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Newborn screening programs for spinal muscular atrophy worldwide: Where we stand and where to go

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Abstract

Spinal muscular atrophy (SMA) is a rare and devastating disease. New disease-modifying treatments have recently been approved and early treatment has been related to a better outcome. In this context, several newborn screening (NBS) programs have been implemented. The aim of the study was to obtain a global overview on the current situation and perspectives on SMA NBS. We conducted a survey and contacted experts from 152 countries, from which we gathered 87 responses. We identified 9 SMA NBS programs that have so far detected 288 newborns with SMA out of 3,674,277 newborns screened. Funding, screening methods, organisation, and consent process were variable between SMA NBS programs. Many respondents pointed the lack of cost/benefit data as a major obstacle to SMA NBS implementation. In the next four years, our data suggest a 24% coverage of newborns from countries where a disease-modifying drug is available and 8,5% coverage in countries with no diseases-modifying drugs. The annual proportion of newborns to be screened in the coming years is expected to increase steadily. The experts expressed a strong need for the implementation of SMA NBS as means to improve care for patients with SMA.

Keywords: Newborn screening; Spinal muscular atrophy; Pre-symptomatic; Nusinersen; Risdiplam; Onasemnogene abeparvovec.

1. Introduction and context

5q Spinal muscular atrophy (SMA) is an autosomal recessive disease, caused by lack of functional survival motor neuron (SMN) protein. The incidence is approximately 1 in 10,000–12,000 live births [1],[2]. Despite a broad phenotypic spectrum, with symptoms onset from birth to adulthood, 95% of patients present with a homozygous deletion of *SMN1* gene, and 5% with a single allelic deletion and a point mutation on the other allele [3].

Three disease-modifying drugs have been approved by the U.S. Food and Drug Administration (FDA), and around the world over the last four years [4]: nusinersen in December 2016 [5], onasemnogene abeparvovec in May 2019 [6],[7], and risdiplam in August 2020 [8]. Disease duration has been demonstrated to be a consistent prognostic factor across the different clinical trials [9]. The most significant treatment effect has been observed in pre-symptomatic patients [10].

In this context, several newborn screening (NBS) programs have been implemented [11] in Australia [12], Belgium [13], Canada [14], Germany [15], Italy, Japan [16], and Taiwan [17]. In the United States [18], SMA was included in the

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Recommended Uniform Screening Panel (RUSP) on July 2, 2018.

Several technical, financial, organisational or ethical considerations may block or slow down NBS implementation throughout the world. To better appreciate the current global situation, and to foresee the development in the coming years, we launched a survey that was distributed to SMA and NBS key leaders in most countries around the world.

2. Methods

We contacted experts in the fields of SMA and NBS in as many countries around the world as possible to obtain a global overview on the availability of disease-modifying drugs for SMA and the current state of SMA NBS in their countries. We also gathered expert opinions on technical and organisational issues related to actual or coming SMA NBS as well as their predictions of how SMA NBS will be implemented in their respective countries in the next ten years. The experts were invited to reply to a questionnaire, which was accessible via a web link that was sent in the invitational e-mail. Queries were sent to clarify any inconsistent data entered in the survey.

2.1. The questionnaire

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University Medical Centre Ljubljana, Slovenia [19]. Surveys were completed between November 26 and December 29, 2020. The questionnaire comprised of four sections:

1. Basic information, such as name and surname, profession or speciality, email, country/region (C/R) for which the expert provided data, and the number of births in that C/R.
2. Questions related to the availability of disease-modifying drugs for SMA in the respective C/R.
3. Questions related to SMA NBS in the respective C/R.
4. Questions related to the existence of NBS for other diseases than SMA and SMA carrier screening in the respective C/R. The respondents could also share other unlisted information in this final part.

The questionnaire is available in Appendix 1, and at the following link: http://sma.pedkl.si.

2.2. Identifying experts with knowledge in the fields of SMA NBS

To establish a list of the contacts, we addressed experts in as many countries around the world as possible from the following fields of expertise: paediatric or adult neurology, paediatrics, genetics, clinical research, newborn screening programs, patient advocacy groups, or other relevant specialties. The list of contacts was compiled using various resources: professional connections (including through Researchgate and LinkedIn), the details given for corresponding authors of relevant peer-reviewed articles, and web searching using the keywords “newborn screening” and “spinal muscular atrophy”.

For each country, one expert was invited to participate in the survey and in case of no response, one or more substitutes were identified. In countries which had two regions that significantly differed regarding SMA NBS, we invited one expert from each region with and without NBS programs.

2.3. Statistical analysis

For answers regarding disease-modifying drugs and implemented SMA NBS, we have combined the responses where two experts have given an answer for two different regions of a particular country. All statistics reported here are descriptive.

The median for continuous variables, or mode for categorical variables, was calculated. A categorical variable (0–10%, 10–20%, etc.) was proposed to estimate the percentage of newborns screened. Statistical analyses were performed using SPSS version 27 (SPSS Inc., Chicago, USA). World maps were designed in Microsoft Excel (2019) for Mac (Microsoft, Redmond, USA), while other images were designed with Prism version 7 for Mac (GraphPad Software, La Jolla California, USA).

2.4. Study group

The respondents were invited to join the SMA NBS World Study Group. The group met on January 15, 2021 on two video calls to discuss the findings. Following the calls, we gathered more precise information on false positives and false negatives encountered in the pilot programs. The draft of the paper was sent to the group for double-checking of the provided data.

3. Results

According to information from the United Nations [20], there are currently 197 countries in the world. The questionnaire was sent to experts in 152 countries. We obtained responses from 87 experts from 82 different countries (54% of contacted countries) in 6 continents (Appendix 2). Altogether, these countries count 8,434,000 newborns per year, which account for 57% of the total number of newborns born per year in the world.

Of 87 respondents, 61 identified themselves (with more than one option possible) as paediatric neurologists, 13 as adult neurologists, 11 as geneticists, 4 as paediatricians, 4 as newborn screening specialists, 2 as patient advocacy group members, and 8 as researchers. For four countries (Australia, Belgium, Canada, Colombia), two independent respondents have provided data for the two distinct regions of their country and the data were combined accordingly for the purpose of analysis; for China, three respondents responded on this basis for the mainland People’s Republic of China, the Hong Kong

Table 1
Availability of SMA disease-modifying drugs in the 53/82 countries where at least one disease-modifying drug was reported to be available.

Drug	Nusinersen	Onasemnogene abeparvovec	Risdiplam
Countries ($n=53$)	53	24	26
Access			
Reimbursement	48	14	6
Compassionate use	1	5	18
Patient charge	4	5	2
Indication (symptoms)			
Symptomatic	53	22	25
Pre-symptomatic	32	15	3
Indication pre-sympto (*SMN2* copies)			
1 copy	18	9	0
2 copies	30	13	1
3 copies	29	12	1
4 copies	14	5	1
5+ copies	7	1	0
Do not know	1	0	1
No criteria (case/case)	2	2	1

SAR and Taiwan respectively. Sixty respondents attended the SMA NBS study group meeting.

3.1. Availability of SMA disease-Modifying drugs

The availability of treatments according to the number of copies and the time of disease onset is reported in Table 1.

The availability of disease-modifying drugs around the world, and the relationship between the availability of disease-modifying drugs and implemented SMA NBS, is illustrated in Figs. 1A and B.

3.2. Countries with implemented SMA NBS

We obtained responses from 82 countries regarding their newborn screening program, except for Mexico where we only received information on disease-modifying drugs. Newborn screening for SMA was implemented in 9 countries, 11% of all responding countries (Fig 1B, Table 2).

Ethical committee approval was required for implementing SMA NBS in all countries, although it was not required in specific regions in Canada with active NBS.

Altogether, the respondents have reported 288 newborns with diagnosed SMA out of 3,674,277 screened newborns in the above mentioned 9 countries with SMA NBS program. This represented an incidence of 1 in 12,757 (Table 2).

False positives in Taiwan and Italy were reported only at the beginning of the program and no new cases were reported after the change of primers. False positives in the US were generally reported to be due to low white blood cell counts resulting in false positive or an unsatisfactory result for SMA.

Patients with the deletions of one allele and point mutations on the other allele in the *SMN1* gene were not considered as false negatives as they are not supposed to be identified by the current methods. Nevertheless, at least 3 such cases were identified (2 in Taiwan, 1 in Belgium).

Respondents from countries with an opt-out consent process reported a much better acceptability rate (99%) than those with an opt-in process (80–87%). The fact that the U.S. has only a 61–70% rate is because not all states have yet included SMA in their NBS.

In countries with an implemented SMA NBS program, when asked about how important they believe it is to have the SMA NBS implemented in their country, all but one expert rated 100, and one rated 90 (on a 0–100 scale). Obstacles faced by the respondents in their respective countries and measures that could be helpful for improving the current SMA NBS are listed in Table 3.

The main obstacles mentioned ($n=5$) related to cost/effectiveness issues and long-term data availability ($n=4$). Other mentioned obstacles were uncertainties about patients with higher *SMN2* copy numbers (≥ 4), reimbursement of treatment, and carrier testing. COVID-19 was also a significant present concern, as it has had a considerable impact on the ability of the national standing committees to meet and has also had a worldwide economic impact.

Each respondent from countries where an SMA NBS program is ongoing highlighted the following points as important for initiating NBS at the national or regional level: (i) to start by pilot project; (ii) to identify the process for implementation of SMA NBS in the country (typical steps include developing the screening assay, identifying the staff need to carry out testing and follow up, identifying funding for the NBS work, completing the regulatory requirements for implementation, identify the speciality healthcare referral centres); (iii) to educate colleagues in NBS and provincial government officials about the importance of pre-symptomatic treatment initiation; (iv) to present long-term efficacy of treatment; (v) to share the experience in the NBS-SMA implementation process; (vi) to use the whole of health systems approach and partnering with patient organisations.

Table 2
Details on SMA NBS program. W: Whole country P: Part of country, NB: newborns, Pilot: pilot program, Official: official program, Cases: number of SMA cases identified; pos: positive, neg: negative, Cons Proc: Consent process, H: funds by hospital, P: funds by parents, G: funds by government, HI: fund by Health insurance, Ph: funds by pharmaceutical companies, Gr: funds by grants, US NBS: usual NBS laboratories, Gen lab: genetic laboratory, qPCR: quantitative Polymerase Chain Reaction, dPCR: droplet digital polymerase chain reaction, MLPA: multiplex ligation dependant probe amplification, var methods: various methods.

Country (W/P)	NB/y	% NB Screened	Year NBS SMA implemented		Cases	NB screened	False Pos	False neg	Cons Proc	Fund	Site test	Genetic method	
			Pilot	Official								Tier 1	Tier 2
Taiwan (W)	170,000	81–90%	11/14	01/18	20	419,102	8	0	Opt-in	H/P	Us NBS	qPCR	MLPA
USA (P)	3,745,540	61–70%	01/16	07/18	180	2,395,718	10	0	Opt-out	G	Us NBS	Var meth.	dPCR/ qPCR
Germany (P)	780,000 (305,000)	11–20% (87%)	01/18	<1y	43	297,163	0	0	Opt-in	HI	Us NBS	qPCR	MLPA
Belgium (P)	120,000 (55,000)	45% (99%)	03/18	03/21	9	127,329	0	0	Opt-out	Ph/G/Gr	1 Us NBS	qPCR	MLPA
Australia (P)	300,000 (100,000)	21–40% (99%)	08/18	>2y	19	202,388	1	0	Opt-out	Gr/G	1 Us NBS	qPCR	dPCR
Italy (P)	435,000 (68,000)	11–20% (86%)	09/19	NA	12	58,558	0	0	Opt-in	Ph	1 gen lab	qPCR	qPCR
Russia (P)	1,373,550 (15,000)	< 10% (80%)	08/19	3y	0	12,000	0	0	Opt-in	Ph	1 gen lab	qPCR	MLPA
Canada (P)	377,000 (140,000)	31–40% (99%)	01/20	06/20	5	139,810	0	0	Opt-out	G/Ph	1 Us NBS	Mass	MLPA
Japan (P)	864,000 (1 district)	< 10%	05/20	3 y	0	22,209	0	0	Opt-in	Ph/P	1 gen lab	qPCR	MLPA
All	**8,100,090**	**3,081,839**			**288**	**3,674,277**	**19**	**0**					

Table 3
Actual or foreseen obstacles and measures for help for establishing SMA NBS.

Obstacles	Countries with SMA NBS ($N=9$)	Countries without SMA NBS ($N=76$)
Lack of professional consensus on an international level		13% (10)
Lack of professional consensus on a national level	11% (1)	17% (13)
Lack of long-term follow-up data	11% (1)	16% (12)
Lack of financial resources	55% (5)	68% (52)
Lack of human resources	11% (1)	29% (22)
Lack of equipment	22% (2)	29% (22)
Organisational issues	33% (3)	21% (16)
Too difficult to be implemented in practice	11% (1)	11% (8)
Lack of support from the hospitals involved	33% (3)	14% (11)
Lack of governmental support	44% (4)	30% (23)
Not a healthcare priority in our country	11% (1)	29% (22)
Ethical issues	0	6% (5)
Other	33% (3)	12% (9)
Measures		
Clear professional consensus on an international level	11% (1)	39% (30)
Clear professional consensus on a national level	22% (2)	32% (24)
Clear professional guidelines / recommendations	22% (2)	45% (34)
Health-economic data	44% (4)	54% (41)
Cost-benefit analysis	55% (5)	70% (53)
Long term follow-up data on treatment of pre-symptomatic patients	55% (5)	53% (40)
Resources and support by institution	0	32% (24)
Resources and support by government	66% (6)	67% (51)
Assistance with implementation practicalities	22% (2)	20% (15)
Measures against genetic discrimination of patients	0	12% (9)
Support from patient advocacy organizations	11% (1)	28% (21)
Other	11% (1)	0

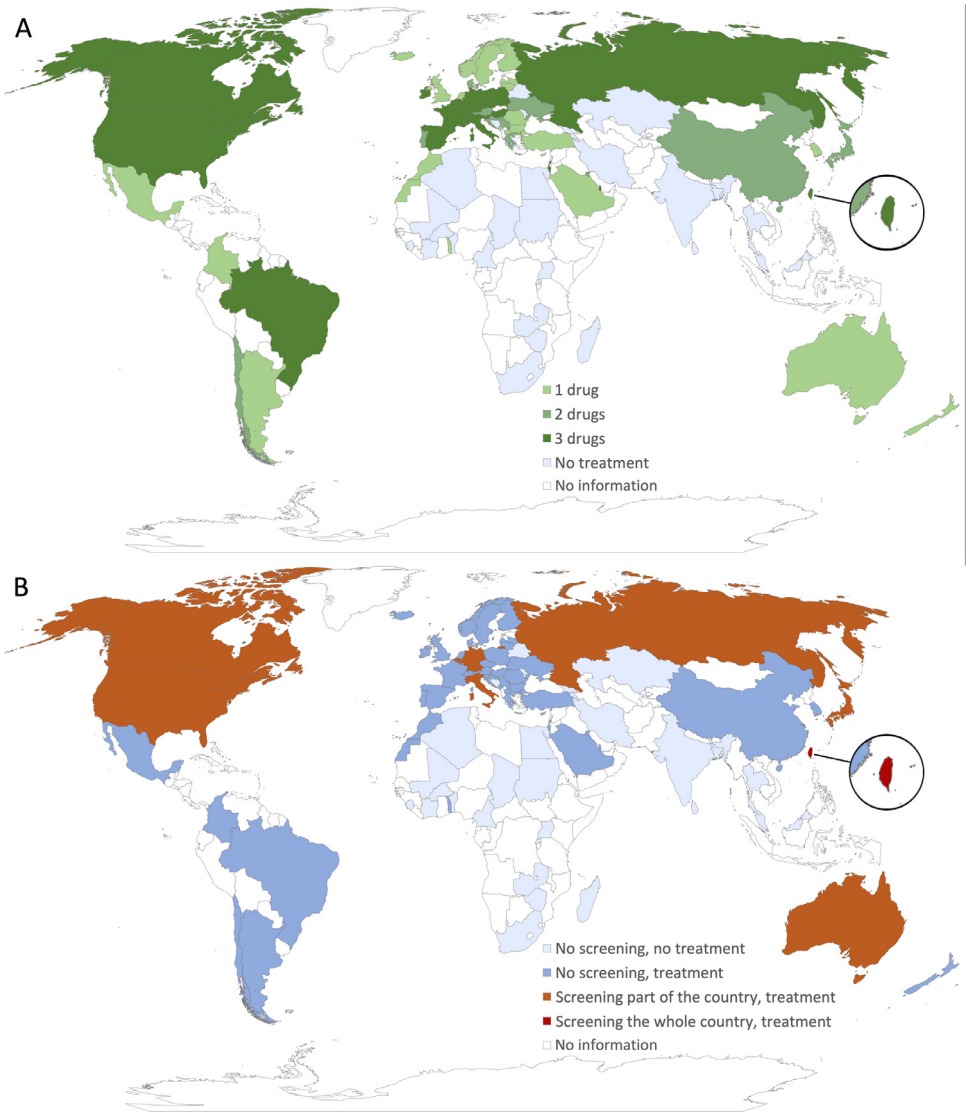

Fig. 1. Availability of treatments and NBS around the world. A: Availability of treatment. B. Availability of treatment related to the status of SMA NBS. We could not gather responses from or identify experts in 115 countries and assumed no NBS.

3.3. Countries without NBS for SMA

We obtained 76 responses regarding SMA NBS from 74 countries that do not yet have an SMA NBS program implemented (the additional two responses were from the regional respondents for Bogota in Colombia and the Hong Kong SAR in China). In countries without an implemented SMA NBS, the average score (on a 0–100 scale) the respondents gave when asked about how important they believed it would be to implement the SMA NBS in their country was 94.5 (range: 10 – 100). Out of 76 respondents from countries without implemented SMA NBS, 37 reported plans for establishing SMA NBS and 39 declared no plan. Ethical committee approval specific to the SMA NBS will be required in 45/76 C/R; ethical committee approval for previously implemented NBS will also cover SMA NBS in 11/76 C/R; and no ethical committee approval will be needed for establishing SMA NBS in 10/76 C/R. The remaining 10 respondents replied that their need for ethical committee approval still needs to be determined.

The respondents predicted that qPCR will be used as a first-tier test in 30/75 C/R; MLPA in 18 C/R; NGS in 1 C/R; multiplex PCR in 1 C/R; and 26 respondents were not sure.

The respondents anticipated that the financial burden for the future SMA NBS will be covered by the government health funds in 36 C/R; public health insurance in 34 C/R; pharmaceutical research funds or grants in 15 C/R; academic research funds or grants in 14 C/R; parents in 11 C/R; regional health funds in 7 C/R; private health insurance in 6 C/R; hospital funds in 1 C/R; and 10 indicated the answer ‘other’.

The respondents described the obstacles they might encounter in establishing SMA NBS and the measures that might be useful in launching SMA NBS in their respective countries in Table 3. Other mentioned obstacles were the need to modify the law to introduce

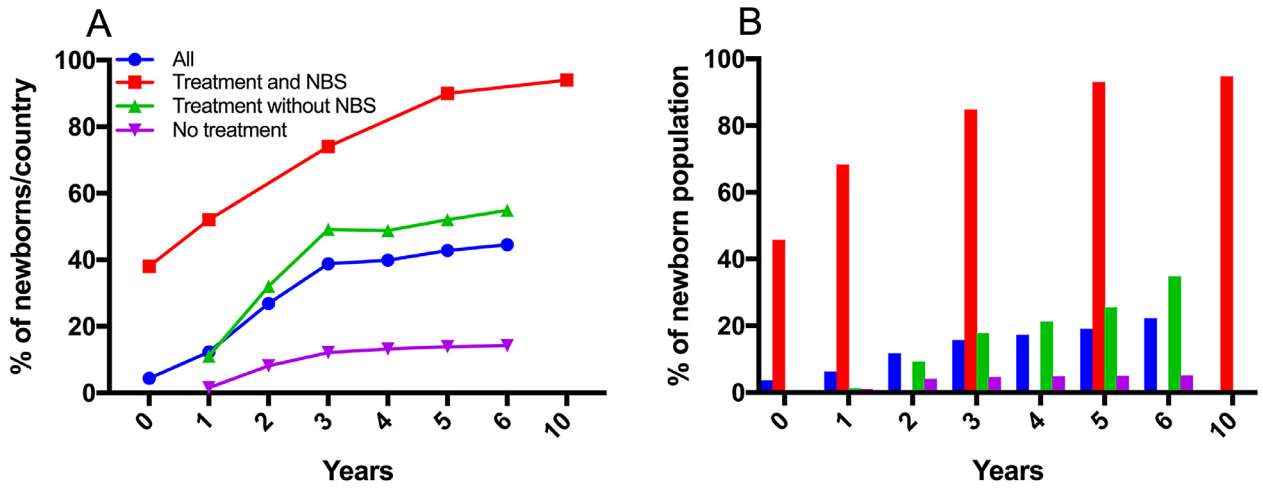

Fig. 2. (A) Current and predicted percentage of newborns screened for SMA in countries for all respondents (blue), respondents from countries with NBS already in place (red), respondents from countries with treatment available but no NBS in place (green) and countries with no treatment and no NBS available (purple). (B) Idem, expressed in% of newborn population screened for the different groups . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the possibility of genetic screening, the need to ask for parental consent, and a lack of consensus about treatments, especially for patients with 4 copies of *SMN2* gene.

3.4. Prediction of future developments of SMA NBS

We have asked the respondents about the current and predicted percentage of newborns screened for SMA in countries with SMA NBS ($N=9$ countries) and predicted percentage in countries without SMA NBS ($N=76$ C/R) in the coming years. The results are depicted in Fig. 2.

3.5. Carrier screening and other NBS programs

There was no implemented SMA carrier screening (CS) in 42 C/R; there was CS for anybody who request it (covered by health insurance) in 9 C/R; CS for a limited number of parents (covered by health insurance) in 10 C/R; CS for a limited number of parents (covered by parents) in 16 C/R; and CS for families with a previously affected member with SMA in 4 C/R. Six respondents did not know whether there was CS in their respective countries. CS outside detection of familial cases was available in 5 of the 9 C/R where NBS is available. CS outside detection of familial cases was available in 20 of the 46 C/R with no NBS and treatment available.

4. Discussion

In this paper, we present a survey of the current situation of NBS for SMA and the perspective for the coming years.

In most European countries and the United States, the existence of SMA NBS was related to the presence of reimbursed disease-modifying treatments and after scientific data proved that early treatment is related to a better outcome.

Taiwan, which has been pioneering in most aspects of SMA NBS [21–23], is currently the only place in the world in which the whole population of newborns is being screened for SMA. Outside Taiwan, several countries have started with a regional pilot before SMA became included in the official NBS programs. Several programs are already planning to transition to official programs in 2021, such as in Germany and Belgium.

We could not gather responses from or identify experts in 115 countries. Nevertheless, it is fair to assume that there is currently no SMA NBS in these countries. We can thus reasonably assume that in 2021, about 2% of the newborns population of the world is currently being screened for SMA. This proportion of newborns screened across the world is low in spite of accumulative evidence of the importance of early [9] and especially pre-symptomatic treatment of patients with SMA [10].

Several obstacles are reported by respondents. The absence of health economic data or cost/effectiveness of SMA NBS was almost unanimously identified by experts as an important obstacle. Indeed, very preliminary data have recently been presented or modelized [24], but important information is still missing. It could be hypothesised that given the very high cost related to SMA, NBS offers the opportunity to decrease the societal cost of SMA by relatively cheap early detection in patients, however this remains to be demonstrated or anchored to unequivocal data. Ethical issues are reported only by 5 respondents, which seems to indicate a global acceptance and understanding of the need of a genetic method for NBS.

Interestingly, no respondent reported the absence of approval/reimbursement of disease-modifying treatment in pre-symptomatic as a potential issue. It is likely that even if the benefit of pre-symptomatic treatment has been clearly established, the initiation of treatments when the very first symptoms occur rather than after a long diagnostic journey appears to be anyways a significant benefit.

In 7 of the 9 countries where NBS is available, carrier screening is also offered, but only for families with a family genetic history ($n=4$), or covered by parents (3), or more broadly, parents may decide based on health insurance coverage as in the United States. Intuitively, carrier screening offers the possibility to avoid a substantial number of SMA cases, but its impact on actual SMA incidence in regions or countries where it is performed remains controversial [25],[26].

In countries where NBS is available, no false negative data have been reported. False negative cases are difficult to clearly identify, except in well-defined regions with well-structured reference centres and case reporting. In addition, false negatives with SMA type 3 may show up later, which means that the proportion of false negatives will still remain approximate in the coming years. The identification of heterozygous deletion/point mutation cases in Taiwan and in Belgium, with an incidence of 10% of the total number of cases, strongly suggests that the reporting process of cases identified in these two countries outside the NBS program has been efficient, and thus that the number of non-identified false negative cases must be very low.

False positive results seem to be mostly commonly related to process and methods. Identification of false positive cases in Taiwan was resolved by the change of primers; in the USA, most false positive cases were due to low white blood cell count. Altogether, the incidence of false positive cases with current methods appears to be extremely low. In comparison, NBS for cystic fibrosis can yield up to 19% of false positives [27],[28]. Benchmarked with other diseases, SMA NBS thus seems to be extremely reliable.

According to respondents' responses, the prediction of the number of countries where at least half of the children will be screened in 1, 2 and 4 years' time was 11, 24 and 39 respectively*. In comparison with the generalization of NBS for SCID, a treatable condition if diagnosed early, this would represent a much faster rate of implementation. Indeed, the first SCID screening programs were initiated in 2006 and SCID is part of the RUSP since 2010 [29]. However, only 20 countries are currently screening for SCID [30].

Our study has several limitations. Firstly, the survey was filled by different types of stakeholders, such as child neurologists, patient advocacy individuals, and geneticists. Also, we opted for asking the stakeholders involved in SMA in their own country rather than national experts responsible for NBS in the respective country, as people deeply involved in SMA care might have a better view of future pilots and SMA specificity. Furthermore, despite an inclusive and systematic approach to all countries, including countries with no treatment and no standard of care available for SMA, we could not identify respondents for 43 countries. We were therefore only able to attempt to contact experts from 78% of countries identified by the UN, and we only received responses from 42% of all countries. Nevertheless, we obtained an answer from almost all European countries and a total of 78% of countries with advanced economies [31]. Of the 114 countries in which we could not identify a respondent, 105 (92%) were from countries with emerging and developing economies, which could indicate that SMA NBS is understandably not considered to be an available option or a priority in these countries. We were able to get responses from only 32% of countries with emerging and developing economies. We believe that the present work has the potential in the near future to increase awareness about SMA NBS including in developing countries.

We plan to follow up with respondents in 1, 3, 5, and 10 years in order to compare the actual evolution of NBS with the projected evolution. This could help to demonstrate how such methods could be used to project NBS implementation of other diseases in the near future.

5. Conclusion

Within the world population of children, today there are still a low proportion who are screened for SMA at birth. This survey has established a clear need for SMA NBS and projects a moderately optimistic view for the development of SMA NBS. Nevertheless, we should be cautious given the different obstacles that need to be tackled in order to organise and implement future NBS programs.

Contributors, SMA NBS study group

The SMA NBS world study group is composed of academics from the following countries and regions, listed alphabetically by family name:

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TD has given lectures sponsored by Biogen and Roche.

EV has served as a consultant for Biogen.

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Supplementary materials

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