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Laboratory-Based Evaluation of the Newborn Screening Programme: A 25-Year Retrospective Study.

Mohammed Salah Bin Suhayl Alosaimi
Specialist-Laboratory.

Mufarreh Ali Saeed Alamri
Lab Technician.

Mohammad Yahya Abdou Jabari
Laboratory Technician.

Emad Yahya Mushabbab Al Jarah
Technician-Laboratory.

Abdulrahman Theeb Alqahtani
Respiratory therapy technician.

Abstract:

As part of an integrated public health program with centralized coordination, the German federal state of Bavaria introduced newborn screening (NBS) utilizing dried blood spots (DBS). The Bavarian NBS Center works with parents, specialized centers of competence, obstetric and pediatric hospitals, and NBS laboratories. Coordination, assessment, quality control, and a long-term follow-up research fall under its purview. An examination of NBS in Bavaria is provided in this paper, along with a long-term follow-up that was treated early because of NBS. A 99.83% NBS coverage rate was attained, and 99.09% of all repeat tests that were requested were finished. Within the first 14 days of life, over 87% of newborns with time-sensitive illnesses received a therapeutic intervention. Systematic tracking allowed for the timely diagnosis of 122 babies and the clarification of all but 54 NBS-positive results. The long-term follow-up study's findings show that nearly every child found through NBS receives continuing medical care and that NBS has helped the majority of impacted children develop in an appropriate age manner. This 25-year assessment of NBS in Bavaria demonstrates that centralised coordination and continuous collaboration among all stakeholders can lead to nearly universal NBS participation and follow-up of nearly all positive NBS results.

Keywords: Laboratory, Newborn, Evaluation, Bavarian Screening, Retrospective Study.

Introduction

One of the most successful population-based secondary prevention strategies is the use of dried blood spots (DBS) for newborn screening (NBS) for specific target disorders. High neonatal

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coverage, thorough follow-up of all positive results, early diagnosis, and timely medical attention for afflicted infants are all necessary for an NBS to be successful. To avoid serious health implications including permanent impairments or death, early detection of NBS problems is essential (Hoffmann et al., 2014).

In Germany, babies have been screened for congenital hypothyroidism and galactosemia since the early 1980s, as well as phenylketonuria (PKU) since the late 1960s. A wider range of conditions can now be screened for thanks to the development of tandem mass spectrometry (MS/MS) and other cutting-edge analytical methods. A pilot project called "Expanded Newborn Screening in Bavaria" was carried out in the German federal state of Bavaria from 1999 to 2003 to evaluate these analytical techniques, identify the best practices, and assess the incorporation of additional conditions into NBS using the screening criteria developed by Wilson and Jungner (Jansen et al ., 2017).

During the first three days of life, all newborns in Bavaria were to be screened for 20 inborn errors of metabolism (IEMs), hypothyroidism, and congenital adrenal hyperplasia as part of this experimental initiative. Only two endocrinological situations and ten of the IEMs satisfied the specified NBS criteria, according to the project's review. These standards were not fulfilled for the other circumstances in terms of either enhancing health outcomes or meeting the requirements for analytical quality (specificity and sensitivity). NBS was launched as a comprehensive program that covered a lot more ground than just laboratory testing during the pilot phase. Within the scope of "Public–Private Partnership," the idea entailed tight cooperation between private laboratories, Bavarian specialized centers of competence (mostly university children's hospitals), and the public health service (González, 2021).

The national Federal Joint Committee (Gemeinsamer Bundesausschuss) decided to include an expanded NBS program in the national Paediatrics Directive (Kinder-Richtlinie) and, consequently, in the benefits catalogue of the statutory health insurance funds across Germany, with effect. This decision was based on evidence from publications in the pertinent scientific literature, the outcomes of the Bavarian pilot project, and position statements from the German Society for Paediatrics and Adolescent Medicine's Screening Committee. Following this, within the first three days of life, every infant in Germany was required to be administered NBS for an initial panel of twelve target conditions. In the meantime, 17 target conditions have been added to the panel. Approximately one infant out of every 730 examined newborns had one of the 17 target conditions (Cornel et al ., 2013).

The unique characteristics of NBS in Bavaria are highlighted in this paper. These include a complete program, a centralized approach, thorough tracking, and long-term follow-up.

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Materials and Methods:

NBS Process:

Parents must first be made aware of the NBS and give their written consent (informed consent) for the screening. After obtaining consent, a newborn's blood sample is drawn between 36 and 72 hours of life, recorded on a Dried Blood Spot (DBS) card, and submitted to an NBS-accredited laboratory (NBS laboratory). Blood should be drawn for screening in advance if the infant is treated in a way that could impact the NBS results or is released from the hospital during the first 36 hours of life. Following analysis, the laboratory reports the NBS results to the person who sent the DBS card, usually the obstetrician.

Laboratory Analysis:

The Paediatrics Directive governs the specificity of laboratory diagnoses for NBS, which generally follow globally recognized analytical procedures. Fluorescence immunoassay, biotinidase deficiency using fluorimetric activity determination, galactosemia using enzymatic determination of total galactose following cleavage of galactose-1-phosphate, and fluorimetric determination of galactose-1-phosphate uridyltransferase are used to screen for hypothyroidism and CAH. MS/MS is used to screen for various IEMs, and quantitative or semi-quantitative polymerase chain reaction (PCR) is used to measure TRECs for severe combination immunodeficiencies (SCID). High-performance liquid chromatography (HPLC) or PCR are used for sickle cell disease (SCD) screening, whereas PCR is used to identify homozygous SMN 1 gene deletions for 5q-associated spinal muscular atrophy (SMA).

The Bavarian NBS Center's duties include conducting NBS in the German federal state of Bavaria in compliance with German NBS laws. Additionally, additional operational procedures and organizational frameworks are provided by the central public health NBS Center .

Ensuring Complete Coverage:

The screening laboratories send screening data to the NBS Center over a secure connection with parental approval. Since 2020, the Bavarian Municipal Data Processing Agency has also been providing weekly birth data to the NBS Center. The screening records and these birth data are then automatically matched. When a parent's child's screening records are missing, the NBS Center gets in touch with them in compliance with Bavaria's legally required health preventative counseling laws (Nennstiel , 2015).

Newborn Screening Using dried blood spots worldwide:

As advised by the WHO, EU experts, and other publications, newborn screening (NBS) using dried blood spots (DBS) is carried out globally, but in some nations, including Germany, it has not been incorporated into an integrated public health program with centralized coordination. For the past 25 years, NBS has been run as a program in Bavaria, with coordination, quality

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control, and evaluation handled by the Public Health Service's central NBS Centre. The excellent caliber of the Bavarian NBS program is guaranteed by the efforts of the NBS Center and the analytical know-how of the NBS laboratories. Nearly total coverage and resolution rates were attained by the NBS Center's persistent tracking efforts. Furthermore, the introduction of new target diseases and the execution of a center-independent, population-based long-term study were made possible by the NBS Center's committee's work and collaboration with disease experts, laboratories, and other stakeholders (Therrell et al ., 2015).

Experiences from 25 Years of the Bavarian Newborn Screening Programme:

After an initial development period with a somewhat lower percentage in the early years, Bavaria achieved a high NBS coverage rate that regularly above 99.8%. About 150 babies are diagnosed with an NBS condition annually, based on an annual birth cohort of approximately 110,000 and a prevalence of roughly 1 in 730 for the 17 illnesses currently screened. This suggests that if NBS coverage fell below 99.3%, one case would be missed annually in Bavaria alone, according to statistics. Due to the possibility of permanent impairments, untreated instances have significant health and financial ramifications in addition to the preventable pain experienced by the afflicted persons and their family. Thus, it is still crucial to guarantee full involvement in this public health initiative.

Processing Times: In the Bavarian NBS program, systematic tracking allowed for the initiation of treatment within the first 14 days of life for roughly 87% of infants with time-sensitive conditions, whereas in Germany, 79% of children receive treatment within the first two weeks of life. However, there are reports of 17 cases where metabolic decompensation has place before positive screening results could be shared, making prevention impossible. Even in well-established NBS programs with early blood collection between 36 and 72 hours and meticulous tracking, these events as well as electrolyte abnormalities in CAH seem inevitable in some circumstances and are well-documented in the literature (Kemper et al., 2019; Maier et al., 2023).

Bavarian NBS Program Quality Criteria:

Although reassuring rates differ by illness and biomarker level, excellent analytical quality allows the suspected diagnosis to be fully ruled out in about two-thirds of instances with positive screening results with repeat testing or confirmatory diagnoses. The PPV was greater than 71.43% in cases where the NBS laboratory reported strong indications for an NBS target condition, meaning that two-thirds of these cases were verified as genuine positives. This made it possible to decrease the number of confirmatory tests needed as well as needless concern among families. When compared to other public health screening programs, such as newborn hearing screening, where PPVs of 1.5% and 4.2% have been documented, these results show promise (Mütze et al ., 2020; Nennstiel, 2023).

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Positive NBS Results and Confirmatory Diagnostics:

Early in the development of the Bavaraian NBS program, university hospitals in Bavaria were participating. This made it possible to designate specialized centers of knowledge for every target condition according to predetermined standards. These centers have completed more than 70% of confirmatory tests early on and collaborate closely with the NBS Center and the partner NBS laboratories. The NBS program's success depends on this structure and the close collaboration, which guarantee prompt and guideline-compliant confirmatory diagnostics of positive screening results, early therapy initiation when needed, and professional, communicative support for families right from the start. This is particularly crucial for the extremely uncommon NBS goal conditions. The creation of these centers is in line with the European Council's strategy on rare diseases (Gramer et al., 2018; Wilson, 2021).

In the context of NBS, positive laboratory results may indicate a problem that has to always be further studied during a recall process; in theory, however, they do not permit a conclusive diagnosis. With parental approval, it is thought to be best for a specialized center to notify parents of a positive NBS result first. This method, which has long been a popular practice in Bavaria, has been shown in numerous studies to assist earlier identification and lessen parental anxiety. Comparing the 2024 edition of the German Pediatrics Directive to earlier versions, the NBS notification procedures were improved. The initial notification of positive NBS results to parents directly through specialized centers was not included in the current Paediatrics Directive, and as a result, it has not yet been implemented nationwide throughout Germany, despite the evidence and clear recommendations of the German Genetic Diagnostics Commission (Liebl et al., 2002; Lüders et al., 2018).

Recommendations:

Strengths and Limitations:

In conclusion, the long-term follow-up study's findings show that almost all Bavarian children identified by NBS receive continuing medical attention and therapy, and that NBS has helped the majority of impacted children develop normally. Specific diagnoses and individual situations are subject to limitations. Nevertheless, the results also point to enduring issues that need further focus. The NBS Center has occasionally been able to react appropriately by working with specialized centers of expertise and screening labs. Assistance from child and adolescent welfare agencies can be essential for excellent treatment results for children from families with additional support requirements. With families' permission, an NBS Center helps with this process by keeping in constant contact with them.

- The Bavarian study's population-based design, which includes an 18-year observation period and a significant amount of data gathered directly from impacted families rather than only from healthcare records, is one of its unique strengths. This strategy helps achieve a high

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participation rate, initially surpassing 90% and staying around 80% over time, even if it may have drawbacks in terms of data validity. Results were highly concordant when compared to those of the multicenter Southwest German research, which included clinical evaluations.

- These findings cast doubt on the widely accepted notion that outcomes reported by parents or patients are inevitably biased or incorrect, indicating that validated and standardized parent or patient surveys might offer a realistic enough depiction of the situation. Thus, a low-threshold, economical approach to program evaluation is the combination of questionnaires and medical records. It is reasonable to expect selection bias even with the high participation rate.

For in-depth clinical themes, individual evaluation, and risk stratification of illness development and consequences, clinical examinations are still essential. There will soon be more papers that provide in-depth analysis of the Bavarian long-term data on particular target conditions. Despite the population-based strategy and high participation rates, the conclusions are constrained by small sample sizes within subgroups due to the rarity of all NBS target conditions. This emphasizes the necessity of patient registries and collaborative follow-up studies that are interregional or worldwide.

Conclusion:

Near-universal participation and thorough follow-up of positive NBS results are made possible by the idea of NBS as a comprehensive program that integrates a central NBS Centre for coordination, quality assurance, and evaluation in close collaboration with screening laboratories and specialized centers, as shown by the findings of this 25-year evaluation of NBS in Bavaria. High NBS coverage rates, positive NBS clarification, and early treatment initiation for Bavarian children were made possible by the NBS Center's intervention. The effort required to determine the cause and speak with the relevant entity directly was generally rewarded in situations like test card loss, the omission of NBS or requested repeat screening tests, or delayed shipping. Systemic adjustments could be suggested if consistent, targeted quality measures turn out to be ineffective. The benefits of quality management and tracking techniques are illustrated by the advancements made possible by the Bavarian NBS program following the first few years and by comparisons with NBS data from other parts of Germany. These tactics have potential if they are put into practice, coordinated according to the current systems, and ideally assisted by digital tools.

The population-based long-term follow-up study's findings show that almost all of the Bavarian children identified by NBS receive continuing medical attention and therapy, and that NBS has helped most impacted children develop normally. These results show the substantial advantages of NBS for impacted kids and their families, but they also draw attention to current issues and the need for more study.

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