Current status of newborn screening worldwide: 2015

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\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

Newborn screening describes various tests that can occur during the first few hours or days of a newborn’s life and have the potential for preventing severe health problems, including death. Newborn screening has evolved from a simple blood or urine screening test to a more comprehensive and complex screening system capable of detecting over 50 different conditions. While a number of papers have described various newborn screening activities around the world, including a series of papers in 2007, a comprehensive review of ongoing activities since that time has not been published. In this report, we divide the world into 5 regions (North America, Europe, Middle East and North Africa, Latin America, and Asia Pacific), assessing the current NBS situation in each region and reviewing activities that have taken place in recent years. We have also provided an extensive reference listing and summary of NBS and health data in tabular form.

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\textbf{Introduction}

The general term “newborn screening” is used to describe various tests that can occur during the first few hours or days of a newborn’s life and which, when properly timed and performed, have the potential for preventing severe health problems, including death. Newborn screening has evolved from a relatively simple blood or urine screening test,

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originally used for detecting a single congenital condition, to a more comprehensive and complex screening system that can detect over 50 different conditions. While typically using blood taken from a heelstick, more recent newborn screening expansion has included bedside testing to detect conditions such as hearing loss and cardiac disease. The latter 2 conditions are now included in the U.S. federally recommended universal screening panel (RUSP) and are included in some programs in other parts of the world. This report focuses on newborn bloodspot screening (NBS) commonly used to identify inborn errors of metabolism or other inherited disorders and updates screening reports that were published in 2007, outlining NBS activities in various parts of the world. More detailed information on hearing screening can be found in an earlier issue of this Journal, and information on CCHD can be found elsewhere in the current issue.

NBS typically uses blood taken from a heelstick, absorbed onto special collection paper (similar consistency to filter paper), and transported to a special screening laboratory. While hospital laboratories may be qualified to perform NBS testing in some settings, the screening laboratory is usually a specialized laboratory because of the micro-techniques used, the cost savings from centralizing the laboratory services, and improvements in quality realized when testing large quantities of specimens for relatively rare conditions. In the U.S., it is most often a special public health laboratory. In some settings, it may be part of a larger clinical genetics laboratory, and in others, particularly in developing countries, it may be in a research setting.

In order to assess NBS activities globally, we have divided the world into 5 regions: North America, Europe, Asia Pacific, Middle East and North Africa (MENA), and Latin America. Obviously missing is Sub-Saharan Africa for which little information is currently available, and limited congenital hypothyroidism (CH) and sickle cell NBS activities are ongoing. A review of the literature and personal contacts working in Africa revealed documentation of various beginning newborn screening activities in Ghana, Nigeria, Tanzania, Angola, Ethiopia, Democratic Republic of Congo, and South Africa. For the remainder of the world, we have drawn on our extensive NBS experience and contacts with NBS program managers within our respective regions to solicit recent updates in order to comprehensively describe ongoing regional NBS activities.

North America

For purposes of this report, North America is comprised of the 51 U.S. programs (50 states and the District of Columbia) and 15 Canadian programs (10 provinces and 3 territories with 1 territory, Nunavut, divided into 3 regions). Because of similar language and culture, Mexico, while a part of North America, is included in the discussion of Latin American programs. Although screening exists in some U.S. territories, little effort has been made to collect systematic data on these programs, and they are not included in the discussion here. It suffices to say that the programs in Puerto Rico, Virgin Islands, and Guam are the most advanced U.S. territorial programs. A recent report summarizes the challenges faced by NBS expansion in the territories, with particular emphasis on the Virgin Islands and Puerto Rico. While nationally managed NBS programs do not exist in either the U.S. or Canada, the state, provincial, and territorial NBS programs have long histories and well established infrastructures similar to national programs in other countries.

Building on federally supported efforts to develop a national newborn screening plan (blueprint by the American Academy of Pediatrics, the U.S. Congress passed legislation supporting national screening efforts, which was signed into law in 2008 and recently reauthorized. In addition to funding for various newborn screening activities, the Secretary of Health and Human Services’ Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) was created. This committee has provided national NBS leadership through its carefully considered recommendations to the Secretary. In addition to approving recommendations for a nationally Recommended Uniform Screening Panel (RUSP) from the American College of Medical Genetics, the SACHDNC has implemented, and periodically refined and updated, an evidence-based protocol for reviewing and recommending other conditions for inclusion on the RUSP. Since adoption of the initial 29 core conditions and 25 recommended secondary targets, 4 additional core conditions have been recommended [severe combined immunodeficiency disease (SCID), critical congenital heart disease (CCHD), Pompe disease, and Mucopolysaccharidosis type I (MPS I)] along with 1 secondary target, T-cell lymphocyte deficiencies. As of March 2, 2015, all except MPS-I have now been accepted for recommendation by the Secretary increasing the RUSP to 32 conditions. Several other conditions have been nominated for inclusion on the RUSP but have not yet met the criteria for inclusion, including early infantile Krabbe disease and Hemoglobin H disease, among others.

Table 1 presents a tabular overview of screening activities in the U.S. Compared to the previous version of this table published in 2007, there are several noteworthy observations. In general, the number of required screening conditions has increased as state funding has permitted, following the recommendations of the SACHDNC. Most notable has been the addition of tandem mass spectrometry (MS/MS) to expand screening for metabolic conditions, screening for SCID, and CCHD screening. Expanded metabolic screening with MS/MS is now included in every state screening program and SCID, added to the RUSP in 2010, is now implemented in over 30 states. The results of SCID screening in Wisconsin (the first state to require NBS for SCID), California, New York, and an 11-state consortium have been published.

All but 4 state programs are at least partially fee based, and the average initial NBS screening fee has increased from about $45 in 2007 to about $76 in 2015. Despite a SACHDNC recommendation that states should consider linking birth certificates to NBS screening, the Secretary of Health and Human Services did not approve the recommendation and many state programs are still unable to accurately determine screening coverage (most “assume” at least 98% coverage). While almost all states require point-of-care screening for hearing loss and CCHD, both included on the RUSP, many programs have elected to monitor hospital CCHD activities.
<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Program Demographics</th>
<th>Conditions Included in Current Newborn Screening Requirements</th>
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<td>2. Lysosomal Storage Disorders</td>
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<td>Washington</td>
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<td>Wisconsin</td>
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<td>Wyoming</td>
<td>564 7 1963</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>308,746 3,942</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates full population screening mandate – for MS/MS indicates mandate for all specified conditions
+ Indicates less than full population mandate – for MS/MS indicates that some but specified conditions are either not mandated or not included in the analytical interpretation
† Newborn screened only if mother not screened during pregnancy.

1. www.census.gov/2010census/ (accessed 12/31/14)
5. See references 2 and 30.
6. Initial fee includes subsequent screening – including states requiring second screening on all newborns – Colorado, Delaware, New Mexico, Nevada, Oregon, Utah, Wyoming – and states strongly recommending second screening – Alabama, Washington
7. $75 birth charge is charged to hospitals on all births, but this is not considered a newborn screening fee.
8. Initial fee includes subsequent screening at a separate charge – including states requiring second screening on all newborns – Arizona ($65), Texas ($33.60) – and states strongly recommending second screening – Idaho ($28)
9. Totals counted only for statewide required program for this condition
rather than to develop a comprehensive CCHD screening system that includes centralized monitoring of case detection, follow-up, and tracking—different from the approach taken with hearing screening.10,11

Beginning with the requirement for Krabbe screening in New York in 2006,39 interest in NBS for lysosomal storage disorders (LSDs) has steadily increased, laboratory quality control materials have been developed,40 and legislation requiring screening for selected LSDs has been enacted in several states. Increasingly, interest has focused on NBS for Pompe disease since it has now been recommended by the SACHDNC. Potential screening algorithms for the LSDs are discussed elsewhere in this issue,41 and pilot data from Missouri has been published.42

Although X-linked adrenoleukodystrophy (X-ALD) is not yet a part of the RUSP, a screening test has been developed and NSB for X-ALD is now required in New York Connecticut, and California, a pilot already having been completed in New York.43–45 Laboratory quality control X-ALD NBS materials are under development.46 Research is also ongoing to develop laboratory methods and assess public perceptions for other conditions including Fragile-X,47,48 spinal muscular atrophy (SMA),49,50 Wilson’s disease,51 and guanidinoacetate methyltransferase (GAMT) deficiency.52

With increasing interest in NBS, and the possibility of extracting DNA from residual dried blood spot (DBS) specimens, has come an increasing awareness of privacy issues, particularly since NBS in the U.S. is legally required and consent is usually not included as part of U.S. screening protocols. The residual DBS specimens that remain after initial screening tests have been completed and reported, present storage and usage challenges. Approximately half of U.S. NBS programs discard residual specimens by 2 years and the rest retain them for more than 18 years.53 Legal questions concerning NBS specimen storage and use have led to lawsuits in Texas and Minnesota resulting in significant policy changes in both states,54 and another lawsuit now exists in Indiana. To help address this issue, the concerns of selected state NBS advisory committees have been assessed, and the SACHDNC has considered the issue and made general recommendations.55,56 As in other countries, researchers in both the U.S. and Canada have investigated parental attitudes and public perceptions concerning potential uses of residual NBS specimens in an effort to inform NBS programs and address any issues revealed.57,58 In Michigan, a model NBS biobank has been developed,59 and a Newborn Screening Translational Research Network (NBSTRN) has been funded by the National Institutes of Health as one way of providing researchers with improved knowledge and access to NBS specimens in participating state NBS programs.60

In Canada, the federal government has no formal role in newborn screening. Healthcare (and NBS) is the responsibility of the 10 provinces and 3 territories, with the notable exception of specific populations of aboriginals, inmates of federal prisons, military and newly arrived immigrants and refugees. These specific populations together make a group larger than most provinces. In the absence of pan-Canadian development and coordination of newborn screening policies and practices, individual provinces have their own advisory and decision-making processes, with varying degrees of public transparency. A recent reorganization of territorial governments across the northern tier of Canada has also had implications for NBS. In particular, the establishment of the territory of Nunavut means that NBS specimens are sent to 3 different provincial NBS labs based on historic patterns of medical services delivery.

Since 2010, when the Canadian College of Medical Genetists took a position supporting NBS for cystic fibrosis (CF),61 most NBS programs have included it on their screening panels. However, only 3 conditions currently are included on the screening panels in all Canadian NBS programs, phenylketonuria (PKU), CH, and medium chain acyl-CoA dehydrogenase deficiency (MCADD). The number of conditions routinely screened varies from 5 to over 30 across programs (Table 2). There appears to be a new focus on newborn screening collaboration and quality improvements through recurring national conferences. An attempt to create national consensus-building took place at a conference in 2007 funded by the province of Ontario, and a fresh effort took place in 2014 as a parallel meeting of the annual symposium of the Garrod Association (made up of the treatment centers for inborn errors of metabolism).

In 2013, Ontario became the first Canadian province to screen for SCID.62 A pilot for GAMT screening is ongoing in British Columbia.63 In addition to bloodspot screening, a urine screening program exists in Quebec offering expanded metabolic screening and considering screening for LSDs.54,64 As in the U.S., there has also been significant interest in the use of residual NBS specimens for research in Canada. A number of studies have been reported addressing concerns of parents, the public, and professionals. With technology moving towards less expensive high-throughput genomic testing, the possibilities of genomic NBS are being discussed, and the ethical, legal, and social implications debated.56–58 In both Canada and the U.S., there is increasing emphasis on the speed with which NBS specimens reach the testing laboratory and have testing results available.

Europe

Europe is considered to consist of 48 jurisdictions situated east of the Atlantic, north of or in the Mediterranean Sea and west of the Ural Mountains, but including the whole of Russia. The total population in 2012 was over 833 million with annual births of more than 9.5 million (Table 3). As in many parts of the world, NBS in Europe began in the mid-1960s, developing from West to East, with the latest program being initiated in Bosnia–Herzegovina in 2000.65 Four of the 48 jurisdictions are so small that screening is performed in a larger neighboring country (Liechtenstein, Andorra, San Marino, and Monaco).

Several reports have been published about the progress of NBS over time,66–73 including a recent summary of activities in Southeastern Europe.74 The data in Table 3 were recently collected by surveying European NBS experts and update similar data reported in 2012.71 Currently, all European jurisdictions have NBS for CH except Moldova, in which screening for CH previously occurred from 1989 to 1993. Screening for CH is planned to restart in Moldova in a few
years. All jurisdictions except Macedonia (formerly called the Former Yugoslavian Republic of Macedonia (FYROM)), Malta and Montenegro, have screening for PKU. While PKU screening in Finland previously targeted newborns of Swedish origin, universal NBS for PKU began on January 1, 2015. Since screening in Finland previously utilized cord blood, the switch to DBS has allowed inclusion of glutaric aciduria type 1 (GA1), MCADD, long-chain hydroxyl acyl-CoA dehydrogenase deficiency (LCHADD), and congenital adrenal hyperplasia (CAH). Malta remains as the only country in which cord blood is used for screening, but a switch to DBS is under discussion. Albania is the only European country without a screening program; however, discussions to implement it have started recently.

NBS in European countries is heterogeneous with no consensus as to what should or should not be included in NBS. Each jurisdiction is governed independently and makes its own decisions concerning conditions that should be included in NBS. Unlike the U.S. where public opinions can influence NBS policies, there is little public knowledge concerning healthcare organization in neighboring countries. As a consequence, advocacy efforts concerning health policies across borders are limited.

There are currently no policy recommendations or direct NBS oversight at the European level. However, in recent years, European best practice guidelines for cystic fibrosis NBS have been published along with treatment guidelines following NBS for both cystic fibrosis (CF) and CH. To add complexity, in some countries, e.g., Belgium, Italy, Spain, and the UK, policy making is decentralized to regions or provinces that function more or less autonomously. The result is less than 100% screening coverage for certain conditions in these countries.
### Table 3 – Program demographics and screened conditions in European newborn screening programs.

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Program Demographics</th>
<th>Conditions Included in Current Newborn Screening Requirements</th>
</tr>
</thead>
<tbody>
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<td>Bosnia-Herzegovina</td>
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<td>Turkey</td>
<td>73,997 1,268 1987</td>
<td>national</td>
</tr>
<tr>
<td>Ukraine</td>
<td>45,530 495</td>
<td>national</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>62,783 771 1969</td>
<td>national</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>833,410 9,665</strong></td>
<td><strong>45 41 10 7 19 12 16 1 22 6 17 10 17 8 0 12 7</strong></td>
</tr>
</tbody>
</table>

* Nationwide screening for this condition
† Indicates less than full population screening
‡ began January 1, 2015
¶ Screening start dates obtained as part of 2014 survey of European countries
|| See references 2 and 30.
*- Based on http://www.infanthearing.org/...europ_e-Granado.pdf (accessed 11/21/14)
‡ Newborns screened in France
§ Newborns screened in Switzerland
¶ Newborns screened in Italy
|| Totals counted only for nationwide implemented program for this condition
Since healthcare funding in Europe is typically organized within a national health service or a statutory health insurance (social security), parents do not usually have to pay a fee for NBS services. This often results in complex government financial decisions when expansion to include new conditions is considered. While each is different, public healthcare systems have defined mechanisms to assess and appraise payment for NBS and most allow for diverse stakeholder participation when considering technology effectiveness, disease severity, and treatment availability. Hearing screening and CHD screening are usually organized and financed separately from NBS.

As in other countries, there has been continuing interest in the storage and use of residual NBS. Researchers have examined various specimen stability issues. There has also been considerable discussion about privacy and consent. While there is experimentation and discussion aimed at expanding current NBS panels to include one or more LSDs, expansion is unlikely to happen on a large scale. On the other hand, several jurisdictions are expanding their NBS panel to include SCID.

Over time, the European Union (EU), presently consisting of 28 countries, has established several treaties on topics to be governed or overseen by the European Commission (EU’s Executive Body). Healthcare has not been included because the member states considered it to be their own responsibility (principle of subsidiarity). It was, therefore, surprising when the European Commission issued a recommendation on collaboration in rare diseases (prevalence of less than 1:2000) in November 2008; included was development of an inventory of NBS programs within the member states, which was subsequently subsidized as a project by the European Agency for Health and Consumers. The project group decided that the inventory should include EU-candidate and potential EU-candidate member countries along with European Free Trade Association member countries. All countries west of Russia were surveyed, and the results have been published. Additionally, recommendations for European policy makers were also developed and published. Following discussion, the European Union Committee of Experts on Rare Diseases (EUCERD) chose to continue the original EU policy of subsidiarity, i.e., healthcare is a matter for individual member states.

### Middle East and North Africa

The MENA region consists of 21 countries with a population of about 440 million with 11 million annual births. There is significant diversity between countries in population size, per capita income, health systems, insurance coverage, and newborn screening implementation. Because there are high rates of consanguinity and first cousin marriages, genetic disorders are relatively common. In the past decade, a reducing (improving) infant mortality rate (IMR) has led to growing recognition of the value of NBS, and there have been a number of collaborations and educational efforts aimed at its introduction and expansion in the MENA.

When we reported in 2007, only 4 countries in the MENA region had ongoing NBS programs, and this led participants at the first MENA Regional NBS Conference to create the Marrakech Declaration. This declaration committed all countries in the region to establish a NBS infrastructure and to implement screening for at least 1 condition. To assess progress over time, we have reviewed the current literature and made personal contacts with MENA NBS program managers and members of and Middle East Metabolic Group (MEMG).

Table 4 summarizes MENA data and provides an overview of current NBS activities. Because of its global appeal as a condition of sufficient prevalence with cost effective and efficacious treatment, CH has usually been the first condition emphasized in MENA NBS programs. Thus, much of the NBS effort within the region has focused on continued assessment of CH screening protocols and treatment outcomes. Because hemoglobinopathies (Hbs) and metabolic conditions are also prevalent, and in order to influence policy makers, studies within the region have often focused on the incidences of various metabolic conditions (although in the case of Hbs, there is competing emphasis on prevention strategies). Several NBS cost-effectiveness studies have also been completed in various countries.

Successful screening experiences across the region have provided a basis for considering internal expansion and for encouraging screening activities in neighboring jurisdictions. Likewise, successful screening models in Lebanon and Qatar have demonstrated the feasibility of using screening laboratories in other countries to provide NBS services. National NBS programs with extensive screening coverage are now present in Bahrain, Egypt, Iran, Israel, Kuwait, Oman, Qatar, State of Palestine, Saudi Arabia, and the United Arab Emirates. Pilot screening programs exist in Libya, Morocco (beginning in 2015), Syria, Yemen, and Algeria. Pilot screening projects have been completed in Jordan, Lebanon, and Tunisia, with expansion to national implementation currently ongoing. Israel is considering the possibility of implementing NBS for SCID. Although technically part of the region, little is known about screening activities in Sudan and Somalia. Noteworthy is the fact that an increased incidence of biotinidase deficiency has been observed in Somali immigrants in Minnesota, USA.

### Latin America

Latin America consists of 20 countries as noted in our 2007 report. The combined population is now approximately 600 million, with annual births of 11 million. As with other regions, there is diversity of geography, demographics, ethnicity, economies, and social and health systems, including newborn screening. Language is perhaps the most important shared characteristics since all countries except Brazil and Haiti, are Spanish speaking. Recent NBS changes in Latin
America are reviewed in this section, with the caveat that point-of-care newborn screening for hearing loss is also expanding across the region.121 It is important to recognize that in some countries like Chile, Brazil, Mexico, Argentina, Colombia, and Venezuela, NBS activities extend beyond those established by a national or regional NBS program. Screening for other diseases, especially those detected by MS/MS, is often available in the private sector. A tabular summary of regional activities is given in Table 5.

NBS programs in countries that have been functioning for 20–30 years (Cuba, Costa Rica, Uruguay, and Chile) have continued expanding their coverage, and now all 4 reach more than 99% of newborns. While programs in Cuba and Chile have not changed their screening panels since 2007, Chile is working to pilot expanded NBS to include 25 conditions in 2015, and researchers in Cuba have reported on several new screening techniques for both traditional (PKU, GAL, and CAH)122–124 and future screening (Gaucher and MPS I heterozygotes).125,126 Currently, NBS in Cuba is decentralized through more than 175 laboratories. In Costa Rica, CF was added to the screening panel in 2009, building on the pilot program previously reported.127 By contrast, NBS in Uruguay experienced the most important changes in the screening panel, adding PKU and CAH in 2007, and CF in 2010; each with official directives from the Ministry of Health that also included MCAD.128,129 A tandem mass spectrometer was purchased in 2008 followed by pilot testing and implementation of expanded metabolic screening.130,131 Thus, Uruguay is the second Latin American country (together with Costa Rica) to implement such expanded NBS. In 2013 BIO and Hbs were added.

The NBS programs in Brazil, Mexico, and Argentina have also increased their screening panels significantly, in turn requiring improvements in all other aspects of the screening system (i.e., education, follow-up, and management). In Brazil, which implemented nationwide NBS in 2001, there has been continued evaluation and refinement of screening for PKU, CH, CF, and Hb. There are now 30 Reference Centers distributed throughout the country, and coverage in 2013 was 83%.123 During the last 2 years, the Ministry of Health has been reformulating the National NBS Program to include CAH and BIO, building on pilots already completed133–135 with anticipated coverage of almost 3 million newborns annually. These activities are supported by 2 decrees passed in 2012, which mandate their inclusion. Additionally, expanded screening for metabolic diseases using MS/MS was implemented in 2010 for the Federal District and recently as a pilot for Minas Gerais.

In Mexico, there has been a significant increase in newborn coverage through the activities of different subsystems of the complex healthcare system.129 Most important is the fact that the Secretary of Health and the Mexican Institute of Social Security together screen more than 70% of all newborns. Current screening coverage for the country exceeds 80% of newborns (tested for CH, PKU, GAL, CAH, and BIO). In some states (Tabasco, Yucatan, and Chiapas), as part of the system of the Secretary of Health, there is additional screening for CF, Hb, and MS/MS detectable metabolic conditions. All conditions screened are included as part of the Mexican Official Rule for the Prevention and Control of Congenital Defects in force since 2012.136

In Argentina, regional NBS programs ongoing in the Province of Buenos Aires,137 Mendoza and the Autonomous City of Buenos Aires (ACBA) since the mid-1990s, became consolidated. In 2006, the National Ministry of Health implemented its Strengthening Program whose activities include distributing

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Table 4 – Program demographics and newborn screening experiences in the Middle East and North Africa.

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>*2012 Total Population (x 1000)</th>
<th>*2012 Number of Births (x 1000)</th>
<th>% Infants Screened for Congenital Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>38,482</td>
<td>962</td>
<td>71</td>
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<tr>
<td>Bahrain</td>
<td>1,318</td>
<td>21</td>
<td>8</td>
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<tr>
<td>Egypt</td>
<td>80,722</td>
<td>1,937</td>
<td>18</td>
</tr>
<tr>
<td>Iran (Islamic Republic of)</td>
<td>76,424</td>
<td>1,452</td>
<td>15</td>
</tr>
<tr>
<td>Iraq</td>
<td>32,778</td>
<td>1,016</td>
<td>28</td>
</tr>
<tr>
<td>Israel</td>
<td>7,644</td>
<td>156</td>
<td>3</td>
</tr>
<tr>
<td>Jordan</td>
<td>7,009</td>
<td>196</td>
<td>16</td>
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<tr>
<td>Kuwait</td>
<td>3,250</td>
<td>68</td>
<td>10</td>
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<tr>
<td>Lebanon</td>
<td>4,647</td>
<td>60</td>
<td>8</td>
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<tr>
<td>Libyan Arab Jamahiriya</td>
<td>6,155</td>
<td>129</td>
<td>13</td>
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<tr>
<td>Morocco</td>
<td>32,511</td>
<td>748</td>
<td>27</td>
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<tr>
<td>Oman</td>
<td>3,314</td>
<td>70</td>
<td>10</td>
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<tr>
<td>Qatar</td>
<td>2,051</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>28,288</td>
<td>566</td>
<td>7</td>
</tr>
<tr>
<td>Somalia</td>
<td>10,195</td>
<td>452</td>
<td>91</td>
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<tr>
<td>State of Palestine</td>
<td>4,219</td>
<td>130</td>
<td>19</td>
</tr>
<tr>
<td>Sudan</td>
<td>37,195</td>
<td>1,265</td>
<td>89</td>
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<tr>
<td>Syrian Arab Republic</td>
<td>21,890</td>
<td>525</td>
<td>12</td>
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<tr>
<td>Tunisia</td>
<td>10,875</td>
<td>185</td>
<td>14</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>9,206</td>
<td>138</td>
<td>7</td>
</tr>
<tr>
<td>Yemen</td>
<td>23,852</td>
<td>739</td>
<td>46</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>442,025</td>
<td>10,838</td>
<td></td>
</tr>
</tbody>
</table>


b The Saint Joseph newborn screening in Beirut is contributing to selective pilot MS/MS screening or second opinion
Argentina
198,656
19,402
3,009
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Regional 1995
National 2006
Private 2008
Public 2009
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coverage was 94% and 31%, respectively. Currently, the national program is focused on increasing the coverage for CF and planning expansion to include piloting CAH, GAL, and MS/MS in 2015. In Panama, the national NBS program for CH and G6PD deficiency began in 2007, expanding to include GAL and PKU in 2008, and CAH and HB more recently. Screening occurs in 11 regional NBS centers of the Ministry of Health, and there is an independent program implemented by the social insurance. Together, the 2 programs cover more than 75% of newborns. Legislation was critical to NBS success in both Paraguay and Panama. In Nicaragua, a regional NBS program was started at the National Autonomous University of Nicaragua—Leon in 2005. Initially it targeted newborns in the Northwest region, extending its scope to the rest of the country’s departments later. Screening is exclusively for CH using cord blood, and the coverage exceeds 86%.

Ecuador, Peru, and Bolivia have shown the most important advances in recent years. The national NBS program in Ecuador began in December of 2011, and included PKU, CH, CAH, and GAL, with current coverage of approximately 90% of newborns. The Universal NBS Program in Peru was created by law in 2012 with PKU, CH, CAH, GAL, CF, and hearing loss as the conditions included in the initial phase. NBS activities are carried out mainly by the Maternal Perinatal National Institute and ESSALUD, organizations belonging to the public and the private sector, respectively. Despite a law, coverage in Peru is only about 20% and screening for some conditions like CF have not yet been implemented. In Bolivia, a 2006 Ministerial Decision declared NBS to be mandatory for CH, but until now a national program has still not been implemented. Similar to Peru, Bolivia has 2 main initiatives: one in Santa Cruz in the public sector and the other in La Paz in a private hospital with departmental (provincial) coverage of 70%. Three additional public programs have recently been implemented in Chuquisaca, Cochabamba, and Tarija, so that total coverage from all programs is about 20%.

NBS in other countries in the region have not exhibited significant changes. A national NBS program was started in Guatemala in 2003, building on pilot CH NBS activities initiated with funding from the International Atomic Energy Agency in the mid-1990s; however its scope is limited only to newborns born in 2 hospitals in Guatemala City. Diseases screened include CH, PKU and CAH covering approximately 1% of newborns. In the Dominican Republic, there are only minimal NBS activities carried out on request in the private sector. Other metabolic diseases are screened by sending samples to private laboratories in USA. At present, specialists are working on a project to include screening for CH, PKU, HB and G6PD in 2015. In El Salvador, a regional NBS program began in 2008 for newborns born exclusively in the metropolitan and paracentral regions of the country, but this program was discontinued by lack of funding. In Honduras, several different projects aimed at implementing NBS have been attempted since 2007, but none have been sustained. In Haiti, there are no known NBS activities.

Asia Pacific

The Asia Pacific region extends from New Zealand on the south to Mongolia on the north, and reaches to Pakistan in the east (see map in 2007 report). Of the 138 million babies born in the world, almost half (67 million) are born in the Asia Pacific region. Countries in the region vary widely in size, economic development, and geography. There are many different languages, cultural sensitivities, and religions, each creating its own challenges in implementing NBS. In some areas, the number of births outside of hospitals approaches 80%, and literacy is very low. Despite these challenges, NBS continues to grow throughout the region.

Almost 80% of the births in the Asia Pacific region occur in 5 countries—China, Indonesia, Bangladesh, India, and Pakistan. The IMR has been found to be a good predictor of when competing health issues acknowledge the need for NBS, and all countries with an IMR lower than of 7 per 1000 live births have been able to reach NBS coverage of more than 90%. The number of conditions screened varies widely across the region. Several recent reports review NBS expansion activities across the region. At the time of our 2007 report, only Australia, New Zealand, and Taiwan included expanded metabolic screening with MS/MS in their screening panels. Since that time, other countries in the Asia Pacific region have expanded to include not only additional metabolic screening, but also a number of other conditions not in their panels at that time. The Japanese Ministry of Health and Welfare decided to expand publicly funded NBS to include inborn errors of amino acid, organic acid, and fatty acid metabolism in 2012, but in most other Asian countries, patients must pay for this additional (optional) testing. There has also been increasing interest in NBS for LSDs, and significant progress with Pompe disease screening has been reported in Taiwan, Japan, and Korea. Additional pilot studies in the region for other LSDs (Niemann-Pick A/B, Krabbe, Gaucher, Fabry, and Hurler syndrome) have been reported. Other conditions for which there have been ongoing NBS pilot studies include citrin deficiency, SCID, Fragile-X syndrome, X-ALD, and Wilson's disease.

Currently, Taiwan is the only country in the region that includes both Pompe disease and SCID in the national panel of conditions. The screening coverage rate is reported to be approximately 95% for Pompe disease and 85–88% for SCID. There have been several pilot programs including Fabry (2006–2014), Gaucher (since 2011), MPS I (since 2008), aromatic amino acid decarboxylase deficiency (AADC deficiency) (since 2013), and newborn screening (since 2014). Preliminary incidences were at least 1:875 in males (Fabry), 1:101,134 (Gaucher), 2:35,285 (MPS I), 3:53,807 AADC deficiency, and 1:12,000 (SMA). (Chien YH., 2015, personal communication).

Pilot NBS project for LSDs, Fragile-X syndrome, and SCID is also ongoing in Australia, and there is continuing interest in public perceptions, privacy, and consent issues. Federal government oversight of NBS has recently surfaced as an issue in Australia (programs are currently state responsibilities). A working party has been tasked with developing a policy for harmonization of NBS across Australia and a mechanism for adding and removing conditions from screening panels. A final submission is due at the end of 2016. (Wiley V., 2015, personal communication)

India has the most births of any country in the world, yet NBS is still not a healthcare priority. While the percentage
coverage from NBS has increased over years, it is still not quantifiable. Some state programs are now beginning, and a number of provincial pilots are ongoing, including some efforts in the private sector. Initiatives include BIO, CAH, CH, Fragile-X, G6PD, GAL, and MS/MS. (Kabra M., 2015, personal communication). The situation has recently been reviewed by Verma et al.168 with suggestions to the government for screening implementation. As a first step, the authors suggest convening a central advisory committee to plan for program development. Three conditions are recommended for immediate introduction in urban hospitals (CH, CAH, and G6PD deficiency), while the recommendation for rural areas is only for CH, especially in the sub Himalayan areas. Screening with MS/MS is suggested once there is a firm infrastructure in place. The challenges noted and their potential solution are similar to those experienced in most developing programs, only they encompass a much larger screening population.169,170

Among the countries that lack total NBS coverage, the obstacles are usually the same: poor economies, insufficient

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Table 6 – Program demographics and screened conditions in Asia Pacific newborn screening programs.

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Program Demographics</th>
<th>Screened Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Covered (% x 1000) 2012</td>
<td>% Covered (% x 1000) 2012</td>
</tr>
<tr>
<td>Australia</td>
<td>23,933</td>
<td>305</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>154,695</td>
<td>313</td>
</tr>
<tr>
<td>Cambodia</td>
<td>14,835</td>
<td>384</td>
</tr>
<tr>
<td>China</td>
<td>1,377,983</td>
<td>18,455</td>
</tr>
<tr>
<td>Hong Kong (China)</td>
<td>7,112</td>
<td>66</td>
</tr>
<tr>
<td>India</td>
<td>1,236,678</td>
<td>25,642</td>
</tr>
<tr>
<td>Indonesia</td>
<td>246,846</td>
<td>4,736</td>
</tr>
<tr>
<td>Japan</td>
<td>127,250</td>
<td>1,071</td>
</tr>
<tr>
<td>Korea (South)</td>
<td>24,763</td>
<td>356</td>
</tr>
<tr>
<td>Laos</td>
<td>49,003</td>
<td>470</td>
</tr>
<tr>
<td>Malaysia</td>
<td>29,240</td>
<td>516</td>
</tr>
<tr>
<td>Mongolia</td>
<td>2,796</td>
<td>64</td>
</tr>
<tr>
<td>Myanmar</td>
<td>52,797</td>
<td>922</td>
</tr>
<tr>
<td>Nepal</td>
<td>27,474</td>
<td>593</td>
</tr>
<tr>
<td>New Zealand</td>
<td>4,460</td>
<td>63</td>
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<tr>
<td>Palau</td>
<td>21</td>
<td>0.22</td>
</tr>
<tr>
<td>Pakistan</td>
<td>179,160</td>
<td>4,604</td>
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<tr>
<td>Philippines</td>
<td>96,707</td>
<td>2,383</td>
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<tr>
<td>Singapore</td>
<td>5,303</td>
<td>53</td>
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<tr>
<td>Sri Lanka</td>
<td>21,998</td>
<td>338</td>
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<tr>
<td>Taiwan</td>
<td>23,359</td>
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<tr>
<td>Thailand</td>
<td>66,785</td>
<td>702</td>
</tr>
<tr>
<td>Vietnam</td>
<td>90,796</td>
<td>1,440</td>
</tr>
<tr>
<td>Totals</td>
<td>3,867,996</td>
<td>66,740</td>
</tr>
</tbody>
</table>

* Offered to full population being screened – for MS/MS indicates screening and interpretations available for all detectable conditions
† Cord blood screening
‡ Pilot testing or select population screening (i.e. optional, not full population screening)
∥ See reference 141.
¶ Personal communication: V. Wiley (Australia); I. Sethikar (Cambodia); X. Gu (China); M Kabra (India); D. Rustama (Indonesia); S. Yamaguchi (Japan); M.K. Thung (Malaysia); E. Ganzbatar (Mongolia); L. Shrestha (Nepal); D. Webster (New Zealand); L. Reyes (Palau); D.H. Lee (S Korea); P. Vesaphong (Laos); M. Hettiarachchi, Sri Lanka; W-H Chen, Taiwan; S. Pangkaran (Thailand)
†† Reported by Philippine Newborn Screening Reference Center
‡‡ See reference 146.
§§ Pilot testing for Fragile X, SCID and LSDs (personal communication, V. Wiley)
** Severe thalassemia screening reported but confirmation unavailable
††† Pilot testing for SCID (personal communication, S Yamaguchi)
‡‡‡ Pilot testing for Gaucher, Pompe and Fabry (personal communication, D.H. Lee)
†††† Pilot testing for SMA, AADC (personal communication, Y-H Chien)

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health education, lack of government support, early hospital discharge, and large numbers of out-of-hospital births. Certain items have been identified as essential to success for sustainable programs: (1) government prioritization, (2) full or partial government financing, (3) public education and acceptance, (4) health practitioner cooperation/involvement, and (5) government participation in program institutionalization. Despite more than a decade of pilot testing, some countries in the region with large numbers of births, i.e., Bangladesh, Indonesia, Pakistan, and India, continue to struggle in securing government support.

In order to provide information sharing and ongoing educational support, a network of developing programs has existed for several years. This network continues with program reviews and goal setting as a major agenda item. A summary of regional activities is given in Table 6. Noteworthy is the success at screening implementation in China, which now reaches over 85% of all Chinese newborns. NBS in the Philippines continues as a model for developing programs with 65% coverage, recent addition of regional comprehensive follow-up/treatment centers to its infrastructure, and implementation of expanded screening, including MS/MS screening and screening for Hbs, CF, and BIO. Based on preliminary clinical estimates, NBS for Hbs in the Philippines should identify larger numbers of thalassemia patients than seen in any other thalassemia NBS program.

Acknowledgments

The authors gratefully acknowledge the cooperation of colleagues in each region in providing information about their screening activities. Many who contributed have not been acknowledged through documented personal communications, but their responsiveness to our requests will not go unnoticed.

Summary comments

While CH remains the most significant condition included in NBS programs worldwide due to its relatively high incidence (particularly in iodine deficient areas), readily available low-cost treatment and successful treatment results, screening for various other conditions is also of high importance. Each condition included in NBS must be carefully evaluated on the basis of medical and scientific evidence surrounding the natural history of the condition and the local ability to decrease morbidity and mortality through screening. Care must be taken in implementing new programs not to make the same mistakes made by others. Carefully planned pilot testing should always include a thorough analysis of public health impact and cost effectiveness with an eye to the future. As an example, while it is true that cord blood screening can be effective as a screening mechanism for some conditions like CH and G6PD, it is equally true that cord blood specimens cannot be reliably used for metabolic screening. So, while cord blood may be appealing for programs beginning to screen for CH or G6PD, blood spot screening is the better choice because of its increased flexibility and the high likelihood of expansion to metabolic testing at some future time.

Developing programs must continually take advantage of progress already made by others. This report has identified various regional training and support activities that have assisted in the development of new programs and the refinement of already established programs. In an effort to encourage worldwide harmonization and to provide guidance in establishing the most effective and efficient protocols, the Clinical and Laboratory Standards Institute has refocused its efforts on international NBS consensus standards and guidelines. At least 6 such documents currently exist and more are planned.

This report emphasizes the complexity of NBS and the continuing need for system-wide evaluation and improvement. It also provides information about global NBS activities and points to the importance of transparency and knowledge in achieving public support worldwide. Through shared commitment and information, we will continue to expand NBS opportunities and, as a consequence, health and life outcomes.

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