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Economic evaluation of newborn deafness gene screening as a public health intervention in China: a modelling study

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ABSTRACT

Background While global newborn hearing screening programmes (NHSP) are far from the optimal level, the combined hearing and genetic screening has emerged as an innovative approach of early healthcare interventions. There is a clear need for economic evaluation to establish whether newborn deafness gene screening (NDGS), currently mandated by many cities in China, is a good investment.

Methods A decision-tree model was constructed to simulate a hypothetical 10-million Chinese newborn cohort over a lifetime with three strategies: (1) no screening, (2) NHSP (standard screening) and (3) NHSP+NDGS (combined screening). The presence of permanent congenital hearing loss (PCHL) and genetic mutation were assigned at birth and held constant for all strategies. Input parameters were obtained from the Cohort of Deafness-gene Screening study and literature review. The government contract price for genetic screening was US$77/child. Outcomes of interest included the number of early diagnosed PCHL, prelingual deafness, total deafness, special education referral, incremental cost-effectiveness ratio (ICER) and benefit–cost ratio (BCR).

Results Both standard and combined screening strategies were more effective and more costly than 'no screening'. Compared with standard screening, combined screening led to 9112 (28.0%) more PCHL cases early detected, avoiding 4071 (66.9%) prelingual deafness cases and 3977 (15.6%) special education referrals. The ICER and BCR for combined screening were US$ 4995/disability-adjusted life-year (95% uncertainty interval, 2963 to 9265) and 1.78 (1.19 to 2.39), from healthcare sector perspective. Combined screening would dominate standard screening from societal perspective. Moreover, it remained cost-effective even in pessimistic scenarios.

Conclusions Our findings have particular implication for the 'scale-up' of genetic screening at the national level in China. The model may serve as a feasible example for hearing screening strategies in other countries, as well as genetic screening for other diseases.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The global newborn hearing screening programmes are far from the optimal level.
⇒ Combined hearing and genetic screening has emerged as an innovative approach of early healthcare intervention.

WHAT THIS STUDY ADDS

⇒ We for the first time modelled the costs of implementing a combined screening programme compared with its potential to mitigate the long-term impact of hearing loss.
⇒ Combined screening strategy could be highly cost-effective in China.
⇒ Combined screening strategy remained the most cost-effective even at higher price, lower willingness-to-pay threshold or limited resource allocation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study has particular implication for the 'scale-up' of genetic screening at national level in China.
⇒ Our framework may provide valuable implications for hearing screening strategies in other countries, as well as genetic screening for other diseases.

INTRODUCTION

Given the auditory dominance of personal communication, hearing health has implications for an individual's well-being on the socioecological levels. Hearing loss (HL) has been ranked as the third-leading cause of years lived with disability (YLD) in the Global Burden of Disease Study 2019.[1] WHO estimated that approximately 430 million people (5.5% of the world's population, including 34 million children) were living with disabling HL.[2] Permanent congenital HL (PCHL) affects 1–6 of every 1000 live born infants

(pooled prevalence 2.21‰ in a meta-analysis)[3] and has negative impacts on their quality of life, education and employment, as well as the healthcare systems.[4] Lifetime costs for those with prelingual deafness exceeded US$1 million in the USA.[5] At least 50%–60% of the newborns with PCHL have a genetic cause.[6] Early diagnosis and audiologic intervention (eg, hearing aids (HA) or cochlear implants (CI)) could mitigate the influence of PCHL on developmental milestones such as speech and language acquisition.[7] Special education has become commonplace ways of providing curriculum to meet the needs of children with disabling HL who may not benefit from regular education.[8]

Current universal newborn hearing screening programmes (NHSP or standard screening) have been implemented successfully to reduce the age of diagnosis and intervention of PCHL.[9–11] However, the otoacoustic emission (OAE)-based protocol is far from optimal. It has relatively low sensitivity (detection rate) and does not determine the aetiology of the HL. NHSP could identify approximately 71%–92% of all children born with PCHL.[12] Detection of deafness-associated gene mutations has the potential to augment NHSP, by identifying additional PCHL cases.[13] Understanding the molecular aetiology of the newborn's HL may encourage timely follow-up and treatment. Moreover, recognition of mitochondrial mutation (ie, mitochondrial encoded ribosomal RNR 1, MTRNR1) carriers has clinical implications for the prevention of aminoglycoside-induced HL (AIHL).[14] Meanwhile, researches exploring the ethical and social implications of clinical genetic screening are ongoing.[15]

Newborn deafness gene screening (NDGS) is not a novel concept in China.[16] Over the past decade, genetic testing has become an integral diagnostic component of paediatric medicine and been incorporated into expanded NHSP in many cities (37 pilot cities in 22 provinces, funded by the local government, online supplemental figure S1A).[17–21] As of the end of 2021, the number of newborns screened by hereditary deafness genetic testing products exceeded 10 million in China (estimated 5 million with CapitalBio products, see https://www.capitalbio.com/gxba/xwzx/gsxw/2020nsjd/28652.shtml.htm; 5 million with BGI products, through communication with Dr Peng ZY from BGI Genomics, Shenzhen, China), but with uncertain benefits and costs. It has been suggested that NDGS should be incorporated the expanded NHSP, but there is still no consensus on the national strategy in China. One of the most serious barriers to the implementation of universal NDGS is the enormous initial cost involved in such a large-scale screening programme. Thus, there is a clear need for the research on long-term costs and outcomes to establish the cost-effectiveness of combined screening programme in relation to the standard screening programme, and to evaluate whether it is a good investment.

PubMed was searched for cost-effectiveness studies of NDGS published up to 1 August 2023, using the terms ("deafness gene" OR "GJB2" OR "SLC26A4" OR "MTRNR1") AND ("newborn" OR "neonatal" OR "neonate" OR "infant") AND ("screening" OR "detection") AND ("economic evaluation" OR "cost-effectiveness" OR "cost-utility" OR "cost-benefit"). The search returned zero results, indicating a lack of economic evaluation of NDGS not only in China but throughout the world. To address the evidence gap, we aim to develop a decision-analytical model that incorporates the transition of HL statuses and makes extensive cost-effectiveness estimates for the combined newborn hearing and genetic screening programmes in China.[22] This study may provide evidence-based policy recommendations to the decision-makers.

METHOD

Data source and study design

The data source of this study included data collected from previous studies conducted by the research team, such as a city-level cohort study of combined newborn hearing and genetic screening,[23] a national survey on the current status of genetic screening,[16] and an economic evaluation for standard screening in eight provinces.[24] Additionally, data from multiple sources, including published studies, unpublished reports and expert opinions, were retrieved for analysis.

In Nantong, a city in east China near Shanghai, combined newborn hearing and genetic screening, was mandated by the local authority in 2014. As part of the government programme, the research team conducted the Cohort of Deafness-gene Screening (CODES) study. This study was retrospectively registered on https://register.clinicaltrials.gov with the ID number NCT06133946. Infant participants were screened for 15 variants in four genes (GJB2, SLC26A4, MT-RNR1 and GJB3) from January 2016 to December 2020. The MT-RNR1 gene mutation served as a genetic biomarker which helps in making informed decisions regarding the use of aminoglycoside antibiotics. The proportion of pathogenic mutations within the three other genes (GJB2, SLC26A4 and GJB3) was used to determine the sensitivity and specificity of the combined screening programme. These infants were followed up for at least 2 years. Among the total of 39 923 infants screened, 35 920 infants completed the follow-up and were included in the analysis. The study map and workflow diagram are reported in online supplemental figure S1B,C.

The research team sent a 'newborn deafness gene screening questionnaire' to 41 institutions in eastern, central and western China. The questionnaire aimed to collect information on the status, methods, total number and positive detection of genetic screening conducted from January 2016 to December 2017. The responses to the questionnaire were summarised in one of the research team's previous studies.[16]

For the economic evaluation study, a decision-tree model-based simulation, was performed using data from

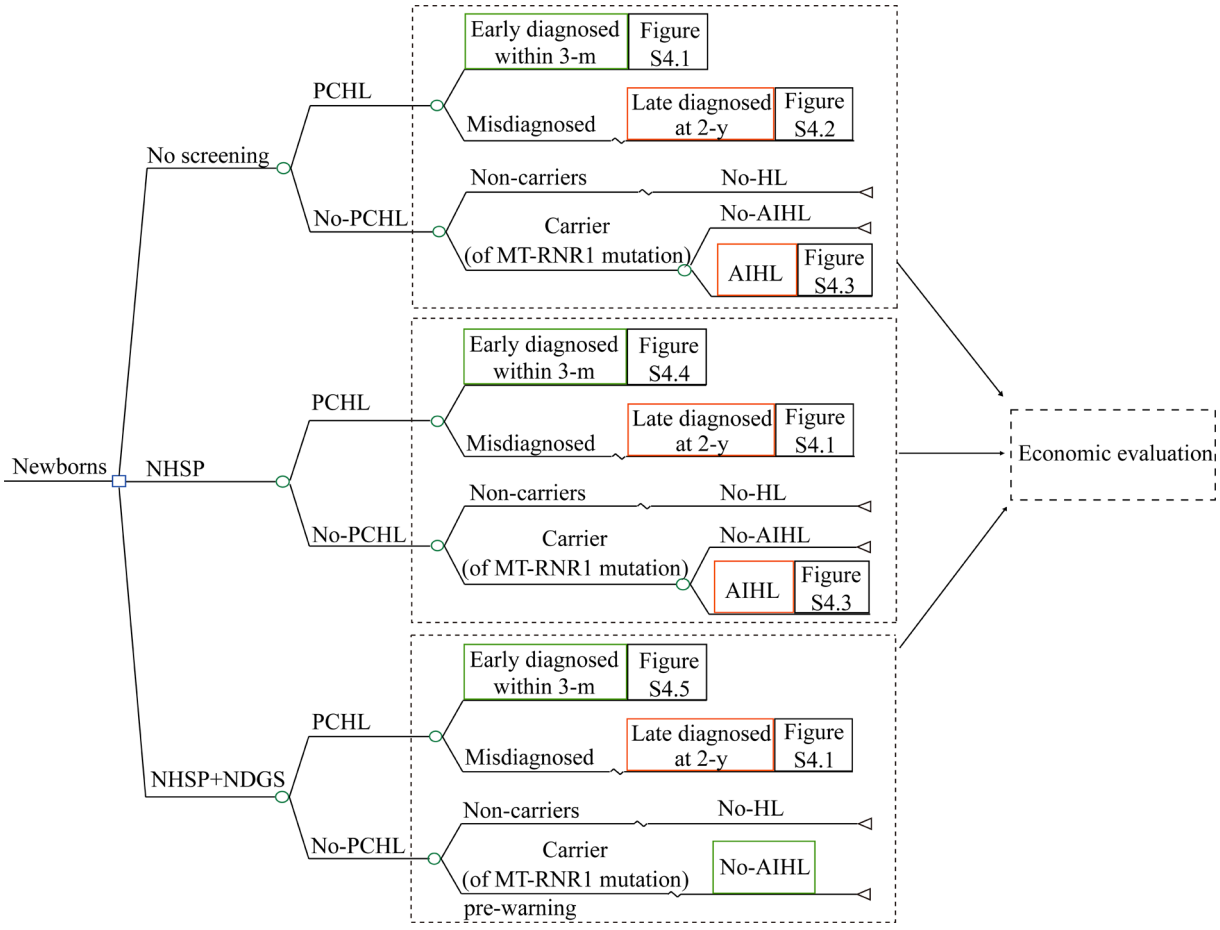

Figure 1 Flow chart illustrating the economic evaluation simulation of newborn hearing screening strategies. The decision-tree models were used to project the outcomes of diagnosing permanent congenital hearing loss (PCHL) early, within 3 months, or later, at the age of 2 years, as well as aminoglycoside-induced hearing loss (AIHL). Detailed visuals of the tree models can be found in online supplemental figure S4.

the cohort study and literature review. The flow chart of the study design is presented in online supplemental figure S2.

Decision model

TreeAge Pro 2022 (TreeAge Software, Williamstown, Massachusetts, USA) was employed to construct a decision-tree model. This model was designed to project the progression of HL in a hypothetical 10 million newborn cohort in China. As per the data from the National Bureau of Statistics for 2021, the number of births was recorded at 10.62 million. The following three strategies were assessed: (1) no screening, (2) NHSP (standard screening, which is currently the policy in China) and (3) NHSP+NDGS (a combination of the standard screening and genetic screening). Under the 'no screening' strategy, the identification of HL could happen by chance, such as when parents notice hearing problems in their child and seek testing. However, selective screening strategies targeting high-risk groups were not considered in this study because they are generally not favoured when universal screening is an option. The core structure of the model is depicted in figure 1, with the assumptions for model parameters detailed in table 1 and online supplemental table S2. A conceptual outline representing the screening strategies, treatment options and monitoring within the model is found in online supplemental figure S3. Detailed referral pathways leading to all possible outcomes (terminal nodes) within the model are illustrated in online supplemental figure S4 and described in online supplemental table S1. During the model development process, a panel of experts with diverse specialisations—including otology, paediatrics, genetics, health economics and statistics—reviewed the model, contributing their expertise to its refinement.

The model considered the entire lifespan as its time frame. The model assigned the probability of PCHL at birth and intervention courses following a diagnosis. The baseline incidence rates of PCHL (0.45%) and carrier status for genetic mutations like the MT-RNR1 carrier rate (0.29%) were consistent across all strategies. Early diagnosis was categorised as PCHL detected within the first 3 months after birth, while a late diagnosis was defined as identification at 2 years of age. The NHSP and NHSP+NDGS strategies had early diagnosis rates of 72.4% and 92.6%, respectively, while the 'no screening' strategy

Table 1 Key input parameters used in the simulation of three strategies for newborn hearing screening

Input	Base-case value	Range for 1000 simulations	Range for sensitivity analysis	Data source
Population simulated				
Cohort size	10 000 000			
Prevalence of PCHL	0.0045	0.0039–0.0053	0.0005–0.005	CODES study, ref[37]
Prevalence of MT-RNR1 carrier	0.0029	0.0023–0.0034	0.0014–0.007	CODES study, ref[38]
Screening strategies				
Detection rate				
NHSP	0.724	0.649–0.791	0.65–0.80	CODES study
NHSP+NDGS	0.926	0.887–0.996	0.80–1.0	CODES study
No screening (opportunistic)	0.2	0.1–0.2	0.1–0.3	[25]
Cost of procedures (US$)				
OAE (first stage of NHSP)	20		±20%	CODES study, ref[39]
AABR (second stage of NHSP)	40		±20%	CODES study, ref[39]
ABR+ASSR (third stage of NHSP or diagnosis)	32		±20%	CODES study, ref[39]
NDGS (government contract price)	77		0–150	CODES study
Interventions				
Coverage				
Hearing aid (HA)	0.7		0.2–1	CODES study, ref[29 40]
Cochlear implant (CI)	0.5		0.1–1	CODES study, ref[29 40]
Cost of procedures (US$)				
HA equipment	3000		±20%	CODES study, ref[29 40]
HA maintenance (including annual fitting, rehabilitation)	300		±20%	CODES study, ref[29 40]
CI surgery (including device)	30 000		±20%	CODES study, ref[29 40]
CI maintenance (including annual fitting, rehabilitation)	500		±20%	CODES study, ref[29 40]
HL follow-up (per visit)	32		±20%	CODES study, ref[39]
Disability weight				
Mild to moderate	0.027		0.015–0.042	[1]
Moderately severe	0.092		0.064–0.129	[1]
Severe to profound	0.204		0.134–0.288	[1]

AABR, automated auditory brainstem response; ABR, auditory brainstem response; ASSR, auditory steady state response; CODES, Cohort of Deafness-gene Screening; MT-RNR1, mitochondrial encoded ribosomal RNR1; NDGS, newborn deafness gene screening; NHSP, newborn screening programme; OAE, otoacoustic emissions; PCHL, permanent congenital hearing loss.

had an assumed opportunistic detection rate of 20%.[25] The frequency of severe or profound (S/P) HL differed under each strategy and was portrayed in online supplemental figure S4. Although individuals can be exposed to aminoglycosides at any age, the model assumed the first exposure at an average age of 6 years, with a risk of exposure at 7.3%.[26] Recognising mitochondrial mutations may help bypass AIHL. Review of literature and expert opinion, due to a paucity of direct data, aided in estimating the probabilities of transition between hearing statuses. It was postulated that children identified with mild or moderate PCHL have a 50% likelihood of their condition worsening to S/P HL by 6 years of age.[27] The status of moderately severe HL would develop only with audiologic procedures such as HA or CI. Referrals to special education depended on thorough audiologic and language assessments as outlined in online supplemental table S1.

The main health outcomes investigated were the count of early diagnoses and interventions, the frequency of prelingual and overall deafness, and referrals to special education programmes.

Cost and economic analyses

An evaluation of costs was performed from two perspectives: the healthcare sector (covering only direct medical

expenses) and the broader societal perspective (encompassing direct medical, direct non-medical and indirect costs). Costs were expressed in 2021 US dollars, with the exchange rate being US$1 to CN¥6.5. Estimates were primarily drawn from the CODES study, comprising screening and healthcare services expenses. The costs associated with the standard screening programme were fairly modest, as outlined in table 1. This could be attributed to several factors: (1) equipment portability and user-friendly design; (2) lower equipment costs and minimal space requirement; (3) training simplicity and scalability; (4) use of existing staff and potential for task sharing and (5) integration into routine care.[28] The government contract price of US$77 per child for genetic screening was made up of several components, including US$40 for the deafness genetic screening test kit, US$6 for blood sample collection, US$2 for the DNA extraction, US$9 for equipment utilisation and depreciation, US$10 for quality control, US$10 for report and genetic counselling (table 1). Recurring expenses linked to HAs, CI procedures, fittings and subsequent rehabilitation were gleaned from the cohort investigation and supplementary external research.[9 29] From societal perspective, we considered the travel costs and productivity loss borne by parents. Calculations for lost productivity costs of the HL patients accounted for in-depth understanding of language, as well as medical and educational outcomes, as illustrated in online supplemental table S3. Health outcomes and the burden of illness were quantified in terms of disability-adjusted life-years (DALYs), with the DALYs attributed to HL determined by adding the YLDs to the average lifespan expectation of 78 years, given that HL is not lethal. Both the costs and DALYs were subjected to an annual discount of 3%.

In our cost-effectiveness analysis (CEA), we calculated two types of cost-effectiveness ratios anchored in distinct health outcomes: (1) average cost-effectiveness ratios (ACERs), which quantify the average cost of screening for each additional case of effectiveness, calculated by the screening cost for each child multiplied by the number needed to screen (NNS) to detect one more case of PCHL, avoid an instance of deafness or circumvent a special education referral; (2) incremental cost-effectiveness ratios (ICERs), determined by the incremental cost per one DALY prevented. The willingness-to-pay (WTP) threshold was established as US$12 458—equivalent to China's gross domestic product per capita in 2021—for each DALY averted. A screening method was termed 'dominant' if it managed to prevent more DALYs at a reduced overall cost.

Cost–benefit analysis (CBA) was also carried out to evaluate the economic viability and appeal of the proposed screening strategy. This process entailed tabulating crucial financial figures like the benefit, the net benefit (NB) and the benefit-to-cost ratio (BCR). Concrete valuations were assigned to these benefits, reflecting both treatment cost reduction and the monetised value of averted DALYs. The NB was ascertained by subtracting the augmented screening costs from the accumulated benefits. To calculate the BCR, the projected benefits were divided by the projected costs.

The documentation of this economic assessment adhered to the Consolidated Health Economic Evaluation Reporting Standards.[30]

Uncertainty analyses

In order to address uncertainty, we ran 1000 simulations where each parameter was selected from its respective probability distribution, and we presented the 95% uncertainty interval (UI) for all the base-case outcome measures. The sensitivity analyses included (1) one-way sensitivity analysis depicted through a tornado diagram that emphasised the 10 variables with the most impact; (2) two-way sensitivity analysis illustrated using a contour plot and (3) probability sensitivity analysis (PSA) displayed through a scatter plot alongside cost-effectiveness acceptability curves.

Scenarios analyses

We designed three scenarios to represent a range of less advantageous economic and clinical situations. The initial scenario was one where the costs were elevated, assuming a market price of US$105 per child for genetic screening. In the second scenario, we adopted a reduced WTP approach, setting the WTP threshold at 0.63 times the national gross domestic product (GDP) per capita, taking into account the trade-offs with other health needs.[31] The final scenario depicted a situation with constrained resources, characterised by reduced availability of HA, for instance, at 50% coverage, and CI, at around 30% coverage.

RESULTS

Improved outcomes in early detection and prevention of prelingual deafness with combined screening strategy

Both the standard and the combined screening approaches were found to be more efficacious than no screening at all, as depicted in figure 2 and outlined in online supplemental tables S4 and S5. With the standard screening, 32 576 cases of PCHL—which is roughly 3.6 times the number identified without any screening—were diagnosed early, with a 95% UI between 27 005 and 38 869 cases. Furthermore, when compared with standard screening, combined screening identified an additional 9112 PCHL cases (95% UI 5717 to 12 748), resulting in an increase of 28.0% (95% UI 16.7% to 42.6%) in early detections. Early treatment following diagnosis was more common in the screening strategies, with 78.9% receiving early HA and 60.3% receiving early CI in the standard screening strategy, and these proportions were even higher in the combined screening strategy at 94.4% for HA and 81.9% for CI. In contrast, the no-screening strategy showed only 18.4% for HA and 19.1% for CI. Subsequently, the combined screening strategy prevented 4071 cases of prelingual deafness (95% UI 2924 to 5296), which is a 66.9% reduction (95% UI 54.0% to 76.8%)

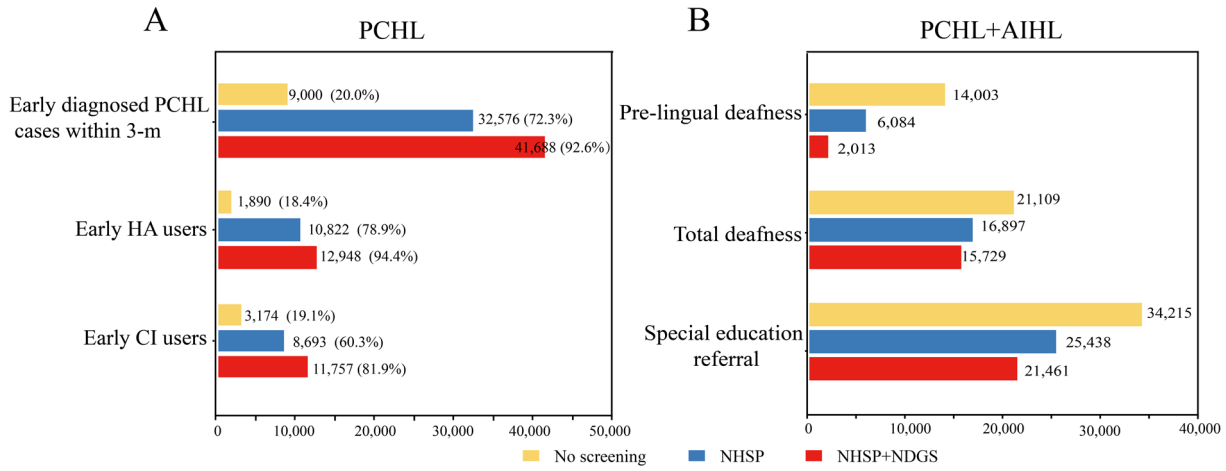

Figure 2 Projected health outcomes from the newborn hearing screening strategies. The modelling study simulated the progression of hearing loss and the resulting health outcomes for a hypothetical 10 million newborns in China under three different strategies. The main health outcomes examined were the number (and proportion) of early diagnoses and interventions (A), the occurrence of prelingual and total deafness, and the number of special education referrals (B). AIHL, aminoglycoside-induced hearing loss; CI, cochlear implant; HA, hearing aid; NDGS, newborn deafness gene screening; NHSP, newborn hearing screening programmes; PCHL, permanent congenital hearing loss.

compared with standard screening alone. It also reduced the incidence of total deafness by 1168 cases, indicating a reduction of 6.9% (95% UI 4.0% to 9.9%). Moreover, combined screening substantially reduced the number of students who needed special education, with the number dropping to 21 461 (95% UI 18 240 to 24 830), compared with 25 438 (95% UI 21 764 to 29 322) for those who received standard screening.

Economic value of combined screening strategy

For the combined screening method, the NNS to identify one additional case of PCHL by 3 months old was 1097 (95% UI 784 to 1749). We calculated the cost-effectiveness ratios of different screening strategies. The ACERs indicated that it cost US$84 469 (95% UI US$60 366 to US$134 692) to detect an additional early case of PCHL, US$189112 (95% UI US$145372 to US$2 169 013) to prevent a case of prelingual deafness, US$898 513 ((95% UI US$613 975 to US$1 635 051) to prevent a case of deafness in general, and US$193 578 ((95% UI US$146 217 to US$2 77 002) to avoid a referral for special education (online supplemental table S6). From the healthcare sector perspective, both screening strategies were more efficacious and costlier than no screening, resulting in ICERs of US$135 (95% UI −US$14 to US$314) and US$1239 (95% UI US$870 to US$1674) per DALY averted for standard and combined screening, respectively. Furthermore, when compared with standard screening, the ICER for the combined strategy was US$4995 (95% UI US$2963 to US$9265) per DALY averted (table 2), with assumed genetic screening costs of US$77 per child. Additionally, adopting the societal perspective, both screening strategies were favoured over no screening due to cost savings. Combined screening, compared with standard screening, saved costs amounting to US$35 522 635 (95% UI US$3 481 110 to US$69 584 767) and prevented 8618 (ranging from 5132 to 12 278) DALYs (considered dominant, online supplemental table S7).

CBA was also applied for decision-making. From the healthcare sector perspective, combined screening avoided 8619 (95% UI 5104 to 12 299) DALYs, with the benefits and NBs totalling US$146.59 million (95% UI US$98.01 to US$195.97 million) and US$64.42 million (95% UI US$15.87 to US$113.80 million), respectively, in comparison with standard screening. The BCR for the combined screening programme was 1.78 (95% UI 1.19 to 2.39) relative to standard screening (table 2). Furthermore, from the societal perspective, the combined screening provided greater benefits and NBs than standard screening and yielded a higher BCR of 2.74 (95% UI 1.81 to 3.67) (online supplemental table S7).

Implications of sensitivity and scenario analyses

We performed various sensitivity analyses to determine how changes in certain parameters might influence the ICERs. The tornado diagram revealed that the ICERs for the combination screening strategy were notably affected by several factors, including the cost of genetic testing, the detection rate, the prevalence of PCHL and gene mutations, and the use rates of HA and CI; these factors consistently figured among the 10 most impactful variables (figure 3A and online supplemental figure S5). Through the tornado diagram, we determined that the combined screening strategy would retain its cost-effectiveness so long as the genetic screening cost did not exceed US$140.1 per child, beyond which the standard screening strategy would be the favoured choice. Moreover, it is essential to keep three additional factors—the discount rate applied to utility and cost, the sensitivity of combined screening, and the prevalence of PCHL—within a certain scope. Should substantial fluctuations occur in any of these parameters, it might additionally influence the comparative analysis of cost-effectiveness

Table 2 Cost and economic analyses of the screening strategies, from healthcare sector perspective

	No screening	NHSP	NHSP+
Intermediate outcomes			
C (total cost, US$ million)	1168.34 (1002.61–1341.36)	1172.30 (1010.48–1340.44)	1215.25 (1051.99–1384.37)
$C_{screening}$ (screening cost)*	0.22 (0.19–0.24)	22.81 (22.67–22.94)	104.98 (104.83–105.12)
$C_{treatment}$ (treatment cost)†	1168.12 (1002.41–1341.12)	1149.49 (987.72–1317.66)	1110.27 (947.25–1279.23)
DALY	135 657 (116 472–156 354)	106 323 (91 016–122 664)	97 705 (83 212–112 588)
	NHSP versus no screening	NHSP+NDGS versus no screening	NHSP+NDGS versus NHSP
ΔC (incremental cost)	3.96 (-0.49–7.65)	46.91 (36.54–56.32)	42.95 (32.86–51.51)
$\Delta C_{screening}$ (incremental screening cost)	22.59 (22.47–22.72)	104.76 (104.62–104.90)	82.17 (81.98–82.34)
$\Delta C_{treatment}$ (treatment cost reduction)	18.63 (14.91–23.09)	57.85 (48.41–68.27)	39.22 (30.69–49.30)
ΔE (DALY averted)	29 334 (24 230–35 693)	37 952 (32 539–44 382)	8618 (5132–12 278)
Results of cost-effectiveness analysis			
ICER (ΔC/ΔE)	135 (-14–314)	1239 (870–1674)	4995 (2963–9265)
Results of cost–benefit analysis			
ΔB ($\Delta C_{treatment}$ + λΔE)‡	384.07 (316.93–467.89)	530.66 (457.55–616.77)	146.59 (98.01–195.97)
NB (ΔB–$\Delta C_{screening}$)	361.48 (294.33–445.24)	425.90 (352.94–512.02)	64.42 (15.87–113.80)
BCR (ΔB/$\Delta C_{screening}$)	17.00 (14.02–20.66)	5.07 (4.37–5.89)	1.78 (1.19–2.39)

Cohort size: 10 million infants. Costs and DALYs were discounted at 3% per year.
*The screening cost encompassed expenses for both screening and diagnostic processes.
†The treatment cost comprised expenses for treatment and rehabilitation (table 1).
‡The λΔE represented the monetised averted DALY benefit, with λ denoting the threshold of willingness-to-pay set at 1×national per capita gross domestic product of US$12 458.
BCR, benefit-cost ratio; DALY, disability-adjusted life-year; ICER, incremental cost- effectiveness ratio; NB, net benefit; NDGS, newborn deafness gene screening; NHSP, newborn screening programme.

between combined and standard screening strategies (figure 3A). According to the two-way sensitivity analysis contour plots, there were several conditions under which combined screening would be preferable: (1) if the combined screening's detection rate went up as the cost for genetic screening went down (figure 3B); (3) if there was a higher prevalence of both PCHL and the MT-RNR1 gene mutation (figure 3C); or (4) if the coverage levels for both HA and CI improved (figure 3D). The PSA showed that the probabilities of combined screening being cost-effective at a threshold of 1×pGDP or 0.63×pGDP were 78.5% and 66.7%, respectively, compared with standard screening (figure 3E,F). Sensitivity analysis from the broader societal perspective corroborated these findings (online supplemental figures S6 and S7).

We also modelled less optimistic scenarios with assumptions less favourable for certain variables. When we introduced a higher genetic screening price, a lower WTP threshold or constraints on resource availability, the optimal screening strategy remained unaltered (online supplemental table S8). Additionally, we assessed the combined and standard screening strategies in terms of costs and benefits under these pessimistic conditions. The results, which showed NB greater than 0 and BCR above 1 for all scenarios, indicated that the advantages of the combined screening strategy surpassed the costs, making it the strategy of choice (online supplemental table S9).

DISCUSSION

Childhood HL constitutes a significant public health challenge. The standard screening programme is relatively cost-effective, primarily due to the portability of the equipment, its affordability, streamlined training, assimilation into existing staff roles and incorporation into routine healthcare. Although NHSP using instrument-based audiologic methods have been established as cost-effective in many countries,[9 25 32] there are ongoing concerns, particularly regarding the limitations of these methods in the early detection of mild HL as well as late-onset or progressive forms of HL. Advances in precision medicine may present solutions to these issues.[15] At the same time, the critical role of genetic testing in paediatric medicine is increasingly acknowledged. Genetic testing provides valuable insights that support prompt and precise diagnoses, along with early interventions. Due to its practical nature and the increasing maturity of its training and implementation, it encourages broad adoption and cost-effectiveness in various healthcare contexts, ultimately improving the health outcomes for children with HL.

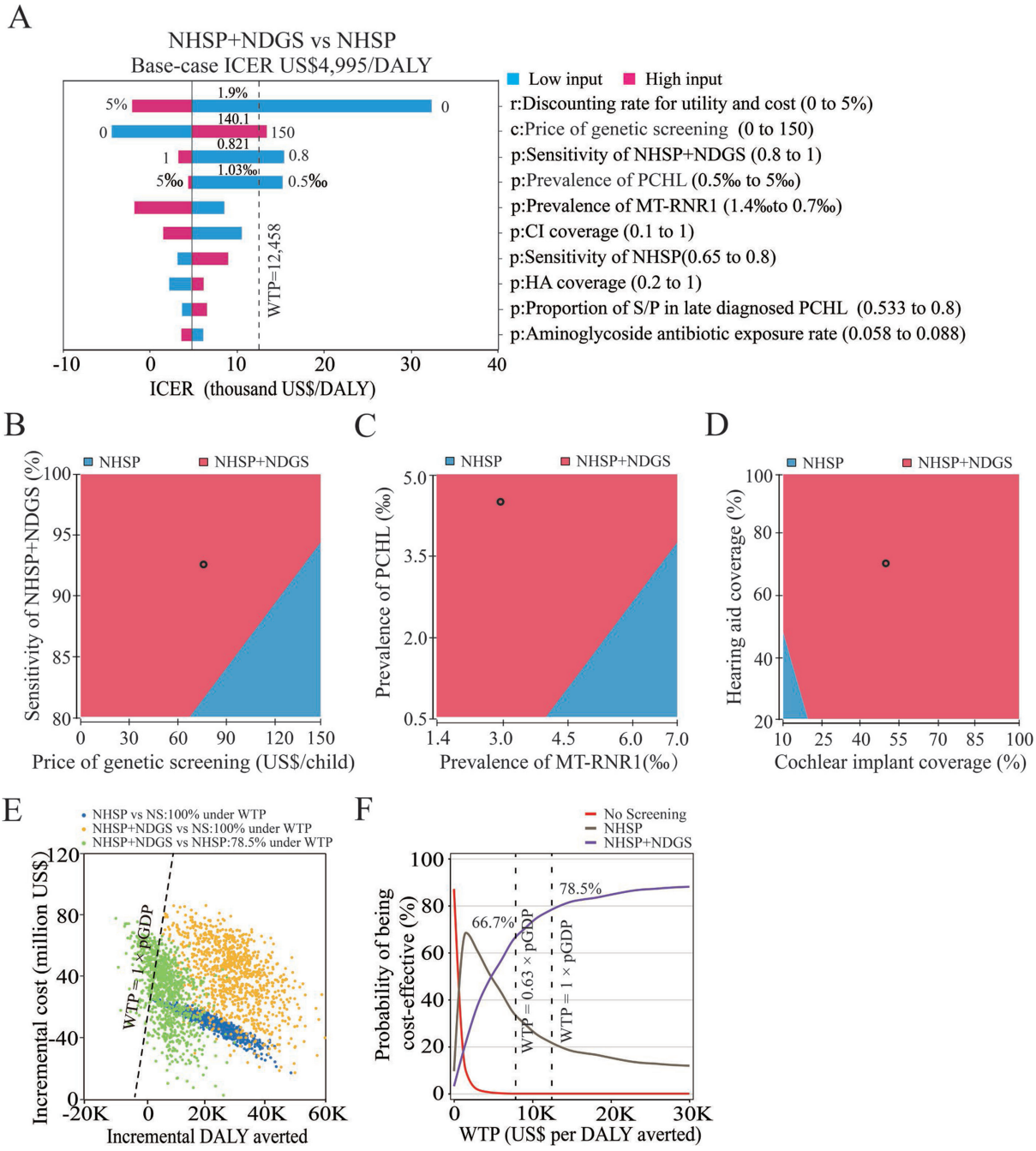

Figure 3 Sensitivity analyses for the newborn hearing screening strategies. (A) One-way sensitivity analysis presented with tornado diagram of ten most influential factors. Two-way sensitivity analyses presented with contour plots for the prices of genetic screening and sensitivity of combined screening (B), the prevalence of PCHL and MT-RNR1 mutation (C), treatment coverage levels of hearing aids and cochlear implants (D). The circles mark the base-case outcomes. Probability sensitivity analyses presented with scatter plot (E) and cost-effectiveness acceptability curve (F). DALY, disability-adjusted life-year; ICER, incremental cost-effectiveness ratio; MT-RNR1, mitochondrial encoded ribosomal RNR1; NHSP, newborn hearing screening programme; NDGS, newborn deafness gene screening; PCHL, permanent congenital hearing loss; WTP, willingness-to-pay.

Principal findings

To the best of our knowledge, this study accomplished the first national estimate for economic benefits of NDGS. The principal findings of CEA reveal that, from the healthcare sector perspective, standard and combined screening strategies for newborns were both more effective and more costly than opting for no screening at all, with the standard screening costing US$135 per DALY averted and combined screening costing US$1239 per DALY averted. Crucially, the combined screening approach illustrated a higher ICER of US$4995 per DALY averted when directly compared with the standard screening. However, from a societal perspective, both screening strategies were not only more cost-effective but also cost saving in comparison to no screening, with combined screening showing superior cost savings and

DALYs averted. In terms of CBA, the combined screening averted more DALYs with significant NBs and a favourable benefit-cost ratio (BCR) of 1.78, indicating it is a more economically advantageous approach compared with standard screening. These outcomes suggest that the combined screening strategy offers a valuable health investment, yielding cost savings and health benefits when viewed from a broader societal perspective.

Comparison with other studies

Our findings for the current universal NHSP are in agreement with those of previous studies conducted in various areas. For instance, in Thailand and Taiwan, the ICERs for OAE-based NHSP were estimated to be US$3702 and US$3284 per QALY gained, respectively, as reported in the literature.[11 33] Furthermore, we incorporated the initial parameters from these studies into our model and recalculated relevant indicators such as cost and effectiveness. The results demonstrated an ICER for standard screening versus no screening of US$3284 and absolute dominance, respectively; these findings are consistent with our estimates. Additionally, the literature from Thailand offers a systematic approach for conducting cost-effectiveness analyses.[33] We integrated the initial parameters from our study into the model. From a societal perspective, the ICER for NHSP was estimated at US$4287 per QALY gained, which suggests cost-effectiveness (see online supplemental table S10). By comparing our findings with those of other studies and applying model adaptions, we have shown the robustness and reliability of our modelling results. The comparative analyses of cost-effectiveness should be interpreted with caution given the variation in costs across settings.

In recent years, clinical genetic testing and counselling services have been introduced in low-income and middle-income countries, usually through research initiatives or international partnerships. Clinicians in some of these countries have begun to approach genetic counselling as a means to reduce birth defects and deleterious genes among the population, an attitude described as having eugenic tendencies.[34]

The rapid developments in precision medicine have led to increased expectation and optimism among the public attitude towards genetic testing.[35] An array of genetic sequencing tools has become available to clinicians with the advent of next-generation sequencing, including panel-based gene sequencing and whole exome sequencing. Our decision model framework may provide valuable insights for hearing screening strategies in other countries, as well as for genetic screening for other genetically predisposed diseases. The cost of genetic testing continues to fall, but the prices for testing a panel of deafness genes still exceed US$500. Furthermore, the heterogeneity of HL, hundreds of deafness-associated genes, and variable penetrance associated with mutations would make the result interpretation difficult, perhaps 'the US$1000 genome, the US$100 000 analysis'.[13] Even if screening large scale populations may be technically and financially feasible, the additional cost associated with statistical analysis, interpretation and counselling may be burdensome and prohibit the universal application. On the other hand, gene therapy is an important consideration of HL treatment research. Identifying the specific genetic mutation and affected cell type is paramount in gene therapy. The use of CIs could be expanded to serve as a potential vehicle for the delivery of gene therapy, through viral or non-viral vectors or gene silencing techniques as with CRISPR/Cas9.[15]

Despite the effectiveness of NDGS in identifying the infants with PCHL and the gene mutation carriers susceptible to AIHL, the integration of genetic screening into standard hearing screening might raise new ethical challenges and controversies.[15] The concerns include risks of discrimination or stigmatisation, respect for an individual's autonomy to make his/her own decisions and undue parental anxiety for their children's health. It is essential to ensure establishment of legal, ethical, privacy and security regulations or frameworks and mechanisms for population genetic screening.

Strengths and limitations

The assessment boasts several notable strengths. First, it uses real-world data derived from a local cohort study to model the costs associated with a combined screening programme relative to its ability to reduce the long-term consequences of HL, yielding more grounded economic projections for both NHSP and genetic screening. The substantial sample size and robust outcome assessment provide ample power to substantiate the advantages of the proposed screening approaches. Second, the evaluation incorporates not only audiological outcomes to calculate DALYs but also evaluates linguistic outcomes to understand their influence on education and employment prospects. Assessing language development is key to comprehending how early detection of HL might enhance overall learning and job skills.[33] Third, the study uses extensive sensitivity analyses with varying distributions rather than fixed figures to ensure the reliability of its conclusions. It also makes comparisons with other studies to verify the rationality of the model. Lastly, the evaluation aligns with the WHO's advocacy for enhancing hearing-related healthcare services. While this study concentrates on the Chinese population, the benefits of combined newborn hearing and genetic screening could extend to other ethnic groups. Despite the heterogeneity in the genetic landscape of deafness among ethnicities,[36] shared pathogenic variants do exist, suggesting the importance of validating combined screening in various countries through panels tailored to specific population-related genetic variations. Additionally, this study, while focused on deafness prevention and management, may also offer a blueprint for economic evaluations of other disease screenings.

Admittedly, this study has certain limitations. Initially, while the majority of the modelling parameters were drawn from a local cohort study and existing literature,

some inputs relied on insights from experts, reflecting the scarcity of extensive long-term cohort studies. While our model provides insights into potential trends and outcomes, the lack of direct comparison with empirical outcome data means these model-generated predictions should be interpreted with caution. Additionally, real-life application of NHSP often suffers from a higher rate of participants not returning for follow-up, which could mean that the actual detection rates for both standard and combined screenings, as projected from one study, may be overly optimistic. Lastly, the model does not take into account the nuanced dynamics of social interactions within the hearing community. For instance, the integration of genetic screening in newborn hearing programmes could have broader implications on family dynamics, such as influencing family planning decisions on identifying siblings and other relatives as carriers of deafness genes.

Policy implications

Based on the findings of the study, several policy implications can be identified. First, the results highlight the effectiveness of NDGS as a method for early diagnosis and intervention for children's HL. Therefore, policy-makers should consider implementing or expanding such screening programme as part of comprehensive NHSP. Second, the study demonstrates that a combined screening strategy is more cost-effective than standard screening. This underscores the importance of prioritising and investing in newborn genetic screening programme. Governments and healthcare authorities should allocate resources and provide necessary funding and support for the implementation and scalability of combined screening programmes. Third, the study's implications extend beyond China, as the research model and findings can serve as a valuable example for hearing screening strategies in other countries. Policy-makers in various national contexts can draw insights from this research to develop and implement effective screening programmes tailored to their specific healthcare systems and populations. Last but not least, the research highlights the potential for genetic screening as a tool for early detection and intervention for other diseases, indicating the need for further exploration and consideration of broader genetic screening policies.

CONCLUSIONS

Deafness gene screening presents a compelling and financially viable strategy for alleviating the impacts of childhood HL. The economic data from our research offers solid evidence to support policy decisions in favour of its large-scale promotion. We believe that as the costs of testing decrease and the accuracy of diagnoses improves, the cost-effectiveness of deafness gene screening could be enhanced even further. Crucially, our approach could be considered a practical model for analogous screening programmes in other countries and for other genetic diseases.

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