More CH cases are potentially more prominent, especially in these endemic areas, and necessitates universal CH screening in Indonesia.

In Indonesia, like most of the world, NBS for CH is conducted when a newborn is 48–72 h old. Health workers must perform screening with three major steps: pre-screening (socialization, education, advocating, and evaluation), screening, and post-screening (confirmation test for positive NBS results). The current cost for NBS screening is Rp 65.000,- per sample (roughly 4 USD), without including the shipment fee to the referral laboratories. The current flowchart of CH screening in Indonesia is presented in Fig. 3.

3.2. Critical congenital heart disease (CCHD)

Congenital heart disease (CHD) is the newborn's most common congenital abnormality [39]. Approximately 25 % of CHDs are classified as critical congenital heart disease (CCHD) [40]. Early surgical intervention in the first year of life is intended for neonates with CCHD. Without intervention, the rates of mortality and survival rates are incredibly high.

The incidence and mortality of CHD were relatively high in developing countries in Africa and Asia. In 2017, the incidence rate of CHD worldwide was September 17, 1000, with January 19, 1000 for males and June 16, 1000 for females [41]. The highest reported total CHD birth prevalence in developing countries was found in Asia, with an incidence of 9.3 per 1000 live births [42]. Although the exact epidemiology is unknown, CHD events were reported to be 8 per 1000 births in Indonesia, with approximately 5 million infants born annually, with approximately 50.000 infants born with CHD and 12.500 of them suffering from CCHD [43].

Between 1990 and 2019, death due to CHD decreased by 43 % worldwide, although mortality due to CHD has decreased. However, it is still one of the leading causes of death in infancy [44,45]. One study conducted in Dr. Soetomo Hospital in Surabaya showed that the hospital mortality rate in patients with CHD from 2004 to 2006 was 11.64 % in 2004, 11.35 % in 2005, and 13.44 % in 2006, with a significant cause of death associated with the first year of life together with respiratory infections such as pneumonia and bronchiolitis

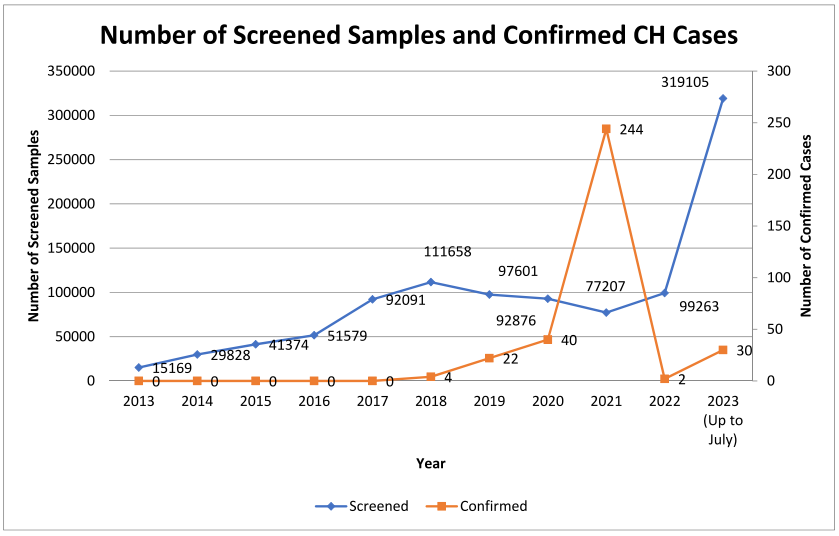

Fig. 2. The number of screened samples and confirmed congenital hypothyroidism (CH) cases. The exact data from 2009 to 2019 per month is unknown, but there were 644 CH cases between those years [33]. Confirmed cases were updated until July 2023.

Table 2
Breakdown of samples and positivity rate up until the third week of August 2023 (Positivity rate of 1:11,801).

Laboratories	Sample received	Rejected samples	Sample analyzed	High TSH (≥20 μIU/ml)	Underwent confirmatory test	Positive cases	Positivity rate	Treated	Other notes
RSUP dr. H. Adam Malik	5818	34	5784	4	1	0	0	0	
RSUP dr. M. Djamil	10,327	87	10,240	2	2	2	1:5120	2	Treated <1 month
RSUP M. Hosein	20,201	434	19,767	14	11	0	0	0	
RSUP dr. Cipto Mangunkusumo	28,876	1230	27,646	5	3	0	0	0	
RSUP dr. Hasan Sadikin	45,504	3140	42,364	3	3	3	1:14,121	3	Treated <1 month
RSUP dr. Kariadi	41,677	1291	40,386	23	15	6	1:6731	6	Treated <1 month
RSUP dr. Sardjito	100,288	2841	97,447	18	14 (1 passed away)	6	1:16,241	5	Treated <1 month
RSUP dr. Soetomo	28,371	2614	25,757	0	0	0	0	0	
RSUP dr, Wahidin Soedirohusodo	13,341	304	13,307	6	3 (1 refused)	1	1:13,037	0	
RSUP Prof. Dr. I.G.N. G. Ngoerah	27,579	3323	24,256	27	22 (1 passed away)	2	1:12,128	2	Treated <1 month
RSUP Prof. Dr. R.D. Kandou	3069	192	2877	4	2	1	1:2877	1	Treated <1 month
Regional laboratories and other laboratories	44,501	29	44,472	93	11	9	1:4678	4	Treated <1 month (3 passed away)
Total	369,552	15,519	354,033	199	87	30	1:11,801	24	

RSUP, *Rumah Sakit Umum Pemerintah* or government-owned hospital; TSH, Thyroid stimulating hormone.

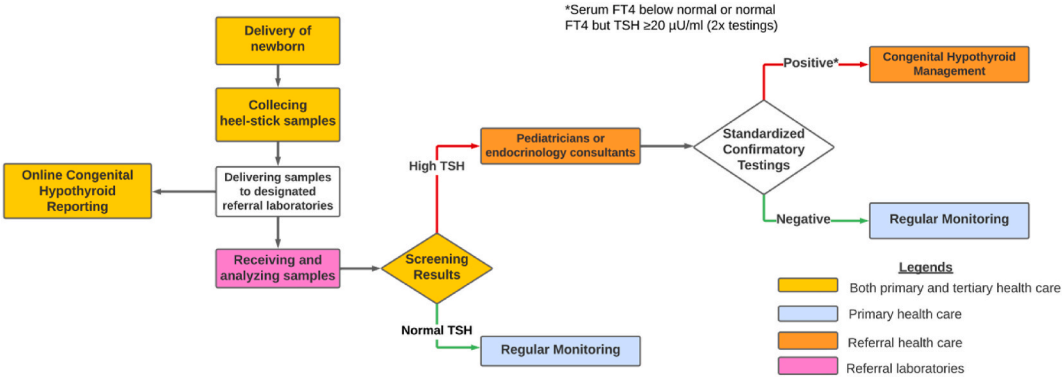

Fig. 3. Flowchart depicting the current mechanism for CH screening in Indonesia.

and malnutrition [46]. Based on one study conducted in the National Cardiovascular Center in Jakarta from 2003 to 2005, 1366 patients underwent open and closed cardiac surgical procedures. The death rate was 5.56 %, concluding that the surgical mortality rate for CHD patients in Indonesia is still high [47]. In a single tertiary-center study conducted from January to December 2014 in Sardjito Hospital, there were 650 new CHD patients, and CHD was 134 per 10,000 person-years amongst children and adults. Among 78 % of children with CHD, most had VSD (30 %), followed by ASD (17 %) [48]. The Ministry of Health estimated that 12,000 babies suffer from congestive heart failure, and only half are being treated [49]. The high incidence and mortality rate of CHD in developing countries such as Indonesia merit more attention and priority in CHD prevention or screening programs.

The rate of consanguineous marriage in Indonesia is currently unknown [50]. This fact is important because genetic causes are increasingly recognized in CHD development [51]. Some tribes and cultures still linger in certain races where they believe that consanguinity is the ideal marriage [52]. One case-control study conducted in Indonesia found that consanguinity was a risk factor for the development of CHD [53]. Hence, this could be a different research topic regarding congenital diseases and their interplay with NBS in Indonesia.

Signs and symptoms for CHD or CCHD are not always present in newborns. Physical examination findings most likely diagnose children with CCHD, but these findings are not always evident before hospital discharge. Approximately 25 % of infants with CCHD were diagnosed after discharge from the newborn nursery, and recognition of CCHD was 20 % in the postnatal ward [54]. The most common physical findings indicate signs of CCHD, such as heart murmurs, tachypnea or cyanosis [55]. A recent study suggested that

delayed or missed diagnosis occurs in 7 per 100.000 live births [54]. Based on Kuehl et al.'s report, 76 out of 4350 infants with CCHD were not diagnosed with CCHD until after death, with over 80 % of all infant deaths occurring within the first week of life [55].

Hence, universal screening is needed to detect newborns with CHD. One of the proposed methods is using pulse oximetry. This tool can be considered a standard vital sign among neonates, performed 24–48 h before discharge, equivalent to pulse, respiration, and blood pressure. Pulse oximetry was recommended as a screening tool to detect CCHD in 2011 by the American Academy of Pediatrics and the American Heart Association [56]. Since 2018, all states in the United States of America have conducted CHD screening using pulse oximetry. However, the same could not be said for the rest of the world. Except for some European countries, other parts of the world still had not screened their children using pulse oximetry. Indonesia also joined them as only multicentre studies and pilot programs are currently being conducted with no mandatory regulation [57].

One of the reasons for low uptake worldwide is the low sensitivity using pulse oximetry. In the PulseOx study where 4822 infants (>6–12 h old) were screened for CHD using pulse oximetry, the sensitivity was only 75 % (19.41–99.37), and the specificity was 99.17 % (98.87–99.41). One meta-analysis also found a similar finding where the pooled sensitivity was 76.5 % (67.6–83.5 %) with a specificity of 99.9 % (99.7–99.9) [58]. Another reason may lie in the false-positive rates. They estimated that out of 100,000 babies, there would be 843 false positives, but only 614 newborns would be completely healthy [59]. The false-positive rate was high enough to present a burden to delivery centers. However, the false-positive rates vary according to different centers and study designs. The false positive rate is only 0.14 % (0.06–0.33) in one meta-analysis, especially when screening was done after 24 h [58]. Screening using pulse oximetry was likely to miss CCHD due to aortic arch obstruction such as coarctation of the aorta and interrupted aortic arch. Lastly, pulse oximetry may also be abnormal in newborns with respiratory or infectious diseases, which are common in newborns. However, it is argued that a screening test does not necessarily need a high sensitivity rate to be recommended in a screening program. Besides, with an additional $0.99 per infant tested when a technician did the screening, pulse oximetry may be a cost-effective approach to screening CHD in newborns [59,60].

One NBS study screened 1452 newborns in four hospitals in Yogyakarta and found ten positive results. Out of those positive results, eight newborns (six per 1000 live births) had CCHD [61]. Other studies in Yogyakarta, although they did not conduct their screening in newborns, deserve a special mention due to the impact they brought. One study that screened 6116 elementary school students found an overall prevalence of 0.29 % (18 out of 6116) for cardiac abnormalities. In turn, this finding led to a national government mandate to make it compulsory that all children receive a cardiac check-up every year during their annual routine height and weight measurements [62].

Screening is even more justified in Indonesia, considering that most children and adults with CHD present with late complications of CHD, such as pulmonary hypertension (PH), cyanosis, arrhythmias, stroke, or even death [40]. One prospective study in Yogyakarta that enrolled 1012 patients found that more than three-quarters (77.1 %) had already developed signs of PH upon presentation [63]. Most CHD-related PH patients in Indonesia presented an increased mortality risk as they belong to the intermediate-risk group [64]. Hence, it should be no surprise that most patients undergoing surgery had variable outcomes in different centers, ranging from 20 % significant complications to 13 % mortality for pediatric cardiac surgery [65] to 20 % in adult cardiac palliative surgery [65]. One study estimated that the potential cost savings each life year could be as low as USD 12,000 [66].

Moving forward, there are plans to make screening more accessible for newborns. The Indonesian Pediatric Society (IPS) launched two programs, namely Indonesian Newborn Pulse Oximetry Screening Training (INPOST), which is a training program for doctors, nurses, and midwives, and Pulse Oximetry Newborn Screening E-learning (PONSEL) which provides e-learning for health workers for a month. Another commitment made by IPS to better serve children with CHD is to collaborate with the Indonesian Heart Association to train doctors and provide better treatment for CHD patients.

3.3. Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is an inherited metabolic disorder predominantly due to 21-hydroxylase deficiency [67]. There are two primary forms of CAH such as classic 21-hydroxylase deficiency, which may lead to death if not detected early enough due to shock, hyponatremia, and hyperkalemia, while the mild, non-classic form that may be asymptomatic or associated with signs of postnatal androgen excess [68,69]. A more thorough review of CAH can be found elsewhere [68].

The current screening method employs a two-tier screening method. The first tier utilizes 17- hydroxyprogesterone assays standardized to a standard technology with norms stratified by gestational age. A second-tier test using liquid chromatography–tandem mass spectrometry is done to increase the screening test's positive predictive value (PPV). Some limitations faced by the first-tier screening include high 17-hydroxyprogesterone (17-OHP) levels at birth, lower mean 17-OHP values in newborn girls, higher 17-OHP levels in premature, sick, or stressed babies, and falsely low 17-OHP levels in newborns whose mothers were administered multiple courses of antenatal corticosteroids [68,70]. A more thorough CAH NBS methodology and rationale can be found elsewhere [69–71]. Screening aims to minimize delay and ultimately lower morbidity and mortality from adrenal crises, particularly in male patients [68]. Despite its clinical usefulness, low PPV, high recall rates, and inconsistent benefits made clinicians question the rationale behind CAH NBS [69,72]. In fact, CAH is not generally included in NBS internationally [73]. However, the incremental cost-effectiveness ratio (ICER) of CAH screening yields USD 30,900 and USD 2.9 million per life-year saved for best-case and worst-case scenarios, respectively, as compared to no screening [74]. Using per hospital day avoided as the indicator, screened cohort yields an ICER of USD 290 in the best case analysis and USD 4786 in the base case analysis [75].

According to national case registries and neonatal screening, the worldwide incidence in most studies is between ~1:14,000 and 1:18,000 births [70]. CAH NBS is not mandated or regulated in Indonesia. Hence, neonates or children will be tested for CAH based on clinical symptoms, resulting in disorganized and incomplete data about the exact epidemiology of CAH in Indonesia. A single-centered

cross-sectional study in Cipto Mangunkusumo Hospital found 76 confirmed CAH cases (4–16 years old) from the 2007–2012 registry [76]. One preliminary study in five major cities and 30 hospitals from 2015 to 2016 found an incidence of 1:1226 confirmatory CAH cases. Out of the ten positive samples, only three patients came for confirmatory testing, yielding a 20 % positive predictive value [33]. According to the data collected by the IPS, 343 CAH nationwide cases were recorded in the IPS registry system up to 2018 [77].

3.4. Newborn hearing loss

Clinically significant bilateral hearing loss happens in one to three per 1000 live births [78]. Besides having a detrimental impact on employment and earnings, permanent childhood hearing loss (PCHL) is linked to delays in language, cognitive, psychosocial, educational, and occupational development [79]. Hence, universal screening is justified due to the potential for early intervention, significantly improving language and educational achievements [78]. Newborn screening for hearing loss uses either automated auditory brainstem responses (AABR) or otoacoustic emissions (OAE), or both in a two-step screening process [80]. A more thorough review of hearing loss in children can be found here [81].

Newborn hearing loss (NHL) screening is not mandatory or regulated in Indonesia, despite unscreened babies being detected much later than screened babies (28 months vs. three months, respectively) [82]. Indonesia, via written statement at the 74th World Health Assembly, supported the notion of monitoring three tracer indicators of effective ear and hearing care such as newborn hearing screening program, the prevalence of chronic ear disease and unaddressed hearing loss in schoolchildren, as well as hearing technology use among adults with hearing loss [83]. Only a few hospital centers are implementing universal NBS hearing loss screening [84].

The current epidemiology of NHL in Indonesia is unknown and best estimated from single-site or multicentre studies. In birth facilities across Indonesia, 30 % used OAE alone, and 70 % used a two-step screening process (OAE-automated auditory brainstem response [AABR] or OAE-auditory brainstem response [ABR]). Ninety percent of the screening was conducted by physicians, with the rest done by audiologists [82]. Screening is sporadic, with 0–1% coverage of newborn and infant hearing screening programs [79,82]. Congenital hearing loss affected roughly 0.08 % of children in 2013, increasing to 0.11 % in 2018 [85]. Between January 2007 and September 2008, one study screened 12,757 newborns from six mother and child hospitals using OAE. The author found that hearing impairment was suspected in 297 newborns (23 per 1000) [86]. In Semarang, one single-center study conducted an OAE test on 1338 newborns, with 41 (3 %) failing to pass the test [84]. One multicentre study in 2020 collected data from 23 hospitals across 17 provinces in Indonesia and found 535 patients with congenital hearing loss [85]. One study conducted a cost-effectiveness analysis (CEA) of newborn hearing loss screening and found that when OAE testing was done at birth and then again at follow-up, it proved to be the least expensive ($13 per newborn) and had the lowest cost-effectiveness ratio ($5100 per infant with detected hearing loss). The only more successful procedure involved screening newborns with auditory brainstem evoked response testing and without doing any screening tests at follow-up. However, this protocol also showed the highest cost ($25 per infant) and cost-effectiveness ratio ($9500 per infant with detected hearing loss) [87].

3.5. Inborn errors of metabolism

Inborn errors of metabolism (IEM) are inherited metabolic diseases with a broad spectrum of signs and symptoms. The incidence of IEM is very low for each case, up to 1:100,000, but collectively it is quite high at 1:1500 cases [88]. Many of them are also treatable, leading to an increasing amount of disorders being screened under the recommended uniform screening panel (RUSP) [89,90]. Screening helps to prevent metabolic decompensations, thwart or prevent disease-specific signs, as well as help with normal development and normal cognitive outcome in children [91].

Among the Association of Southeast Asian Nations (ASEAN) countries, Singapore has started NBS screening for IEM since 1990, Thailand and the Philippines in 1996, and Malaysia in 2006, which the government fully supports. In Indonesia, NBS for IEM is also not mandated or regulated by the government. It was only in 2000 that services for inborn error of metabolisms were developed. The first case to be handled entirely was glycogen storage disease. This genetic disorder can cause children to fail to thrive and experience a blood sugar deficiency during fasting. Subsequently, several lysosomal diseases (Mucopolysaccharides [MPS], Gaucher Disease, Metachromatic Leukodystrophy, Nieman-Pick, Glycogen Storage Disease, and Mannosidosis), mitochondrial, peroxisomal, amino acid defects (Metyhlmalonyl-CoA Mutase and tyrosinemia type I), Lesch-Nyhan disease, and 6-pyruvoyltetrahydropterin synthase (PTPS) deficiency were diagnosed [92–94]. Likewise, phenylketonuria (PKU), previously thought impossible to find in Indonesia, was diagnosed in a native Indonesian child. Most cases seen in Indonesia have an entree point of malnutrition or failure to thrive [92,93]. The first enzyme replacement therapy for MPS IV in Indonesia happened in 2015, reflecting the current state of IEM diagnosis and management in Indonesia [93]. The prevalence is unknown due to the number of undiagnosed cases, but discovering various IEM cases proves that this disease exists in Indonesia. Even worse, no large studies are being conducted for IEMs, which made estimating epidemiology even more difficult. The perceived rarity of this condition in Indonesia makes it extremely difficult to justify screening this condition. However, one study found that the mean incremental cost for PKU and medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency screening coupled utilizing tandem MS from the model was −23,312 British pounds for each cohort of 100,000 neonates screened, with an operational range of 50,000–60,000 specimens per system per year [95]. More data on Indonesian newborns is needed to calculate the cost-effectiveness analysis.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most extensive IEM disorder studied in Indonesia because malaria is an endemic disease in Indonesia [96–99]. These regions comprise the majority of eastern Indonesia, such as Sumba and Papua, as well as south Lampung, central, and south Kalimantan. Some variations, such as Viangchan, Vanua-Lava, and Coimbra Shunde, are primarily found in eastern Indonesia [100]. However, studies assessing the NBS program for G6PD deficiency or other IEM disorders in

Indonesia are still non-existent.

4. Rough estimates for the future

As mentioned above, HTA is absolutely needed to judge whether a screening test may be worthwhile regarding lives saved and monetary gain. However, the studies must be done in Indonesia as numerous factors affect the CEA calculation. For example, an OAE test will be cheaper in a public hospital than a private one. The price also differs between islands and ease of availability. We also do not include the costs of labor and skilled healthcare workers, items, tools, or machine procurement, maintenance, quality control, and treatment. Since no studies currently assess these factors, we are making several informed assumptions that may help estimate the benefits of expanding NBS in Indonesia.

In order to fill the missing gaps, private laboratories and companies in Indonesia offer expanded NBS beyond CH screening. One company uses DBS to detect CH, G6PD, and CAH for Rp 340,000 (roughly 22 USD), and when the screening is bundled with amino acid disorder screening using liquid chromatography–mass spectrometry (LC-MS/MS), the cost becomes Rp 900,000 (roughly 58 USD). Another private company focuses on newborn screening for IEM using gas chromatography–mass spectrometry (GC-MS). The company offered two packages, one that can screen for 38 disorders (31 for amino-acidopathies & organic academia, disorders for sugar metabolism, and disorders of fatty acid metabolism) and the other can screen 106 disorders (on top of the 38 disorders mentioned above there are peroxisomal disorders, disorders of purine & pyrimidine disorders, lactic academia, hyperpyruvic metabolism disorders, and other IEMs). The first package costs Rp 2,830,500 (roughly 182 USD), and the other costs Rp 3,441,000 (roughly 221 USD). Keep in mind that these prices may be significantly lower once the tests are available for public health use.

Pulse oximetry is a commonly used tool in Indonesia nowadays. Hence, we assume no additional costs are incurred in providing the screening. Even if individuals, private clinics, or small hospitals have to shell out some capital to procure the pulse oximetry, they should be able to obtain them reasonably. The price for the OAE test varies widely, ranging from Rp 130,000 to Rp 300,000 (roughly 8.3 to 19.3 USD), depending on the machines used. On the other hand, if the centers use brainstem evoked response auditory (BERA), it will cost Rp 378,000 to Rp 455,000 (roughly 24 to 29.2 USD).

The incremental cost-effectiveness ratio (ICER), determined by dividing the incremental change in expenditures by the incremental change in health outcome, is the primary outcome of an economic evaluation. This metric can help stakeholders justify the expansion of NBS in Indonesia [101]. Based on the data above, the cheapest NBS expansion will cost Rp 3,678,500 (~236 USD) per newborn and the largest and most expensive NBS expansion will cost Rp 4,849,000 (~311 USD) per newborn. Since only CH NBS is currently being provided in Indonesia, the cost of the existing program is only Rp 65,000, as stated previously. Since there is no data on the incremental change in the program's effectiveness, we assume a range of 10 % (lowest change possible) up to 50 % (realistically the highest change attainable). The cheapest NBS expansion will estimate $ICER_{10\ \%}$ of Rp 36,135,000 (~2317 USD) per percentage point of effectiveness gained and $ICER_{50\ \%}$ of Rp 7,227,000 (~464 USD). Meanwhile, the most expensive NBS expansion yields an $ICER_{10\ \%}$ of Rp 47,840,000 (~3067 USD) per percentage point of effectiveness gained and $ICER_{50\ \%}$ of Rp 9,568,000 (~613 USD).

It is also important to gauge how many lives could be saved by expanding NBS in Indonesia. The following simplified formula is used to estimate the gain:

$$CI = (P\,X\,N)\,X\,E$$

Where:

CI: Number of cases identified
P: The proportion of newborns affected by the condition
N: Population (in this case, the number of newborn)
E: The percentage of cases that the screening program successfully identifies, in this case, we are equating this to the positive predictive value (PPV) of the test.

There were 10,880 newborns in Indonesia in 2020, which represents the N [10]. Using the data mentioned above as an estimate for the prevalence of cases in Indonesia, the prevalence of CAH is estimated at 1:16,000 births with a 0.7 %–50 % PPV [70], 8 per 1000 births for CCHD with a 20 % PPV [43,102], 23 per 1000 births for congenital hearing loss with a 2–84 % PPV [86,103], and 1:1500 cases for IEM with a 4.5 %–16 % PPV [88,104]. Hence, the potential number of lives saved will be 0.5 to 34 in CAH, 17 for CCHD, 2.5 to 103 for congenital hearing loss, and 3 to 12 in IEM disorders. It is imperative to note that this assumes that all cases are detected and treated effectively, without any loss to follow-up or dropout.

5. Conclusion

Since its inception in 2000, Indonesia still screens only CH with unsatisfactory results. While other Asian countries may face similar challenges, Indonesia is still struggling. Despite the evidence and benefits, the government does not mandate or regulate newborn diseases such as CHD, CAH, hearing loss, and IEMs. The lack of regulation exists despite multiple pilot projects and studies showing a benefit in at least trying to screen newborns for those conditions. Other conditions that can be screened are not mentioned as there is insufficient data, such as spinal muscular atrophy (SMA) in Indonesia (as of March 2018, 68 people were joining the SMA community) [105]. Researchers need to conduct more studies and include convincing data on the estimate of preventable newborn deaths

attributed to NBS screening, the cost of inclusion of a new NBS program, and ultimately, the cost per life year gained.

Ethics approval and consent to paricipate

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Consent for publication

All authors have read and agreed on publishing this article.

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Gilbert Sterling Octavius: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Vamela Adman Daleni:** Writing – review & editing, Writing – original draft, Resources, Formal analysis. **Yulita Delfia Sari Sagala:** Writing – review & editing, Writing – original draft, Resources, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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