Worldwide Recall Rate in Newborn Screening Programs for Congenital Hypothyroidism

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Received 2017 January 25; Revised 2017 April 03; Accepted 2017 April 16.

Abstract

Context: Neonatal mass screening program for congenital hypothyroidism provides the best tool for prevention of its devastating effects on mental development. Despite the overall success of the screening programs in detecting congenital hypothyroidism and eliminating its sequelae and new developments made in the program design, high recall rate and false positive results impose a great challenge worldwide. Lower recall rate and false positive results may properly organize project expenses by reducing the unnecessary repeated laboratory tests, increase physicians and parents’ assurance and cooperation, as well as reduce the psychological effects in families.

Evidence Acquisition: In this review, we assessed the recall rate in different programs and its risk factors worldwide.

Methods: Publications reporting the results of the CH screening program from 1997 to 2016 focusing on the recall rate have been searched.

Results: Recall rates vary from 0.01% to 13.3% in different programs; this wide range may be due to different protocols of screening (use of T4 or TSH or both), different laboratory techniques, size of sample collection, recall cutoff, iodine status, human error, and even CH incidence as affected by social, cultural, and regional factors of the population.

Conclusions: It is suggested to implement suitable interventions to reduce the contributing factors by improving the quality of laboratory tests, selecting conservative cut off points, control iodine deficiency, use of iodine free antiseptic during delivery, and use of more specific markers or molecular tests. Applying an age dependent criteria for thyrotropin levels can be helpful in regions with a varied time of discharge after delivery or for preterm babies.

Keywords: Congenital Hypothyroidism, Newborn Screening, Recall Rate

1. Context

Primary congenital hypothyroidism is one of the common preventable causes of intellectual disability in neonates (1). It is seldom diagnosed based on clinical features in the first few weeks after birth, in which thyroid hormones are precious for neurological development. Devastating effects of CH on brain development can be reversible in case of prompt treatment; therefore, neonatal mass screening program provides the best tool for early diagnosis (2,3).

Heel-prick dried whole blood spot samples taken onto Guthrie cards (filter paper cards) is routinely used in newborn thyroid screening and other conditions such as phenylketonuria, cystic fibrosis, etc. at 3 - 5 days after birth. Since the establishment of the CH screening program in Quebec and Pittsburg in 1974, neonatal screening has been routinely implemented in developed as well as some developing countries (4). It is estimated that 25% of the birth population, worldwide (127 million), undergo screening for CH (5).

First the program was introduced, the incidence rate of CH was 1/3000 to 1/4000 and remained constant until 1990 (6); however, over the years, the incidence approximately rose worldwide e.g. in United States (7,8), Europe (9), Australia (10), Israel (11).

The project coverage percentage is achieved by calculating the ratio of screened neonates to total number of live births. The recall rate is the percentage of tests where the physician notifies the authorities to contact the parents in order to arrange another test. According to the protocol of screening, neonates with abnormal TSH or T4 (in heel prick or cord blood) are recalled for confirmatory tests. According to the American academy of pediatrics, appropriate recall rate after primary thyroid stimulating hormone (TSH) screening is approximately 0.05% (12).
Despite the overall success of screening programs in detecting congenital hypothyroidism and eliminating its devastating sequelae, most programs have encountered problems that were not evident initially and became apparent with patient observation and more experience obtained thereafter over longer periods of time; therefore, many programs have modified their strategies. One of these challenges is adjustment of the recall rate in order to keep the program viable.

Selection of the accurate recall criteria, despite providing suitable coverage for neonatal screening programs in communities, would decrease false positive results in screening programs, which is of great importance as success in taking a repeated blood sample is variable and surely less than 100%. In the Asian populations, the response rate to recall rate is poor due to high mobility, ignorance, false addresses, cultural beliefs and taboos. On the other hand, lower false positive results increase physicians and parents cooperation, minimize toxic psychological effects and stress in families, as well as appropriately organize project expenses by reducing the unnecessary repeated laboratory tests.

Furthermore, larger numbers of false-positive results impose a great challenge of risk communication with parents, an aspect of newborn screening, which has been highly ignored and should be given much attention in the future. False positive screening creates undue anxiety and psychological harm in families and normal neonates as well as excess workload for staff. There are no comprehensive reports regarding the world wide recall rates and related contributing factors, most articles just report the recall rate as a part of the evaluation process and do not focus on it separately; therefore we assessed the worldwide recall rate considering various contributing factors.

2. Method of Data Source and Selection Criteria

The terms ‘congenital hypothyroidism’ and ‘newborn screening’, both separately and in conjunction with the terms ‘recall’ or ‘cut off’, were searched in the literature for original papers, reviews, and guidelines published between 1975 and 2016. We searched these key words in the title, abstract, and text by using the international databases including PubMed, Embase, Scopus, ISI, web of Knowledge and web of Science. All abstracts were reviewed; studies with appropriate design and English language were included if they were related to the evaluation of screening program focusing on recall rate and false positive results. 167 abstract were found, 95 of which were included in the study. Next all articles meeting the criteria were completely reviewed to extract details of the program with respect to the recall rate, positive predictive value, false positive results extracting date, method, and geographical region, cut offs laboratory, and sampling method. We prioritized the review articles by prominent scholars and important studies in this field. Reviewers were not blinded to the study authors’ names, as we wanted to include all pertinent studies, which necessitated the exposure to the articles and the study authors. Two reviewers critically appraised all papers independently. Data was extracted by 1 reviewer and checked by the second reviewer. Risk factors related to the recall rate were classified and discussed separately. Disagreements between reviewers were resolved by consensus. Studies with overlapped results or inappropriate study design and inadequate reports were excluded. The data regarding the year of study, geographical location, author, title, setting, simple size, recall rate, incidence, laboratory methods, false positive rate or positive predictive value (PPV), and method of screening were extracted.

Search strategy was developed with the assistance of a research librarian at the research institute for endocrine sciences of Shahid Beheshti University of Medical Sciences.

3. Definitions

Characteristics of each screening test are determined by specificity, sensitivity, as well as positive and predictive values. The sensitivity and specificity are related to the quality of the test, however the positive and negative predictive values are influenced by disease prevalence. For reaching judgments about the quantitative impacts of false-positive results in screening of congenital hypothyroidism, PPV is more pivotal than test specificity. Values approximating 0.5% translate into about 200 false-positive test results for every confirmed case. Little change has been reported in the PPVs in newborn screening in the current decade indicating that no improvement has been achieved in the number of false-positive results in newborn screening programs.

For a screening test to be fully effective, the sensitivity (the probability that an affected person will have a positive test result) is of high concern and should ideally approach 100%, as it must reliably detect almost every case to reassure health care professionals and parents on screening test results. High sensitivity of screening test also affects the manner that parents are counseled, however, it should be considered that no screening test could truly achieve 100% sensitivity due to potential human error and biologic variability. On the other hand, in attempt to find all cases in newborn screening programs, the creation of false-positive test results has been greatly ignored, which can be statistically presented by test specificity (the probability that a normal person will have a negative test re-
sult) or by PPV (the proportion of persons with positive test results who are truly affected), however due to low prevalence of congenital diseases currently screened, PPV is more meaningful and useful than test specificity (13, 14).

4. Results

Recall rates in various programs differ from 0.01% to 13.3%. This wide difference may be due to different screening strategies (use of T4 or TSH or both), different laboratory techniques, site of sample collection, iodine status, different recall criteria, human error, and even the incidence of CH due to social, cultural, and regional factors of the population (15-18). The recall rates in different studies have been reported in Table 1. Here we also discussed the factors contributed to recall rate worldwide, each separately.

5. Iodine Deficiency

Iodine deficiency is an important factor in increasing the recall rate. Infants born in an iodine deplete areas tend to have a high TSH concentration as an adaptive mechanism to maintain serum t4 within normal or low normal ranges, where as those born in iodine replete areas could have low filter paper spot T4 concentrations only in case of TBG deficiency or congenital hypothyroidism (19).

In a study by Azizi et al. used cord blood TSH level, before national salt iodization in Iran, a high recall rate of 5% led to a study termination; however, following the implementation of universal salt iodization, the recall rate decreased to 1.6% (20).

A recall rate of 7.3% was reported in the study done by Karamizadeh and Amirhakimi (21), in 1990, before the iodine fortification of salt in the Fars province, Iran, using the T4 cord level, however, after universal salt iodization (22), the recall rate reduced to 2%, based on TSH measurement in filter paper blood spots (23).

There is high concern regarding maternal iodine deficiency. Despite universal salt iodination, iodine deficiency may be reappearing in developed countries (24); on the other hand there are some reports of iodine deficiency in pregnant women in iodine sufficient areas, as diet-conscious pregnant women may avoid iodine-supplemented salt (25, 26). Iodine supplementation before or during a pregnancy returns thyroid function to normal condition in the mother and their neonates (27). In Iran, supplementation of pregnant women with recently produced iodofolic tablets (containing 150 µg iodine, 500 µg folic acid), from 3 months before conception to the end of lactation period, has been recommended.

6. Different Strategies

Different strategies are currently used in the screening programs for congenital hypothyroidism. Each strategy has some advantages and disadvantages and the recall rate based on each protocol may differ; however most countries have switched to primary TSH measurement (12, 28).

Primary TSH/T4 backup approach-primary TSH method detects overt and compensated primary hypothyroidism, however, central hypothyroidism (secondary/tertiary), hyperthyroxinemia, thyroid binding globulin (TBG) deficiency, and delayed TSH elevation such as seen in premature infants would be missed (29, 30). This approach is mostly used in Europe, Japan, Canada, Mexico, and the United States (12, 29, 30). Despite the physiological surge of TSH at birth, trends towards early discharge of mothers (29) may increase the rate of false positive results. Primary TSH approach has a higher specificity with a less false positive rate than Primary T4 program and negligible false negative rate due to higher sensitivity of improved current laboratory techniques and age-adjusted TSH cutoffs in infants discharged after 24 hours of age. In this approach the cutoff point would depend on the site and time of sampling and the diagnostic assay used.

Primary T4/backup TSH approach (12, 29, 30) identifies infants with low or low normal thyroxine values and elevated TSH concentrations, hyperthyroxinemia with delayed TSH surge especially in LBW infants, TBG deficiency or central hypothyroidism (low or low-normal T4 with normal TSH) (12, 29, 30), and hyperthyroxinemia. This program is being used by most North American countries; primary T4 program has higher sensitivity than a primary TSH program, (12, 29) however, it has a higher recall (false positive) rate mainly in premature and low birth weight babies (29) and in programs using an absolute cutoff for T4, otherwise the recall rate is almost the same with primary TSH (12, 29, 30). On the other hand, the sensitivity of TSH assay with current laboratory techniques (enzyme-linked immunoassays, chemiluminescent assays, and fluoroimmunoassays) has been improved. The recall rate in this approach is approximately similar to a primary TSH approach (0.05%), although, the false positive rate will be higher (approaching 0.30%), in a few primary T4 screening programs, in which lower values of T4 below an absolute cutoff (39 nmol/L), despite normal TSH values, are considered. For example, the recall rate in California was 0.08%, contrary to a higher recall rate of 0.30% in Oregon, where infants with lower T4 results (< 3rd percentile) were recalled (31), showing that up to 12 normal neonates may be recalled for each hypothyroid case.

Combined TSH and T4 approach represents the ideal screening approach, (12, 30) due to a lower recall rate and...
not having the limitations of both primary T4 and primary TSH approaches, however, it is not cost effective (29).

In Italy (32), the recall rate was 2.5% in screening neonates based on the T4 level and would decrease to 0.11% if neonates were screened based on both T4 and TSH values. These findings are similar to the study by Amini et al. in Isfahan, with the recall rate of 1.63% using the primary T4 and 0.13% using both T4 and TSH level (33). The study, in a municipal hospital, reported the recall rate of 3% based on the T4 ≤ 6.5 ng/dL (16) and indicated that the neonates recall based on low T4 level alone would increase false positive results, however, infants with secondary and tertiary hypothyroidism can be detected; the higher recall rate compared to the report of Amini et al. based on T4 may be due to differences in the T4 assay. In the study done by Najafi et al. (34), on 9,118 neonates using primary TSH / back up TSH, TSH values of 5 - 25 mU/L were recalled between the 10th and 15th days of age, those with the secondary TSH > 5 mU/L and primary TSH > 25 mU/L were recalled; the recall rate had reduced to 0.85 in comparison with the recall of 3.6% in their previous report using only first TSH filter paper > 5 (35).

7. Lowering Cut Off

Lowering the threshold for recall in screening program over time reflect the debate regarding screening sensitivity versus specificity; those programs that select a lower threshold have argued that by using the higher cut-off, some cases of CHT can be missed (36). Although it is less likely to miss cases with lower cut-offs, the increased number of recalls will compel more work, cost, as well as psychological pressure. The reasons that make other programs choose a higher cut off in order to decrease the number of normal infants who are retested are anxiety for parents, pain for the babies, and expenses; on the other hand, these programs based on some evidence claim that more subtle abnormalities are found by reducing threshold are unlikely to result in neurological deficit (37). In the UK, reducing the threshold to 6 mU/L showed that routine repeat testing for preterm babies is not needed anymore (38). The TSH cut off values for CH screening program varies from 5 - 20 based on the screening protocol, date and site of sampling, as well as the region (Table 1). There is no defined cut-off point for such a screening program. Each country should start screening with a conservative cut-off point and collect enough data to make the final decision for an optimum threshold with the intent to reduce false positive and recall rates.

8. Laboratory Methods

Development of more sensitive and accurate laboratory methods (enzyme-linked immunosorbent assays, chemiluminescent assays, and fluoroimmunoassays) have improved sensitivity of TSH assay, thus many screening programs have led to: 1. switching to primary TSH approach in many programs and 2. decreased the cut-off threshold from 20 or 25 mU/L to 6 or 10 mU/L.

Lowering cut-off induced detection of some transient cases and neonates with hypoplastic glands, which may have led to the increased incidence now being found. In a report done by Korada et al. reducing the TSH cut-off to 6 mU/L increased false positive results, however, the additional expenses are justified (39). Accuracy of different laboratory methods in the screening programs for congenital hypothyroidism, based on TSH measurement, was assessed in a study in Slovakia and reported that IRMA was more accurate and the recall rate was 2.34% and 0.89% using RIA and IRMA, respectively (40). The rate of false positive results also varies based on the employed kits (19).

Switching to a primary TSH approach presents a problem in settings with early discharge of mothers and infants, as the first screening test usually is obtained before 48 hours of age and the normal surge in TSH postnata tally, however, in a recent report, using a sensitive and specific immunofluorometric assay showed that normal TSH concentrations during 24 hours of age are usually lower than those obtained in previous assays (less than the cutoff value of 20 to 25 mU/L) (41, 42). On the other hand, in case of applying age-adjusted TSH cutoffs, there would be a 50% reduction in abnormal values (43). Newer assays in a primary TSH screening approach in settings with discharge after 24 hours of age reported lower rates of recall with negligible false-negative test results.

9. Iodinated Disinfectants

Skin disinfection with iodine containing antiseptics such as povidone-iodine (PVP-I) is widely used in obstetrics or caesarean section. A few studies have reported that iodine overload in mothers exposed to cutaneous application of iodine containing antiseptics at delivery induces a transient impairment of thyroid function in their infants by transient rise of their infants’ blood TSH level, which is responsible for a high false-positive rate in CH screening program, necessitating recall of a large number of infants for retesting (44-49), and suggesting that iodine containing antiseptics such as PVP-I should not be recommended in obstetrics.

Iodine daily requirement ranges between 150 - 250 µg during pregnancy and lactation. Each milliliter of PVP-I
the effect of iodine overload. A study from Japan, an iodine-sufficient area, iodine exposure during the prenatal period, resulted in an increase in the recall rate (53). Therefore, the mechanism underlying the influence of iodine overload on recall rate during delivery seems to be more complex. Indeed, iodine deficiency just sensitizes neonates to the transient thyroidal disorders caused by the iodine overload.

In Isfahan, Hashemipour et al. reported that 73.5% of pregnant women, in the third trimester, have iodine deficiency and the exposure to Povidone-iodine, induced a 2 fold increase in median urinary iodine. Another national study showed the prevalence of iodine deficiency to be 40.2% among pregnant women (48). Reports of NHANES (55), in the United States and other studies conducted in Iran, China etc., also reveal that despite of iodine-containing salt program efficiency, pregnant and breastfeeding women are still in danger of iodine deficiency and may need iodine supplements (56).

Hashemipour et al. showed that iodine excess may play a role in incidence of CH, as milk iodine in mothers of hypothyroid neonates was higher than in healthy ones, despite the acceptable values of mean iodine levels in mothers' urine and milk in both hypothyroid and euthyroid neonates. However, they measured urinary iodine only in the postpartum period, when mothers had been exposed to high-iodine-content antiseptics during delivery, which confounded urinary iodine measurement (57).

Different results of studies regarding the effect of topical iodine-containing antiseptics on recall rates can be attributed to varying prevalences of iodine sufficiency and the time of screening. Maternity hospitals should be recommended not to apply povidone iodine during the course of delivery, as far as possible; however, the acceptance and implementation of this advice should be ascertained.

10. Site of Sample Collection

Most countries use filter paper dried whole blood spot samples from a heel prick at 3 - 6 days to avoid false positive results due to TSH physiological surge during first 48 hours after delivery. With this method little difference has been found between using thyroxin (T4) and thyroid stimulating hormone (TSH) as the primary measurement in detecting CH (19). In countries where it is difficult to call back families after discharge, cord blood sampling may be a preferred option (18, 58). There are many reports on capillary heel prick TSH and free T4 (FT4) or T4 screening, but relatively little on cord TSH screening (18, 58-60), and even less on cord blood FT4 screening (5). Cord FT4 has not been mentioned by any paper as the sole screening method; however, cord FT4 and TSH have been used together (61).

(10%) contains 10 mg (10,000 µg) of iodine. At least 200 mL PVP-I is needed for prepping during delivery. A significant amount of this iodine is absorbed from mother’s skin, crosses the placenta, and enters the fetus blood circulation. The thyroid gland of fetus and preterm neonates is more sensitive to suppression by iodine overload than that of adults (50). PVP-I used during delivery passes into the milk up to 5 days following the delivery (51); this dose of iodine suppresses the thyroid gland in the early days of life. The higher the level of plasma iodine, the lower the level of T4 and subsequently the higher level of TSH because of the Wolff-Chaikoff phenomenon.

False positive results in screening were significantly higher in babies treated with povidone-iodine (4.6%) than those treated with either alcohol or triple dye (0.7%). The study by Valizadeh et al. on 2282 neonates in Zanjan demonstrated a 73% reduction in the recall rate for CH screening program when chlorhexidine (CHL), which is free of iodine, replaced iodine-containing antiseptics like Povidone-iodine (PVP-I) during delivery or surgical preparation. In Belgium, Chanoine et al. (46) proved that replacement of Povidone-iodine, with iodine-free antiseptics, reduces the recall rate, especially among breast fed infants; their study included 4,745 cases, in 2 groups of Povidone-iodine users (1,659 neonates) and iodine-free antiseptic users (3086 neonates). The recall rate in neonates exposed to Povidone-iodine at delivery was 25 to 30 times higher than the non-iodine group and the rate was higher in the breast fed infants (46). Chabrolle and Rossier reported that the application of PVP-I directly on the infants’ skin increases their serum thyroid stimulating hormone concentrations. Other studies conducted in different areas, showed the same results (47, 52, 53).

In the study done by Ordookhani et al. (48) on 48131 cases in Tehran and Damavand, an iodine sufficient area, no difference was observed in the recall rate in vaginal deliveries and between 2 groups of Povidone-iodine with chlorhexidine; however, they used a cord blood sample and there was no sufficient time for iodine absorbed from the mother’s skin and to be transferred to neonates via placenta, to affect the infants’ thyroid gland. The Brown et al. study on preterm neonates, demonstrated that replacement of Povidone-iodine with iodine-free antiseptics is ineffective in altering the recall rate, despite the significant increase in urinary iodine of neonates with a positive history of maternal exposure (54), the findings are contrary to reports from Europe. An area of borderline iodine deficiency, indicating that the prior iodine status may be responsible for the difference, both prematurity, as a cause of false-positive results, and cold stress during early hours of birth, which significantly increases TSH level, could mask the effect of iodine overload. A study from Japan, an iodine sufficient area, iodine exposure during the prenatal period, resulted in an increase in the recall rate (53). Therefore, the mechanism underlying the influence of iodine overload on recall rate during delivery seems to be more complex. Indeed, iodine deficiency just sensitizes neonates to the transient thyroidal disorders caused by the iodine overload.
Cord TSH measurement was found to be a good screening method by Walfish (17) and Fuse et al. (62), however, not by Majeed-Saidan et al. (60). With the limited information on cord FT4 screening and the differing results on cord TSH screening, further studies are of interest.

A study done by Hardy et al. (63), similar results were reported in cord FT4 and TSH measurements in diagnosis of some or most cases of CH, respectively. Cord TSH measurement was more successful, with 6 out of 8 cases diagnosed, as opposed to 6 out of 13 with cord FT4. The failure of cord FT4 to diagnose all cases of CH is not surprising as there is considerable maternal placental transfer of thyroxin (64). In addition, 10% - 20% of infants with CH had T4 values in the low normal range. Cord FT4 did pick up the infants with more severe hypothyroidism, i.e those for whom early start of treatment is most important. Although, better than FT4 measurement outcome, cord TSH measurement missed 2 out of 8 infants with CH, results similar to those recorded by Majeed-Saidan et al. in a larger screened population from Riyadh (60), however Walfish (17) and Fuse et al. (62) found this method satisfactory. TSH measurement often miss the rare cases of hypopituitary and hypothalamic hypothyroidism (12, 65).

Hardy et al. reported a high recall rate of 1 in 23 for cord TSH and the heel prick TSH was superior to both cord FT4 and TSH in diagnosing CH, and cord TSH was superior to cord FT4 measurement. In countries where recall is difficult, cord blood screening may be the method of choice, however, it is not possible to use cord blood for screening for phenylketonuria. Cord FT4 only detects infants with severe CH. Cord TSH is a superior screening method, however with a high recall rate a high recall rate. The most sensitive method is Capillary dried blood spot TSH testing on the 3rd to 5th day. Whatever the method used, an efficient process from sampling to acting upon positive results must be in place.

11. CH Incidence

Overall, the incidence is influenced by race, ethnicity, sex, pregnancy outcomes (i.e prematurity and low birth weight), environmental, genetic, and autoimmune factors (66, 67). Doubling of the incidence reported in the last decade may be due to several factors such as improved detection of neonates with delayed TSH elevations or with mild form of disease due to lowering cut point of screening test (68), changes in demographic pattern (69), and increase in multiple pregnancies (70). Asian countries with higher incidence of CH are reported to have a higher recall rate. The recall rates increase in parallel with increasing incidence of CH.

12. Human Error

There are also human errors, which lead to invalid results and increased recall rate, for example unsatisfactory filter-paper specimens due to technical error, double spotting, insufficient amounts of blood or spotting blood over a previous blood spot. Technically blood should be applied to one side of the filter paper and saturate it completely, dried at room temperature, and not exposed to high heat or contamination by any substance such as milk or coffee. Human errors are inevitable, however, the associated samples should not be assayed and therefore are not considered in the recall rate in many programs.

13. Conclusions

Recall rates in various programs in different parts of the world range from 0.01% to 13.3%; the difference being mainly due to various screening methodologies including, screening protocols (use of T4 or TSH or both), different laboratory techniques and kits, site of sample collection, and different recall criteria (cut offs). Regarding cost effectiveness and feasibility, the best advisable protocol is measuring TSH level through heel-prick blood specimens, however, there is no defined cut-off point for such a screening program. Each country should start screening with a conservative cut-off point and collect enough data to make the final decision for an optimum threshold with the intent to reduce false positive and recall rates.

Iodine status is the other important and prevalent contributing factor. Last but not least, human error and even the incidence of CH due to social, cultural and regional factors of the population may have role in the rate of recall in any region (15-18).

Newborn screening has made extraordinary contributions to public health through detection of congenital disorders worldwide. Despite its indisputable significant role, high recall rate reflecting by false-positive results should be recognized as an adverse effect and more care should be devoted to address associated morbidities and to reduce their magnitude. High false-positive results generated in many of congenital screening programs, impose an enormous challenge for improvement of this public health program. PPVs ranges determined in the reports are quite wide. The highest false-positive results in new born screening is related to congenital hypothyroidism, based on the 1994 CORN report, imposing over than $2 million in costs annually for repeated testing.

Suitable interventions should be implemented to reduce the contributing factors based on the circumstances in each region. Suggestions made are to improve laboratory tests by using tests with higher sensitivity and speci-
ficity to reduce the recall rate, select conservative cut off points to ensure no neonates are missed while keeping with minimum false positive results, control iodine deficiency, and use of iodine free antiseptic during delivery. Applying an age dependent criteria for thyrotropin levels can be helpful in regions in which the time of discharge after delivery is varied or for preterm babies. On the other hand, many new tests can be expected through improving laboratory techniques and the use of more specific markers, molecular tests (13, 71) and completion of the human genome project (72). Research activities should be conducted from time to time to ensure high quality laboratory tests, acceptable recall rate, false positive results, and to find whether or not cut off sneds any adjustment, therefore routine data collection should routinely be included in any program's infrastructure.

New improvements have been made in screening methods worldwide, however implementing them nationally is more important. Due to noticeable variations in laboratory cutoffs and types of assays yielding variable results, implementing conformity at national level in the process of newborn screenings would definitely facilitate improvements; certainly, complete data collection can be helpful regarding this purpose. It is not practical to completely eliminate false-positive test results and its associated morbidities, therefore more attention should be paid to reduce risk communication and counsel families, in a sensitive and rational manner, before and after the screening results by making this obligatory in newborn screening programs.

Footnotes

Authors' Contribution: Fereidoun Azizi: study design, supervision, interpretation, and writing the manuscript. Ladan Mehran: searching literature, study design, and writing the manuscript, Davood Khalli: interpretation and writing the manuscript, Shahin Yarahmadi: interpretation writing the manuscript, Ateieh Amouzegar: interpretation and writing the manuscript; Mehdi Mojarrad: searching literature.

Declaration of Interest: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding/Support: This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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| Author                  | Country     | Year       | CH incidence | Recall, % | Screening, n | Sampling Method | Cut-Off             | Laboratory Method | More                                      |
|-------------------------|-------------|------------|--------------|-----------|---------------|----------------|---------------------|--------------------|-------------------------------------------|
| Dussault et al. (73)    | Quebec      | 1974       | 1:7000       | 0.85      | 18237         | T4 < 0.4 µg/L   | RIA                 | False positive 50.8 |
| Travis et al. (74)      | Quebec      | 1979       | 1:5000       | T4, T3; T4, TSH, 0.3 | 6264 | T4, T4, TSH; T4 < 0.4 µg/L, TSH > 20 | RIA |
| Dussault et al. (73)    | Quebec      | -          | 1:1576       | T4; 0.5; T3, TSH 0.27 | 95800 | T4 & TSH; TSH < 2.5 µg/L, TSH < 5 µg/TL | RIA |
| Antonozzi et al. (19)   | Italy       | 1978       | 1:747        | 0.38      | 25400         | TSH              | RIA                 | Permanent: 1:000; | |
| Low et al. (75)         | Hong Kong   | 1982-84    | 1:2058       | 5.4       | 14411         | Cord TSH 15      | HBHA                | False positive |
| Pharngh et al. (77)     | England     | 1988-89    | 1:0370       | 0.1       | 89365         | TSH 5            | -                   | False positive [3], Sensitivity = 100%, Specificity = 98% |
| Yordam et al. (79)      | Turkey/pilot| 1989-92    | 1:2726       | 2.3<0.10; 2.5<0.15 | 361997 | TSH 20 & 25 | HBHA                | False positive |
| Constantine et al. (78) | Italy/Catalia| 1990       | 1:0599       | 0.09; 14.6 | 23704 | TSH TSH: 20; TSH: 5 | DELFIA            | Inadequate deficiency |
| Antonozzi et al. (75)   | Italy/Calabia| 1993       | 1:1599       | 0.09; 14.6 | 23704 | TSH TSH: 20; TSH: 5 | DELFIA            | Inadequate deficiency |
| Joseph et al. (76)      | Italy       | 1994-95    | 1:3000       | 15; 0.15  | 22030         | Cord TSH/TSH before discharge 25; 20 | Chemoluminomoe (90th percentile value of normal population) |
| Wu et al. (77)          | Malaysia    | 1995       | 1:3666       | 2.27      | 11000         | Cord TSH 20      | DELFIA              | -                      |
| Klett et al. (69)       | Germany     | 1995-96    | 1:3215       | 0.2       | 52697         | TSH 10 x 10      | HBHA, HBHA, RIA, ELIZA |
| Mikelsaar et al. (82)   | Estonia     | 1996       | 1:2860       | 3.3       | 20021         | TSH 12            | DELFIA              | -                      |
| Mahachoklert-Wattana et al. (83) | Thailand | 1995-98    | 1:2949       | 11; 10; 09; 50 | 35250 | Cord TSH 20 | HBHA                | -                      |
| Lee et al. (78)         | Korea       | 1999-2001  | 1:2000       | 1.27      | 20070         | TSH 20            | HBHA                | False positive [5], PPV = 91.5, NPV = 96.4 |
| Olszok et al. (79)      | Italy       | 2000-2002  | 1:1583       | 0.25      | 99580         | TSH 25            | HBHA, ELIZA         | -                      |
| Stein et al. (80)       | Italy       | 2000-2002  | 1:2562; Transient: 1:02022 | 1.6 | 18105 | TSH 10 x 10 | HBHA, ELIZA         | -                      |
| Ng et al. (81)          | Malaysia    | 2000       | 1:3065       | 5; 13; 5 ; 9; 0.4; 10; 0; 0.25; 0.05 | 6421 | TSH 5 | DELFIA |
| Dabous et al. (82)      | Egypt       | 2000-2003  | 1:3074       | 0.04      | 17088 | TSH 20 | - | False positive [5], PPV = 91.5, NPV = 96.4 |
| Zaffanello et al. (83)  | Italy       | 2002-2003  | 1:165        | 1.05      | 24901 | TSH TSH: 20; TSH: 40 | HBHA |
| Manglik et al. (84)     | India       | 2000-2004  | 1:1300       | 7; 2; 10; 1.8; 20; 1.0; 9.5; 10; 0.6; 11; 0.06 | 62000 | Cord TSH 20 | RIA Enzyme immunoassay |
| Rendon-Macias et al. (85) | Mexico     | 2002-2004  | 1:2315       | 0.04      | 277782 | TSH Cord 30 | HBHA, ELIZA |
| Ogunkeye et al. (86)    | Saudi Arabia| 1990-2006  | 1:2930       | 3.4       | 143123 | Cord TSH 30 | DELFIA |
| Kreiner et al. (87)     | Bangladesh  | 2000-2006  | 1:2930       | 3.4       | 143123 | Cord TSH 30 | DELFIA |
| Rusnak-DeWitt et al. (88) | USA | 1995-2001  | 1:2946       | 1.07 with cut off of; 0.75 with cut off 0.6 | 420042 | TSH 10 & 12 | DELFIA |
| Amini et al. (89)       | Iran        | 2002-2005  | 1:3500       | 2.2; 0.6  | 28453; 52515 | T4, TSH; TSH < 6.5 µg/L | HBHA, RIA, T4 |
| Tahirovic and Toromanovic (90) | India   | 2000-2007  | 1:3957       | 0.06      | 87 | TSH 20 | DELFIA |
| Gjirkova et al. (91)    | Macedonia   | 2002-2007  | 1:2804       | 0.3       | 70314 | TSH 15 | DELFIA |

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| Reference | Country | Time Period | Study Design | TSH Dilution | TSH Analyzed | Technique | Notes |
|-----------|---------|-------------|--------------|--------------|--------------|-----------|-------|
| Kusdal et al. (101) | Turkey | 2009-2010 | 1:650 | 13.3 | 25188 TSH | ELISA | - |
| Dillili (102) | Turkey | 2008-2010 | 1:649 | 2.6 | 3223765 TSH | ELISA | - |
| Kocova et al. (106) | Macedonia | 2002-2013 | 1:2591 | 0.15 | 20507 TSH | DELFIA | - |
| Veisani et al. (107) | Iran | 2002-2013 | 1:1682 | 0.69 | 75261 TSH | Chemoluminescence | False positive (TSH < 13.5) |
| Dorreh et al. (105) | Iran | 2006-2012 | 1:307 | 4.8 | 12702 TSH | ELISA | False positive (TSH > 40) |
| Veisani et al. (107) | Iran | 2002-2013 | 1:500 | 0.014 | 1425124 TSH | DELFIA | - |