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Sensorineural hearing loss (SNHL) as an adverse event following immunization (AEFI): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data

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ABSTRACT

This is a Brighton Collaboration case definition of the term "Sensorineural Hearing Loss" to be utilized in the evaluation of adverse events following immunization. The case definition was developed by a group of experts convened by the Coalition for Epidemic Preparedness Innovations (CEPI) in the context of active development of vaccines for Lassa Fever and other emerging pathogens. The case definition format of the Brighton Collaboration was followed to develop a consensus definition and define levels of diagnostic certainty, after an exhaustive review of the literature and expert consultation. The document underwent peer review by the Brighton Collaboration Network.

Abbreviations: AAOHNS, American Academy of Otolaryngology-Head and Neck Surgery; ABR, Auditory brainstem response; AEFI, Adverse event following immunization; ASHA, American Speech-Language-Hearing Association; AIED, Autoimmune inner ear disease; AISNHL, Autoimmune sensorineural hearing loss; ASSR, Auditory steady state response; BAER, Brainstem auditory evoked response; CHL, Conductive hearing loss; CNS, Central nervous system; CMV, Cytomegalovirus; COM, Chronic otitis media; DPOAE, Distortion product otoacoustic emissions; dB, Decibel; GBD, Global burden of disease; HL, Hearing loss; Hz, Hertz; ISSNHL, Idiopathic sudden sensorineural hearing loss; JCIH, Joint Committee on Infant Hearing; LMIC, Low- and middle-income countries; MHL, Mixed hearing loss; NIDCD, National Institute of Deafness and Other Communication Disorders; NMDA, N-methyl-D-aspartate receptor; OAE, Otoacoustic emissions; OM, Otitis media; PSHNL, Profound sensorineural hearing loss; ROS, Reactive oxygen species; SHL, Sudden hearing loss; SNHL, Sensorineural hearing loss; SOSNHL, Sudden onset sensorineural hearing loss; SSNHL, Sudden sensorineural hearing loss; TEOAE, Transient evoked otoacoustic emissions.

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1. Preamble

Need for Developing Case Definitions and Guidelines for Data Collection, Analysis, and Presentation for SNHL as an Adverse Event Following Immunization (AEFI).

1.1. Introduction

Sensorineural hearing loss (SNHL) is a specific type of hearing deficit, first described by De Kleyn in 1944 and distinct from conductive hearing loss (CHL). SNHL results from damage to the inner ear, the vestibulocochlear nerve, or the central processing centers of the brain. SNHL can be unilateral or bilateral and the degree of the hearing loss is graded as mild to profound. SNHL can be described by location, severity, audiometric configuration and method of onset. The predominant form of SNHL is unilateral, and the main etiology is idiopathic. Most unilateral disease recovers spontaneously and therefore is considered benign, whereas bilateral SNHL is usually related to more serious systemic pathology and is associated with more severe degree of hearing loss and poorer prognosis [1].

1.2. Existing case definitions of SNHL

The most commonly used definition of SNHL, as endorsed by the American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS) and the National Institute of Deafness and Other Communication Disorders (NIDCD), is hearing loss of at least 30 dB (dB) in three sequential frequencies in the standard pure tone audiogram [2,3]. However, this definition is not universally utilized and variations of the definition and related terms are used in various publications (Table 1).

Not using a uniform definition of SNHL, particularly in the setting of the assessment of SNHL following immunizations, is a missed opportunity, as data comparability across trials or surveillance systems would facilitate data interpretation and promote the scientific understanding of SNHL following immunization. This document proposes a case definition of SNHL based on review of the existing literature and expert consensus, for the assessment of SNHL following immunizations.

1.3. Diagnosis and classification of hearing loss

The diagnosis of SNHL depends on the demonstration of reduced hearing acuity by auditory testing. Hearing is measured in decibels (dB), with the threshold of 0 dB for each frequency denoting the value at which normal young adults perceive a tone burst of a given intensity and frequency 50% of the time.

The threshold for normal hearing is −10 to 15 dB in children and adults. Hearing loss is present when hearing acuity drops below 30 dB [21–24]. While various classifications of hearing loss are described, accepted and commonly utilized thresholds for slight, mild, moderate, severe and profound hearing loss are shown in Table 2. A change of more than 10 dB in hearing acuity over time is not likely to occur due to expected testing variability, and is therefore considered significant. Frequency of hearing loss is designated as low (<500 Hz), middle (501–2000 Hz), or high (>2000 Hz).

Hearing loss may be unilateral or bilateral, high or low frequency, symmetrical or asymmetrical (same vs. different severity and shape of hearing loss in each ear), sudden or progressive, fluctuating or stable. (https://www.asha.org/public/hearing/Configuration-of-Hearing-Loss/).

1.4. Epidemiology of hearing loss and SNHL

1.4.1. Incidence, prevalence, and background rates

Hearing loss (HL) is the most frequent sensory deficit. The most recent Global Burden of Disease (GBD) study estimated that adult onset HL was the fifth leading cause of disability [25]. The specific prevalence of SNHL is not well described. The World Health Organization (WHO) estimates that 6.1% of the world's population (466 million persons) have disabling hearing loss. Disabling hearing loss refers to hearing loss greater than 40 dB in the better hearing ear in adults (15 years or older) and greater than 30 dB in the better hearing ear in children (0 to 14 years). (https://www.who.int/pbd/deafness/hearing_impairment_grades/en/). Of those with HL, 7% (34 million) are children, 93% (432 million) are adults. [26] The WHO estimates that the number of people with disabling hearing loss will grow to up to 630 million by 2030, and to over 900 million by 2050.

The prevalence of HL varies with age, sex, geographic region, and the definition of HL used. Although childhood onset HL is less common than adult onset, it has serious implications for language acquisition, communication and learning. The prevalence is higher in males as compared to females across all age groups. Age-related HL is a major concern worldwide with increasing life expectancy. Age-related HL begins in the third decade of life and is common after 65 years with estimated incidence of 1 in 3 people over 65 years having disabling HL.

According to WHO criteria, an overall prevalence of mild HL (>25 dB) of 16.2% has been reported in adults. [27] Mild HL is diagnosed in 6.6% of patients 50 to 59 years of age, 20.3% of patients 60 to 69 years of age, 42.3% of patients 70 to 79 years of age, and 71.5% of patients over 80 years of age. A national household survey conducted in Egypt reported higher prevalence of HL in Egypt (16.02%) as compared to the United States (9.6%). The three most common causes of HL were otitis media with effusion, presbycusis and chronic suppurative otitis media. [28] Disabling HL is more frequent in low- and middle-income countries (LMIC) as compared to high income countries, particularly in South Asia, Asia Pacific, and Sub-Saharan Africa, though there is paucity of data from LMIC (Fig. 1).

The Global Burden of Disease project estimates HL levels by country, age, sex and hearing threshold by using the better ear hearing threshold in decibels averaged over frequencies of 500, 1000, 2000, and 4000 Hz. [29] The prevalence of child and adult onset HL is reported to be substantially higher in LMIC as compared to high income countries. (Table 3) This may be explained by sequelae of otitis media. A prospective epidemiological survey was conducted to study the impact of otitis media (OM) on hearing in school children in Indonesia. OM-related disabling HL was found at a rate of 44.2/10,000, mostly due to chronic serous OM (CSOM) (37.1/10,000). [30] A systematic review estimated that globally OM-related hearing impairment has a prevalence of 30.82/10,000. [31] Other factors causing higher rates of hearing impairment in LMIC may include higher rates of pre- and post-natal childhood infections such as measles, rubella, central nervous system (CNS) infections, and high use of ototoxic drugs.

1.4.2. Prevalence of childhood hearing loss by universal newborn hearing screen

In most developed countries there are routine universal newborn hearing screening programs. A meta-analysis of studies done in developed countries with such programs, the prevalence of permanent childhood hearing loss was reported to be 1 per 1000 screened children. Prevalence of hearing loss in babies admitted to the neonatal intensive care unit (NICU) was almost seven times higher than for those not admitted. [32]

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Table 1
Existing definitions of sensorineural hearing loss (SNHL) and related terms.

Existing definitions of SNHL		
Term	Definition	Reference
SNHL	Collection of common auditory disorders resulting from dysfunction of the inner ear, auditory nerve, or the auditory processing pathway in the central nervous system. OR Hearing loss resulting from abnormal function of the cochlea, auditory nerve, or higher aspects of central auditory perception or processing. OR Clinical condition resulting from dysfunction in one or more parts in the auditory pathway between the inner ear and auditory cortex.	[4]
SSNHL (Sudden SNHL) or SOSNHL (Sudden onset SNHL)	Defined by the National Institute on Deafness and other Communications Disorders as a minimum of 30 dB hearing loss over 3 consecutive frequencies in a pure tone audiogram, occurring in<3 days. **Variations of the same definition as reported in the literature:** • Hearing loss of at least 30 dB in three sequential frequencies in the standard pure tone audiogram over 3 days or less. • The rapid hearing loss of at least 30 dB in 3 contiguous audiometric frequencies within 3 days. • Sensorineural hearing loss of 30 dB or greater over at least three contiguous audiometric frequencies occurring within a 72-hour period. • Unilateral decrease in pure tone audiogram of > 30 dB in at least 3 continuous frequencies over 3 days or less. • Damage to the cochlear hair cells or inner nerve and diagnosed by a hearing loss of 30 dB or greater over the minimum of 3 different auditory frequencies within 72 h. • A subset of SNHL that (a) is sensorineural in nature, (b) occurs within a 72-hour window, and (c) consists of a decrease in hearing of > 30 dB affecting at least 3 consecutive frequencies.	[1,5][3,6][7–9] [10,11][12,13] [11,14]
Rapidly progressive SNHL	Initial presentation with SSNHL followed by rapid progression (over weeks to months) or additional sudden drops in hearing.	[15,6]
ISSNHL (Idiopathic sudden SNHL)	Hearing loss of >30 dB that occurs in at least 3 consecutive frequencies occurring within 3 days, for which etiology is unknown OR SSNHL with no identifiable cause despite adequate investigation.	[3,16]
AISNHL (Autoimmune SNHL)OR**AIED** (Autoimmune inner ear disease	Also known as autoimmune inner ear disease (AIED), autoimmune cochleopathy, and immune mediated cochleovestibular disease. A form of SNHL that is different from other forms of deafness by virtue of its clinical presentation, laboratory test results and response to treatment. May be the result of a systemic disease or an organ specific disorder. Usually presents as bilateral hearing loss with occasional involvement of balance function. Deafness progresses over weeks or months. Is more common in middle aged women. OR Bilateral SNHL of 30 dB or more at any frequency, with evidence of progression in at least one ear or two serial audiograms performed less than 3 months apart. Diagnosis requires the appropriate clinical presentation, exclusion of other known causes of SNHL and positive response to steroid therapy.	[15,17][18,19]
Related terms and synonyms of SNHL		
Sudden hearing loss (SHL)	A rapid-onset (occurring in < 72 h) subjective sensation of hearing impairment in one or both ears. This can include both SNHL and conductive hearing loss (CHL).	
Conductive hearing loss (CHL)	Hearing loss resulting from a problem conducting sound waves anywhere along the route through the outer ear, tympanic membrane, or middle ear.	
Mixed hearing loss (MHL)	Hearing loss resulting from both SNHL and CHL occurring in the same ear	
Hearing disorder	The result of impaired auditory sensitivity of the physiological auditory system.	[20]
Hard of hearing	A hearing disorder which adversely affects an individual's ability to communicate. The hard-of-hearing individual continues to rely on the auditory channel as the primary sensory input for communication.	[20]
Hearing impaired/ hearing impairment	A hearing disorder that limits an individual's aural/oral communication performance to the extent that the primary sensory input for communication may be other than the auditory channel.	[20]
Deaf	An individual who is hard of hearing or who has no hearing	
Deafness	The condition of lack of hearing or impaired hearing	

Table 2
Classification of hearing loss by severity.

Degree of Hearing Loss (HL) (pure tone threshold on hearing level audiogram)	
0–15 dB	Within normal limits
16–25 dB	Slight HL
26–40 dB	Mild HL
41–55 dB	Moderate HL
56–70 dB	Moderate to severe (or moderately severe) HL
71–90 dB	Severe HL
91+	Profound HL

Source: References [21–24].

1.4.3. Prevalence of sudden sensorineural hearing loss

Sudden sensorineural hearing loss, defined as the onset of hearing loss over a period of 72 h or less in one or both ears, is considered an otologic emergency. The audiometric criterion for diagnosis is a decrease in hearing of at least 30 dB, affecting at least three sound frequencies. The prevalence of sudden, idiopathic hearing loss is 5 to 27 cases per 100,000 population, with approximately 4000 new cases per year in the United States [31].

1.5. Etiology of SNHL

The etiology of SNHL may be difficult to ascertain. Causes are broadly classified into congenital or acquired. A summary of the various etiologies of SNHL is shown in Table 4. Common specific causes include infections, vascular lesions, hematologic, neoplastic, autoimmune, trauma, ototoxic drugs, central nervous system disorders and idiopathic [11,21,33–36].

The congenital causes of SNHL present largely in the neonatal period and infancy. Half are of genetic etiology and the other half are related to environmental exposures. The genetic causes are either part of a syndrome, or a recessive, dominant or X-linked

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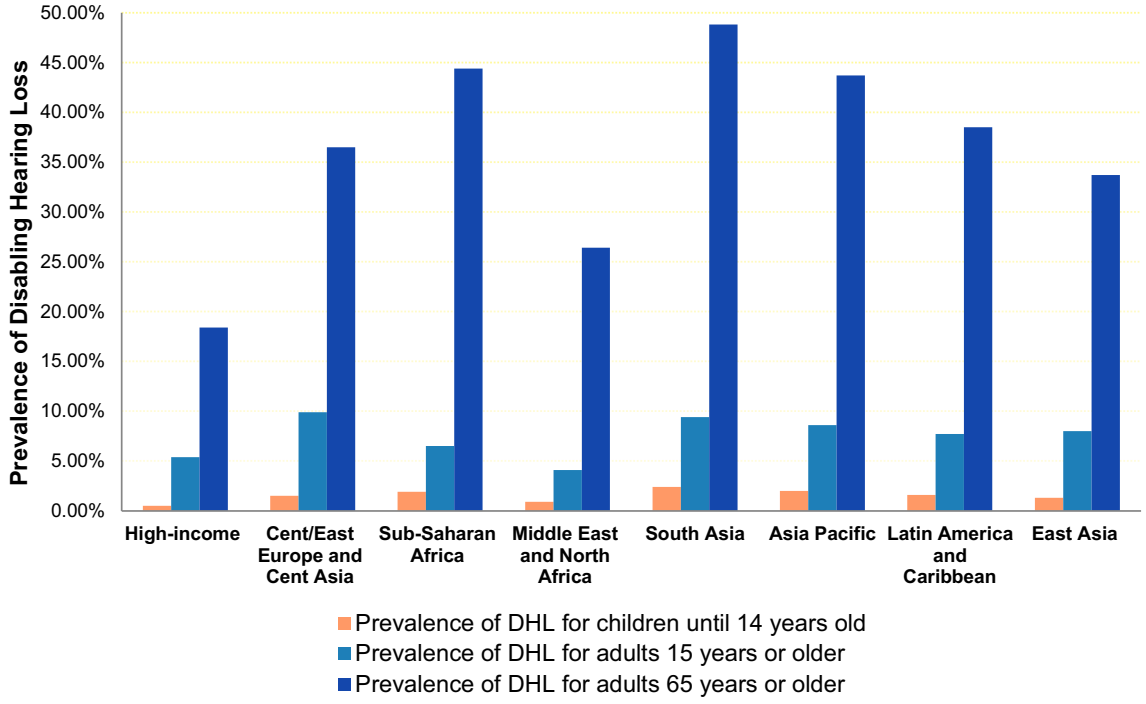

Fig. 1. Prevalence of disabling hearing loss (>40 dB) for children, adults >15 years, and adults > 65 years of age, by region. Source: https://www.who.int/pbd/deafness/estimates/en/

Table 3
Estimated percent prevalence (range) of hearing loss across different regions by severity of hearing loss, gender and age.

Region	Mild (20–34 dBHL)	Moderate (35–49 dBHL)	Moderately severe (50–64 dBHL)	Severe (65–79 dBHL)
Males > 15 years % (range)				
High-income region	16.8 (14.9–19.3)	5.8 (4.9–7.2)	1.6 (1.3–2.2)	0.4 (0.3–0.6)
Sub-Saharan Africa region	24.1 (19.3–28.8)	8.3 (6.0–10.9)	2.5 (1.7–3.5)	0.7 (0.5–1.1)
Middle East and North Africa region	16.4 (10.1–25.3)	4.9 (2.6–9.0)	1.3 (0.6–2.8)	0.4 (0.2–0.8)
South Asia region	26.9 (20.1–33.4)	10.2 (6.6–15.6)	3.2 (1.8–5.5)	1.0 (0.5–1.9)
World	**22.7 (19.8–25.7)**	**8.4 (6.8–10.6)**	**2.6 (2.0–3.7)**	**0.8 (0.6–1.2)**
Females > 15 years % (range)				
High-income region	15 (13.3–17.2)	5.3 (4.4–6.6)	1.4 (1.1–2.0)	0.4 (0.3–0.5)
Sub-Saharan Africa region	19.6 (15.3–23.9)	6.4 (4.6–8.5)	1.8 (1.2–2.6)	0.5 (0.3–0.8)
Middle East and North Africa region	12.8 (7.7–20.4)	3.7 (1.9–6.9)	0.9 (0.4–2.0)	0.2 (0.1–0.6)
South Asia region	22.3 (16.2–29.4)	7.8 (5.0–12.2)	2.4 (1.3–4.2)	0.7 (0.4–1.3)
World	**19.0 (16.4–21.8)**	**6.8 (5.5–8.6)**	**2.0 (1.5–3.0)**	**0.6 (0.4–1.0)**
Children, 5–14 years (cases per 1000)				
High-income region	17 (12.4–25)	2.7 (2.0–4.0)	0.5 (0.4–0.8)	0.1 (0.1–0.2)
Sub-Saharan Africa region	70.9 (46.4–103.5)	12.2 (7.6–18.9)	2.4 (1.5–3.7)	0.6 (0.4–0.9)
Middle East and North Africa region	32.3 (14.5–76.1)	5.2 (2.3–13)	1.0 (0.4–2.6)	0.2 (0.1–0.6)
South Asia region	82.5 (45–151.4)	14.3 (7.4–29.7)	2.8 (1.4–6.0)	0.7 (0.3–1.4)
World	**62.2 (46.1–88.1)**	**10.7 (7.7–16.9)**	**2.1 (1.5–3.4)**	**0.5 (0.4–0.8)**

Source: Reference [29]

mitochondrial genetic abnormality [34]. The specific syndromes that are known to be associated with SNHL include Pendred syndrome which is the most common type followed by Usher syndrome, STAR syndrome (Syndactyly, telecanthus, anogenital and renal malformations), Alport syndrome, JS-X syndrome, and X-linked hypophosphatemia. All these present with variable grades of hearing loss [35,36]. Environmental causes include prenatal infections, prematurity, prenatal ototoxic medications exposure, neonatal jaundice, birth asphyxia and other environmental exposures [14,26,37].

The acquired causes of SNHL are largely due to infections and predominantly occur in resource limited settings. However, the overall prevalence has decreased due to vaccination [21]. In a meta-analysis, infections accounted for 13% of SNHL etiologies [11]. Infections that result in to SNHL may be part of systemic infections, central nervous system infections, or specific infections that result in SNHL as sequelae. Several viruses can cause SNHL, including HIV, herpes simplex virus, measles, mumps, varicella zoster, Ebstein-Bar virus, enteroviruses, Lassa fever and other hemorrhagic fever viruses, influenza and other viral upper respiratory tract infections [1,5,14,33]. Other infections known to result in SNHL include syphilis, Lyme disease, toxoplasmosis, bacterial meningitis, and cryptococcal meningitis, among others [11]. SNHL is an important sequelae of Lassa fever. Approximately 25% of patients that recover from Lassa fever develop unilateral or bilateral SNHL [22]. SNHL occurs usually during Lassa fever convalescence but can also occur during the acute infection, ranging between 8 and 22 days from fever onset [14,38].

Table 4
Summary of etiologies of SNHL.

Groups (reference)	Sub-groups	Pathogenesis	Class of hearing loss
Congenital			
Non Syndromic [26,37]	Autosomal dominant (e.g. DFNA)	Genetic abnormalities	Mild to profound
	Autosomal recessive (e.g. DFNB)		Unilateral or Bilateral
	X-Linked (e.g. DFNX)		
Syndromic [26,37]	Autosomal Dominant (e.g. Branchio-oto-renal syndrome, Crouzon, Neurofibromatosis 2)	Genetic abnormalities	Mild to profound Unilateral or Bilateral
	Autosomal Recessive Syndromic Pendred Syndrome		
	Usher Syndrome		
	X-Linked Syndromic (e.g. Alport Syndrome, Kearns-Sayre Syndrome)		
Perinatal			
Perinatal [39]	Birth asphyxia	Cerebral palsy, sometimes primary injuries to the organ of Corti, outer hair cells and cochlear nerve	Mild to profound Usually Bilateral
[39,40]	Neonatal jaundice/Kernicterus	Toxicity of the immature auditory pathway and damages to basal ganglion	Mild to profound Usually Bilateral
Acquired			
[38]	Infection/Inflammation (labyrinthitis, neuronitis)	Elaboration of destructive endotoxin, direct invasion of the cochlear hair cells/neurons of cochleovestibular nerves, indirect destruction of hair cells via immunological reactions and abnormal calcification of the cochlear labyrinths	Mild to profound Unilateral or bilateral
	Noise Induced HL	Hypoxia and destruction of cochlea hair cells	High frequency hearing loss Commonly bilateral
[41]	Exposure to ototoxic drugs	Damage to cochlea hair cells	Mild to moderate Almost always bilateral
	Age related Presbycusis	Loss of hair cells, Degeneration of organ of Corti and cells of spiral ganglia	Low frequency (mild to severe) hearing loss Usually bilateral
[42]	Systemic Disorders (e.g. Hypertension, diabetes, chronic kidney disease)	Neuropathies and destruction of myelin sheets of the vestibulocochlear nerves	Mild to profound Usually bilateral
	Trauma (e.g. Temporal bone fractures)	Transverse fractures of the temporalbone usually cross the vestibule or the basal turn ofthe cochlea, resulting in total, sudden sensorineuralhearing loss	Severe to profoundUnilateral or bilateral
	Immunologic, such as Cogan syndrome, temporal arteritis	Deposition of immune complexes	Mild to profound Usually bilateral
[43]	Tumors Acoustic neuroma	Pressure on the cochlear nerve	Mild to moderate Associated with tinnitus, unilateral.
[42]	Vascular (e.g. coagulopathies, occlusive crises)	Vessel contraction vs. occlusion and cochlear hypoxia	Mild to severe Usually bilateral
	Idiopathic	Non-specific and sometimes follows the pattern of infections, inflammations	Moderate to severe Unilateral or bilateralUp to 50% of cases are reversible
[44–48]	Vaccine associated (no known definitive causality)	Possible autoimmune (adverse) reactions or demyelination of nerve fibers linked with viral invasion, with localized arteritis, or particular genetic predisposition. Acoustic neuritis with fibrosis and direct cytolytic damage with atrophy of the organ of Corti.	Mild to profound Unilateral or bilateral. Temporary or permanent

1.6. Risk factors for SNHL

The risk factors for SNHL depend on the age of the patient and exposure to a plausible etiology. The Joint Committee on Infant Hearing (JCIH) identified risk factors related to hearing loss in infants and children in their 2007 and 2019 position statements [49,50]. These include cytomegalovirus (CMV), toxoplasmosis, syphilis, or rubella infection, syndromes associated with progressive hearing loss, neurodegenerative disorders, trauma, culture-positive postnatal infections, hyperbilirubinemia, meningitis, low APGAR scores, low birth weight, extracorporeal membrane oxygenation (ECMO) and chemotherapy [51,52].

In a meta-analysis, the major risk factor in the adult population was cardiovascular dissease, including hypertension, hypotension, stroke, myocardial infection and ischemic cardiomyopathy. All these lead to perturbation of labyrinthine blood supply. The pooled odds ratio (95% confidence interval) of some other risk factors are as follows: heavy smoking 1.34 (1.16–1.61), heavy alcohol consumption (>2 pints/day) 2.21 (1.68–2.91), hypertension 1.00 (0.74–1.36) and diabetes mellitus 1.53 (0.96–2.42). Other reported risk factors include short sleep duration (<7 h/ day), sedentary lifestyle, lower plasma levels of coenzyme Q, vitamin A and folate, high fibrinogen levels, high plasma viscosity, high erythrocyte aggregation, high Intercellular Adhesion Molecule 1 (ICAM) and vascular cell adhesion molecule 1 (VCAM-1), hypercholesterolemia, high levels of homocysteine or nervonic acid. There are also various known genetic factors that predispose to development of SNHL [37,53,54].

1.6.1. Age of onset of SNHL

The age of onset of SNHL varies according to etiology. In the absence of neonatal hearing screening, children with congenital hearing loss are usually detected only after their second birthday [36]. In a review of age of onset of bilateral SNHL the following ages were reported in years (SD) based on possible etiology: Toxic 33 (±15), neoplastic 57 (±16), vascular 50 (±14), autoimmune 31 (±23), infections 32 (±22), trauma 28 (±0), iatrogenic 52 (±17), idiopathic 32 (±25) [5].

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1.7. Outcomes – Progressive hearing loss

Changes in hearing over time pose a unique challenge to audiologic and educational management and can occur with congenital, acquired or late onset hearing loss [55]. Children with mild and minimal HL (e.g., high-frequency loss) not detected during screening, and those with unilateral loss can be at risk for further deterioration. Given the lack of information about progressive hearing loss since universal hearing screening, additional investigations are required to inform audiologic care and timely amplification services.

In a population-based study from Ontario, Canada, among a group of 330 children with HL identified by the universal newborn hearing screen (UNHS), 158 were classified with progressive HL and close to half of these children experienced onset before age 6 months (32.9% congenital and 14.6% early onset). Almost one-third (28.5%) had late onset HL (after age 6 months). The remaining had acquired loss (9.5%) or unknown onset (14.6%) [46]. It is often not possible to document the true progression in hearing loss for the children with late onset because the exact point of onset is unknown. Overall, the constellation of degree of HL was different for the progressive vs. the late onset groups ($p < 0.001$). In the progressive group, there was considerable variability in the amount of deterioration in thresholds, resulting in 148 ears (from the 158 children initially diagnosed with bilateral or unilateral loss) being classified in a different category of severity. Progressive loss was documented in 47.9% of children, and almost a quarter (23%) experienced $\geq$20 dB deterioration.

There are varying estimates on progressive hearing loss, with studies reporting ranges from 6 to 56% of children affected [56–60]. Even children who pass hearing screening are at risk for progressive hearing loss [46]. There is a heightened awareness of the need to maintain clinical pathways for the detection of postneonatal hearing loss [55,57,61–63]. Some investigators stress the importance of monitoring hearing throughout early childhood [60,64].

Early identified children with mild bilateral or unilateral hearing loss can develop auditory and spoken language skills on par with their normal hearing peers in the early preschool years [65]. Almost 40% of children with unilateral hearing loss may experience more than 10 dB deterioration in the impaired ear or progression to bilateral loss [66,67]. Unilateral hearing loss may not always be a unilateral process, but it may be the initial manifestation of bilateral auditory dysfunction [46,66]. One previous study of school-age children conducted in the 1980s also found greater deterioration in the better ear in children with bilateral hearing loss and that the frequencies with better hearing were more affected [68]. Exploration of the five most common risk indicators; NICU (39.1%), family history (29.9%), syndromes (11.5%), craniofacial anomalies (6.9%), and postnatal infections (5.7%), did not reveal any association with progressive loss [46].

The main causes for progressive SNHL in adults are degenerative processes associated with aging, genetic mutations, noise exposure, exposure to drugs with ototoxity side effects and chronic conditions.

The leading cause of adult onset progressive hearing loss is age-related hearing loss or presbycusis. Age-related hearing loss is generally a slow, progressive hearing loss that affects both ears equally. It begins in the high frequencies and later affects the lower frequencies. One of the first signs of hearing loss is often an inability to hear and understand speech in noisy environments [69,70]. Because of this slow progression, adults with presbycusis do not readily acknowledge their hearing loss, considering it a normal sign of aging.

There are more than 100 gene mutations that can cause non-syndromic hearing loss. Approximately 30 of these genes are associated with adult onset progressive hearing loss and are inherited in an autosomal dominant fashion [71]. Most of the monogenetic causes of hearing loss involve mutations of genes that are required for normal cochlear function [72]. The estimated heritability of adult-onset hearing loss ranges from 25 to 55% [73].

Noise damages the sensory hair cells of the cochlea through stress of intense sound pressure [74]. Approximately 104 million people in the United States are exposed to noise levels that can cause hearing loss [75]. Workers who work in noisy locations tend to underestimate the level of noise in their work environment and the risk of hearing loss associated with the daily noise exposures.

Exposure to drugs with ototoxic side effects can cause progressive hearing loss. Various drugs can adversely affect the auditory system such as aminoglycoside antibiotics, cisplatin and loop diuretics. Hearing loss can develop in 20% of patients who received aminoglycosides and in 60–65% of cancer patients who received cisplatin [76–78]. Loop diuretics such as furosemide can induce ototoxicity by causing edema and cystic degeneration of the stria vascularis in the cochlea [79].

Chronic autoimmune diseases (rheumatoid disease, systemic lupus erythematosus, Cogan syndrome, sarcoidosis, etc) can cause progressive and fluctuating hearing loss with a variable time course. The hearing loss typically presents bilaterally but can also present unilaterally [19].

Progressive hearing loss is highly variable in onset, amount of deterioration, and audiometric frequencies affected. Continued research with screening cohorts followed over several years is required to better understand the onset and trajectory of progressive loss. Hearing loss adversely affects social engagement and partner relationships in addition to being associated with decreased quality of life, dementia, depression, debility, delirium, falls, and mortality [80–82]. Medical costs related to hearing loss is estimated to range from $3.3 million to $12.8 million annually in the United States [83].

1.8. Pathophysiology of SNHL

The damage to inner ear structures or the vestibulocochlear nerve that lead to SNHL has several potential causes as previously outlined. The potential mechanisms by which these etiologies result in SNHL include direct damage from drugs or infectious agents and inflammatory and immunologic responses. There may be considerable overlap between these mechanisms. For example, infectious agents may stimulate both specific (immune) and non-specific inflammatory responses that ultimately lead to tissue damage. Because the target organ (inner ear) cannot be biopsied, studies have largely been based on post-mortem samples and animal models [17].

1.8.1. Drugs

Aminoglycoside antibiotics are proposed to cause hearing loss by several mechanisms. They generate reactive oxygen species (ROS) that cause destruction of cochlear hair cells by apoptosis [84]. The drugs disrupt mitochondrial protein synthesis in hair cells, and some mitochondrial polymorphisms have been associated with aminoglycoside-induced hearing loss [85]. Also, they can cause "excitotoxicity" where neurons are damaged by overactivation of certain receptors such as the N-methyl-D-aspartate (NMDA) receptor by the medications [86]. Cisplatin-induced ototoxicity also appears primarily due to ROS-induced apoptotic hair cell death [87].

1.8.2. Inflammatory

Inflammation is a very broad term used to describe a biologic response to some stimulus. Some amount of inflammation is an appropriate response to potentially harmful stimuli such as pathogens which can be eliminated but may leave residual damage to

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previously healthy tissue [88]. Inflammation typically involves the infiltration of some type of leukocytes, the products of which can cause cell damage. Such products include reactive oxygen species.

1.8.3. Immunologic

Immunologic damage to cellular structures can be mediated by humoral or cellular immune reactions. Since the target of such reactions in SNHL are self or endogenous, the reactions can be characterized as autoimmune. Humoral responses result in the production of antibodies from B lymphocytes against specific antigens which can damage cells through complement activation or antibody dependent cellular cytotoxicity. The presence of immune complexes can further propagate inflammation. Cellular immune responses involve T lymphocytes recognizing specific antigens through T-cell receptors and then inducing damage directly or by the release of cytokines which can cause direct cell damage and/or stimulate the influx of other inflammatory cells. The inner ear had been thought to be immunologically "privileged", that is not accessible to immune responses because of the blood–labyrinth barrier. However, immunoglobulins have been found in inner ear structures and lymphocytes can gain access to the cochlea from the circulation [17]. Autoimmune SNHL may be organ-specific or associated with systemic autoimmune diseases which cause vasculitis [17]. SNHL associated with this vasculitis may be due to inflammation and occlusion of blood vessels resulting in cochlear hypoxia [89].

1.8.4. Infectious

Some pathogens, particularly viruses, are capable of attaching to, entering and replicating in cells resulting in cellular damage. Congenital infection with cytomegalovirus and rubella can cause SNHL either through direct viral damage to cells or through an immune response [90]. Hearing loss can also be a complication of measles and mumps infection and virus has been detected in the inner ear structures [90].

A recent report described three nonhuman primates (macaques) who survived beyond the acute phase of Lassa virus infection [89]. The animals remained chronically ill, and displayed apparent hearing loss, including lack of response to auditory stimulation and tuning fork tests. Profound sensorineural hearing losses were confirmed in two by brainstem auditory evoked response (BAER) analysis. Histologic examination of inner ear structures did not detect virus although this may have been due to the harsh processing necessary to obtain the samples. However, the histology did reveal an immune-mediated vasculitis that may underlie Lassa fever-associated deafness in this animal model [89].

1.9. SNHL following immunization

Several case reports have described the occurrence of SNHL shortly after immunization, with hearing loss temporally occurring following influenza [47,91], mumps and/or measles [34,92–94], hepatitis B [95], tetanus, diphtheria [44,96], meningococcal polysaccharide [44] and rabies vaccines [48]. The 2011 Institute of Medicine report concluded that there was insufficient evidence to accept or reject a causal relationship between MMR and hearing loss [97].

Beyond isolated case reports, however, only one study in the published literature has assessed for risk of sudden hearing loss following a range of vaccines. This study evaluated for sudden SNHL during the 14 days after immunization using data on 28 vaccines (including influenza vaccines) encompassing more than 20 million doses administered within Kaiser Permanente Northern California from 2007 to 2013. The analyses compared SNHL cases with matched vaccinated controls and assessed for immunization exposures during the 14 days prior to onset of hearing loss. Secondary analyses using risk intervals of days 1 to 28 and days 15 to 28 after vaccination were also evaluated. This large scale study did not detect an association between sudden SNHL and prior receipt of any vaccine in any of the risk intervals evaluated [45].

There are no published systematic studies evaluating SNHL occurring as a late (>28 days) adverse event following immunization.

1.10. Diagnosis of SNHL

The diagnosis of SNHL depends on the demonstration of reduced hearing acuity by auditory testing. The Clinical presentation is variable, and persons with hearing loss might not report symptoms when the hearing loss is unilateral or mild. Hearing acuity can be measured with objective or subjective testing conditions. In order to accurately diagnose SNHL, a complete medical history and physical examination are necessary to determine the most appropriate testing and type of hearing loss.

1.10.1. Medical history and physical exam

The key elements of medical history and physical exam are described in Table 5.

Table 5
History and physical exam in children and adults.

	Child	Adult
History	• Parent/caregiver report of poor responsiveness to sound • Family history of hearing loss • Medical history relating to hearing or hearing loss • History of ear infections and ear surgeries • Newborn hearing screening results • Joint Commission on Infant Hearing (JCIH) risk factors (include CMV infection, syndromes associated with progressive hearing loss, neurodegenerative disorders, trauma, culture-positive postnatal infections associated with SNHL, ECMO, chemotherapy) [50] • Development of speech, language, motor, or global delays • History of exposure to ototoxic medications • Immunization history	• Family/other perception and/or self-perception of hearing loss • Medical history relating to hearing or hearing loss • History of: ■ Ear infections and ear surgeries ■ Amplification use ■ Noise exposure ■ Exposure to ototoxic medications • In addition to a complete medical history for chronic medical conditions such as diabetes mellitus, a neurologic history review should also be carried out including history of stroke, vasculitis, head or ear trauma. History should include duration of hearing loss and whether symptoms are bilateral, fluctuating, or progressive. Presbycusis characteristically involves gradual onset of bilateral high-frequency hearing loss associated with difficulty in speech discrimination causing difficulty in conversation, especially with background noise. [98]
Physical Exam	• Observation of outer ear for abnormalities including ear tags, ear pits and ears that are misshapen • Observation of outer ears in reference to each other and to the rest of the face. Look for ears that are not positioned correctly. • Performing otoscopy using an otoscope, looking for debris in the ear canal including wax, foreign object, tumor or vernix. • Assessing the tympanic membrane by looking for cone of light, ventilation tubes, perforations, retraction, fluid line, fluid bubbles, or bulges. • Pneumatic otoscopy or tympanometry can be used assess the mobility of the tympanic membrane.	

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1.10.2. Otoscopy and pneumatic otoscopy

Otoscopy, through the utilization of an otoscope, refers the visualization of the ear canal and the tympanic membrane. Pneumatic otoscopy is used to evaluate the mobility of the tympanic membrane by insufflating air through the ear canal with the otoscope's air bulb, while properly sealing the entrance of the ear canal with the otoscope speculum. A normal ear canal will be unobstructed, with healthy mucosa; and a normal tympanic membrane will appear translucent, reflect light, allow for the identification of anatomic landmarks (e.g. Pars Flaccida, Pars Tensa; Manubrium, Umbo), and have normal inward and outward mobility during pneumatic otoscopy (no bulging, no retraction).

1.10.3. Tympanometry

Tympanometry is used to examine the condition of the middle ear, the mobility of the tympanic membrane, and the conduction bones, by the use of various air pressures through the each canal. Tympanometry does not measure hearing, but rather, the transmission of energy through the middle ear. Otoscopy must be performed before tympanometry to ensure the patency of the ear canal and the absence of tympanic perforations. After inserting the tympanometer probe in the ear canal, the instrument will change the pressure in the ear, generate a pure tone of 226 Hz, and measure the tympanic membrane responses to the sound at different pressures as the sound perceived by the tympanic membrane through vibrations reflected back to the instrument. These are plotted in a graphic, allowing to assess whether there is normal pressure in the middle ear with normal mobility of the tympanic membrane and ossicles (type A or normal tympanogram); middle ear fluid, a perforation of the tympanic membrane, or a tumor of the middle ear (type B tympanogram); or Eustachian tube dysfunction resulting in negative pressure in the middle ear and retraction of the tympanic membrane (type C tympanogram). Tympanometry can therefore assist with the assessment of potential causes of conductive hearing loss.

1.11. Diagnostic tools

Various diagnostic tools are available to assess hearing, as described in Table 6.

1.12. Differential diagnosis

1.12.1. Differentiation between SNHL and conductive hearing loss or mixed hearing loss

Hearing loss is grouped into conductive, sensorineural, or mixed types. Conductive problems involve the tympanic membrane and middle ear, and interfere with transmitting sound and converting it to mechanical vibrations. Sensorineural problems affect the conversion of mechanical sound to neuroelectric signals in the inner ear or auditory nerve. Table 7 shows the approach for the evaluation of conductive vs. sensorineural hearing loss.

1.12.2. Developmental delay, autism spectrum and other neurodevelopmental disorders

Depression and dementia should be considered in the differential diagnosis of hearing loss. Both conditions may present with the apathy, inattentiveness, and social disengagement that can occur with hearing loss. Patients with dementia should be evaluated for hearing loss because hearing impairment can create disengagement and make cognitive impairment seem more severe than it is. [80,81] Similarly, if hearing loss is detected, cognitive screening should be performed because cognitive impairment often accompanies hearing loss.

1.12.3. Cerumen/wax impaction

Cerumen build up in the external auditory canal can result in conductive hearing loss. The cerumen can be removed by irrigation, manual extraction, cerumenolytic agents, or a combination of the above.

1.13. Management and treatment

The management of the hearing loss will depend on the etiology. After an ear examination to rule out ear canal or middle ear disease, patients should then proceed with an audiometry. Laboratory evaluation is not indicated unless systemic illness is suspected. Imaging is recommended in patients with conductive hearing loss without middle ear effusion, asymmetrical hearing loss (a difference of 15 dB or more) and sudden sensorineural hearing loss [3,101]. Additional workup including ophthalmology, cardiology and genetic evaluation but should only be ordered after an evaluation by an otolaryngologist.

1.13.1. Sudden sensorineural hearing loss

A Cochrane review from 2013 found unclear benefit for the use of glucocorticoids for idiopathic sudden sensorineural hearing loss [102]. However, some studies have found benefit from systemic or intratympanic steroids. Steroids should be started within two weeks of onset of symptoms if this treatment is used. There are limited data on hyperbaric oxygen therapy.

1.13.2. Auditory rehabilitation

Auditory rehabilitation refers to strategies that focus on adjusting patients and their families to hearing deficits and providing listening and speaking strategies to improve communication.

1.13.3. Hearing assistive devices

These include the use of visual cues for doorbells, telephones, or alarms, and sound amplifiers to televisions, telephones, or theaters, etc.

1.13.4. Hearing aids

A Cochrane review from 2017 found evidence that hearing aids use in patients with mild to moderate hearing loss improve hearing-related quality of life and overall health-related quality of life [103].

1.13.5. Surgically placed hearing aids

Cochlear implant is a surgically placed device that bypass damaged portion of the inner ear and directly stimulates the auditory nerve. A cochlear implant can be a treatment in patient with moderate to profound bilateral sensorineural hearing loss.

1.14. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation for SNHL as an adverse event following immunization (AEFI)

Following the process described on the Brighton Collaboration Website https://brightoncollaboration.us/about/the-brighton-method/, the Brighton Collaboration SNHL *Working Group* was formed in July 2019 and included members of clinical, academic, public health, and research background.

To guide the decision-making for the case definition and guidelines, existing literature reviews on relevant topics were thoroughly examined. Search terms used in these reviews were updated and rerun in PubMed to obtain any more recently published relevant articles to add to their results. (Appendix A) The resulting articles were analyzed for relevance and included as

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Table 6
Diagnostic Tools*

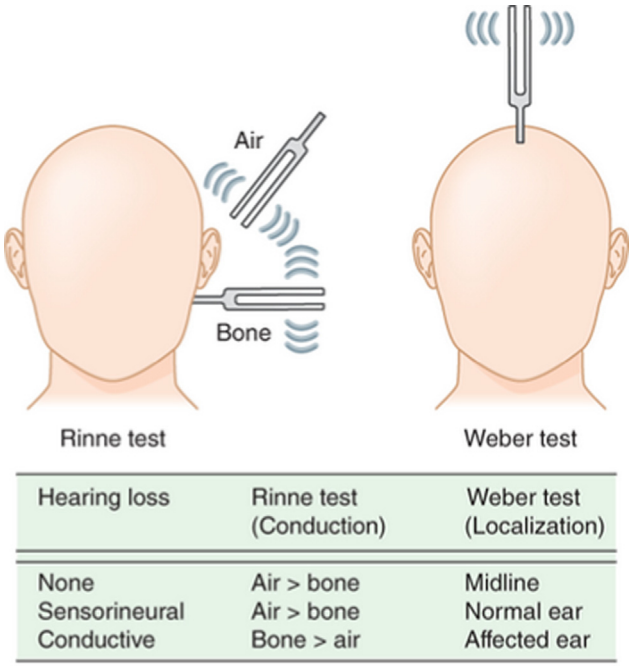
Test	Description
Otoacoustic emissions (OAEs) test	• OAEs are a test of cochlear outer hair cell function. There are two types used clinically, transient evoked otoacoustic emissions (TEOAE), and distortion product otoacoustic emissions (DPOAE). OAEs are not an actual hearing test. They provide information to help determine the presence or absence of hearing loss and are often used as a hearing screen tool. If hearing loss is present, OAEs can be used to determine if the hearing loss is caused by damage to the cochlea or by neural damage. People with mild degrees of hearing loss may have normal OAEs. [93] • Physiologic noise, external noise and movement must be kept to a minimum for effective assessment • OAE devices can be purchased as diagnostic or screening equipment. Some devices are powered by AA batteries, or rechargeable batteries. The following link is a comparison of OAE and ABR equipment: http://www.infanthearing.org/newborn-hearing-screening/equipment.html
Auditory Brainstem Response (ABR) sedated and non-sedated	• ABR is an evaluation that tests the auditory neural pathway. It assesses how well the acoustic nerve transmits information to the brain. It can be used to determine the presence of hearing loss and to estimate of the degree and frequency specificity of hearing loss. [93] • ABR can be used with people of all ages, but it is typically used for infants under the age of six months and for older children who are unable or unwilling to respond consistently to acoustic stimuli. ABR in adults is primarily used in patients with neurological deficit and can also be used for detection of lesions such as acoustic neuroma by testing the brainstem pathway • Screening ABRs are non-sedated procedures used to screen the hearing of an individual, and commonly used in newborns. Some devices are powered by AA batteries, or rechargeable batteries. The sensitivity and specificity of these tests is variable • Non-sedated ABRs are typically used to evaluate hearing of infants less than six months of age • Sedated ABRs can be used to evaluate children older than six months, or adult with cognitive impairment. Sedation is necessary given the potential for inadequate results caused by noise generated by the person being tested. The type of sedation used and the location of the assessment varies depending the subject's medical condition and institutional practices. ABR must be performed in a quiet location. • Using ABRs requires proper equipment and expertise of the person conducting the test. • **Auditory steady state response (ASSR**) is another method of assessing the auditory neural pathway. It enables the examiner to assess multiple frequencies, in both ears, at one time. In contrast, ABR is evaluated by assessing each frequency independently, one ear at a time.
Audiometry	Audiometry is the gold standard for the diagnosis of hearing loss, and it has the ability to diagnose specifically sensorineural hearing loss. • **Behavioral Audiometry** is typically performed with an audiometer in a sound booth or in a quiet location. The purpose is to determine the presence or absence of hearing loss. If hearing loss is present, the type, degree, and frequency specificity can be determined. Behavioral audiometry testing techniques vary based on the age and developmental level of the patient. This test is the most commonly utilized in children and adults. Children and adults can typically push a response button or raise their hand when they hear the test stimuli. Testing can be performed through a variety of transducers including sound field speakers, bone conduction vibrator, insert earphones or circumaural ear earphones. Insert earphones or circumaural earphones provide ear specific information. Bone conduction provides information on the type of hearing loss. • **Behavioral Observation Audiometry (BOA)** is typically used with children under six months of age and for children with developmental delays. The audiologist presents tonal and speech stimuli and watches the child for responses to stimuli. This is typically performed by presenting stimuli through sound field speakers. • **Visual Reinforcement Audiometry (VRA)** is typically used with children six to 24 months of age and for children with developmental delays. The audiologist conditions the child to respond by pairing an auditory stimulus and a reinforcer. The preferred response is a 90-degree head turn to the reinforcer. The audiologist must be alert to less overt consistent responses • **Conditioned Play Audiometry (CPA)** is typically used with children between two and five years of age and for children with developmental delays. The audiologist conditions the child to perform a task when the child hears the stimuli, such as dropping a block in a bucket • **Audiometer programs on tablet computers** present an option to traditional clinical audiometers. They are effective for children and adults who can respond to auditory stimuli presented via bone conduction, insert earphones or circumaural transducers. Automatic and professionally administered test versions are available • **Hearing Screening Smartphone apps** are available on Android and Apple smart phones. They are effective with the use of calibrated headphones in quiet environments • **Functional auditory assessment questionnaires** can be completed by a patient or their parents (such as the Early Listening Function). [99] This gives professionals information about responses to sound outside of the testing session
Tuning fork tests – using the 512 Hz tuning fork	• **The Weber and Rinne tuning fork tests** can be used to give information on the type of hearing loss and affected ear (s). This can be useful when more specific testing (audiometry) cannot be obtained. Both tests must be performed in order to interpret the results. (Fig. 2) • Normally, air conduction through the ear canal is greater than bone conduction. Inability to detect air-conducted sound through the ear canal indicates conductive hearing loss in the affected side. Inability to detect bone-conducted sound is indicative of SNHL in the affected side • **Weber test or Localization test** – The examiner strikes a tuning fork and places it mid-forehead. A patient with normal hearing will perceive sound on both sides (as coming from the midline). Patients with conductive hearing loss will indicate that the sound is perceived as coming from the affected ear (lateralization to the affected ear). Patients with SNHL will indicate that the sound is perceived as coming from their normal ear (lateralization to the normal ear)
Other indirect assessment for screening for hearing loss	• **Validated questionnaire** for adults and children. [94] These may include validated questionnaires in adults, or survey for hearing loss in the context of neurodevelopmental testing in children. Standard neurodevelopmental tests include specific questions and observations that allow the examiner to assess the hearing capacity of the patient. While non-specific for the type of hearing, these observations by experienced examiners may be able to identify hearing loss as a factor for poor performance in a neurodevelopmental test and are therefore routinely performed as part of the neurodevelopmental testing. A description of the various tests is beyond the scope of this review. • **Finger rub test**: refers to the perception of sound when fingers are rubbed near the ear. This is a crude test for which sensitivity and specificity data is not available.

(*continued on next page*)

Table 6 (*continued*)

Test	Description
	• **Whispered voice test**: refers to the perception of sound when whispering near the ear. This is a crude test for which sensitivity and specificity data is not available. • **Remote screening:** refers to distance screening via an electronic online or telehealth system when in person testing cannot be performed. These are feasible and reasonably accurate tests, with sensitivity of various tests ranging from 87 to 100% with specificity ranges from 60 to 96%. [100]

Decibel (dB): One-tenth of a Bel (named for Alexander Graham Bell) – is a unit to express intensity of sound; more specifically the logarithm of the ratio of two sound intensities.
Frequency: number of cycles (complete oscillations) of a vibrating medium per unit of time; the psychoacoustic correlate is pitch. Time for completion of one cycle is the period.
Hertz (Hz): in acoustics, unit to express frequency (formerly cycles per second or cps). The human ear is capable of hearing from approximately 20 to 20,000 Hz.
Pure tone: single-frequency sound; rarely occurs in nature.
* Important terminology to know to properly utilize these tools includes:



Hearing loss	Rinne test (Conduction)	Weber test (Localization)
None	Air > bone	Midline
Sensorineural	Air > bone	Normal ear
Conductive	Bone > air	Affected ear

Fig. 2. Tuning Fork Tests and their Interpretation. Source: medicinespecifics.com.

appropriate. Relevant references from these articles that were not captured in the reviews were also retrieved and considered.

In the 2018 book by Dudley et. al entitled "The Clinician's Vaccine Safety Resource Guide: Optimizing Prevention of Vaccine-Preventable Diseases Across the Lifespan" [104], a systematic literature review was performed on the association of hearing loss and vaccination. Our update added one new article to the eleven already cited [44]. In addition, Mateer et. al performed a literature review on Lassa fever-induced SNHL in June 2017 [14]. Our update surfaced three results aside from the Mateer et al. publication itself [105–107]. Finally, we searched PubMed to find the most current and detailed reviews of SNHL, and twenty reviews were selected for further examination and potential inclusion.

All abstracts were screened for possible reports of SNHL following immunization. Articles with potentially relevant material were reviewed in more detail, in order to identify studies using case definitions or, in their absence, providing clinical descriptions of the case material. General medical, pediatric and infectious diseases books were also consulted.

1.15. Rationale for selected decisions about the case definition of SNHL as an adverse event following immunization

The working group agreed that the diagnosis of SNHL depends on the demonstration of reduced hearing acuity by auditory testing, specifically audiometry. (Appendix B) The working group agreed to accept the definition of SNHL as hearing loss of at least 30 dB in three sequential frequencies in the standard pure tone audiogram. Performing an audiometry can be a limiting factor to the diagnosis, when adequate equipment and appropriately trained personnel are not available.

Hearing is measured in decibels (dB), with the threshold of 0 dB for each frequency, denoting the value at which normal young adults perceive a tone burst of a given intensity and frequency 50% of the time. Hearing acuity is classified as normal if it is within −10 to 15 dB. The working group suggests that the severity of hearing loss is graded as slight (15 to 25 dB), mild (26–40 dB), moderate (41–55 dB), moderately severe (56–70 dB), severe (71–90 dB), or profound (>90 dB). Frequency of hearing loss is designated as low (<500 Hz), middle (500–2000 Hz), or high (>2000 Hz).

1.15.1. The meaning of "Sudden Onset" and "Rapid Progression" in the context of SNHL

The term "sudden onset" refers to an event that occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition. Sudden onset or sudden sensorineural hearing loss (SSNHL) refers to hearing loss of at least 30 dB involving three consecutive frequencies occurring over less than 72 h. Some of the potential causes of SSNHL can be treated if identified early.

The term 'rapid progression' is a conventional clinical term. An exact timeframe for the progression of hearing loss is not always feasible to establish given the variability of clinical presentations of SNHL. However, the working group considered the progression of hearing loss as the variability in audiometry results over time. A significant progression of hearing loss is considered when there is a change of more the 10 dB per frequency between two measurements, or when the variability results in a change in category, for example, from normal hearing to mild hearing loss, or from mild to moderate hearing loss, and so forth. When variability indicating hearing loss is identified, close follow up with subsequent testing within a relatively short time interval (e.g. 2–4 weeks) from the time the abnormality is identified, should be conducted.

1.15.2. Rationale for individual criteria or decision made related to the case definition

The working group agreed to a definition of SNHL as established by audiometry testing and physical examination. Pathology, radiology and laboratory findings are not included in the case definition, although they can provide important information regarding the causes of SNHL.

1.15.3. Influence of treatment on fulfilment of case definition

The benefit of the use of glucocorticoids for idiopathic sudden sensorineural hearing loss is uncertain, however, some studies have found benefit from systemic or intratympanic steroids

Table 7
Evaluation of sensorineural hearing loss vs. conductive hearing loss.

conductive hearing loss

Location	Condition	Typical History	Physical examination	Diagnosis	Management
Pinna and Cerumen	external auditory canal removal	Cerumen impaction of the external auditory canal	Hearing loss, fluctuating or gradual hearing loss	Occlusive cerumen in the external auditory canal	Examination
	Ear canal neoplasm (e.g., exostosis, osteoma)	Gradual hearing loss	Ear canal with abnormal bony growth causing obstruction.	Examination	Excision of the exostosis
	Foreign body in the ear canal	Hearing loss, otalgia	Foreign body in the ear canal	Examination	Foreign body removal
	Otitis externa	Otalgia, otorrhea	Edematous and inflamed ear canal	Examination	Topical antimicrobial and steroid
Middle Ear	Cholesteatoma	Recurrent otitis media, history of perforation, otorrhea, otalgia, gradual onset of hearing loss	Tympanic membrane with retraction pocket and debris or perforation, otorrhea, pearly white mass in the middle ear	Computed tomography of temporal bone with no contrast.	Tympanoplasty with excision of the cholesteatoma with or without mastoidectomy. Ossicular chain reconstructed as needed.
	Tympanic membrane perforation	Trauma, recurrent otitis media	Tympanic membrane perforation	Examination	Observation, surgical closure of the perforation (tympanoplasty)
	Ossicular chain discontinuity	Trauma, recurrent otitis media, cholesteatoma	Usually normal ear examination although can have tympanic membrane perforation	Computed tomography of temporal bone with no contrast.	Tympanoplasty with ossicular chain reconstruction.
	Otitis media with effusion	Fever, otalgia, hearing loss	Middle ear effusion with tympanic membrane immobile on pneumatic otoscopy	Examination	Expectant management with antibiotics as needed. Myringotomy with ear tubes placement for refractory effusion longer than 3 months.
	Otosclerosis	Gradual onset of hearing loss starting at 30–50 years old, tinnitus	Usually normal tympanic membrane	Audiogram, CT of temporal bone with no contrast	Hearing aids and potential tympanoplasty with stapedectomy in selected patients.
	Glomus tumor	Pulsatile tinnitus	Reddish mass behind the tympanic membrane	CT of temporal bone with contrast, MRI of IAC and MRA	Surgical excision in symptomatic patients; hearing aids and conservative management in asymptomatic patients.
Sensorineural Hearing Loss					
Location	**Condition**	**Typical History**	**Physical examination**	**Diagnosis**	**Management**
Inner ear	Noise exposure	Acoustic trauma (acute exposure to > 130 dB noise) or chronic exposure to loud (>85 dB) noise. Tinnitus.	Usually normal tympanic membrane	Examination Audiogram	Hearing aids as needed (acoustic trauma lasts hours to days)
	Presbycusis	Hearing loss associated with age.Family history of hearing loss.	Usually normal tympanic membrane	Examination Audiogram	Hearing aids
	Ototoxin exposure (e.g., aminoglycosides, loop diuretics, quinine, aspirin, platinum-based chemotherapy agents)	Exposure of medications or toxins. Hearing loss develops over weeks.	Usually normal tympanic membrane	ExaminationAudiogram	Stop the medication or prevent further exposure to the toxin. Hearing aids
	Trauma	Current or past head or neck trauma	Hemotympanum, tympanic membrane perforation	CT of the temporal bone without contrastAudiogram	Refer to an otolaryngologist
	Meniere disease	Episodic, fluctuating ear fullness associated with tinnitus, hearing loss and/or vertigo	Usually normal tympanic membrane with possible rotary nystagmus and ataxia	ExaminationAudiogram	Acute episodes - vestibular suppressants;Long term treatments - diuretics, vestibular rehab, *trans*-tympanic injection of corticosteroid or gentamicin, and rarely, surgery (endolymphatic sac decompression)
	Autoimmune	Bilateral, rapid progressive hearing loss, ataxia, vertigo, symptoms of recognized autoimmune disease	Usually normal tympanic membrane	Auto-immune laboratory evaluationAudiogram	Immuno-suppressive drugs, *trans*-tympanic corticosteroids
	Tumor/neoplasm (e.g., acoustic neuroma, meningioma, paraganglioma, endolymphatic sac tumor)	Gradual and progressive hearing loss, tinnitus, vertigo and headache	Usually normal tympanic membrane	MRI with contrastAudiogram	Surgical excision
	Vascular cause (e.g., stroke, thromboembolic phenomena, hypercoagulable states)	Gradual or sudden hearing loss, tinnitus, vertigo	Usually normal tympanic membrane	MRI with contrastAudiogram	Conservative management of the vascular cause

(*continued on next page*)

Table 7 (*continued*)

conductive hearing loss					
Location	**Condition**	**Typical History**	**Physical examination**	**Diagnosis**	**Management**
	Non-congenital infectious condition (e.g., meningitis, labyrinthitis)	Potential history of otitis media, fever, vertigo, tinnitus, hearing loss develops over hours to days	Possible evidence of erythematous tympanic membrane with middle ear effusion. Nuchal rigidity and fever in patient with meningitis. Nystagmus and ataxia in labyrinthitis.	CT of temporal bone without contrast or MRI of IAC, lumbar punctureAudiogram	Antibiotics for meningitis, expectant management or vestibular rehabilitation for labyrinthitis. Consultation with otolaryngologist, neurologist, or infectious disease specialist.
	Congenital infectious (e.g., syphilis, cytomegalovirus, herpes, rubella, rubeola, mumps)	Varies depending on if it is a symptomatic vs. non-symptomatic infection	Usually normal tympanic membrane	ExaminationAudiogram MRI as needed	Potential anti-viral pending on the timing of diagnosis
	Neuro-degenerative or demyelination disorders (Alport, Cogan syndrome)	Gradual onset of hearing loss, vertigo and tinnitus	Usually normal tympanic membrane	Examination and Audiogram	Hearing aids and conservative treatment for the underlying disorder
	Neurogenic (e.g., Multiple sclerosis)	Gradual onset with variable progression	Usually normal tympanic membrane	Examination and Audiogram	Hearing aids and conservative treatment for the underlying disorder
	Inner ear malformation (Labyrinthine aplasia, cochlear aplasia, common cavity, cochlear hypoplasia, incomplete partition, cochlear nerve hypoplasia vs aplasia	Varying degrees of hearing loss since birth with variable progression	Usually normal tympanic membrane	CT of temporal bone without contrast for bony abnormality andMRI for evaluation of cochlear nerveAudiogram	Hearing aids or hearing implants pending on the degree of hearing loss
	Osseous disorders (e.g., Paget disease, cochlear otosclerosis)	Gradual onset of hearing loss	Usually normal tympanic membrane	CT of temporal bone without contrast for bony abnormality andMRI for evaluation of cochlear nerveAudiogram	Hearing aids

Abbreviations: CT – computed tomography, IAC – internal auditory canal, MRA - magnetic resonance angiography, MRI – magnetic resonance imaging

[102]. The working group decided against using treatment or treatment response towards the fulfillment of the SNHL case definition. A standard treatment is not established, and a treatment response or its failure is not in itself diagnostic of SNHL.

1.15.4. Timing post immunization

Specific time frames for onset of SNHL following immunization should be considered. Cases of SNHL have been reported in the literature after receipt of certain immunizations, however a causal association has not been established. As reviewed in Sections 1.5 and 1.8, some infections are associated with SNHL through various possible pathogenic mechanisms.

Although the purpose of this case definition is NOT to establish a causal relationship between immunization and SNHL, we postulate that a definition designed to be a suitable tool for testing potential causal relationships requires ascertainment of the outcome (SNHL) independent from the exposure (immunization). Therefore, to avoid selection bias, a restrictive time interval from immunization to onset of SNHL should not be an integral part of this definition. Instead, where feasible, details of this interval should be assessed and reported as described in the data collection guidelines. (Appendix C)

Further, SNHL often occurs outside the controlled setting of a clinical trial or hospital. In some settings it may be impossible to obtain a clear timeline of the event, particularly in less developed or rural settings. In order to avoid selecting against such cases, the SNHL case definition avoids setting arbitrary time frames. Also, SNHL may have occurred prior to vaccination. Therefore, evaluation of hearing prior to the first (baseline) and any subsequent vaccinations is recommended when there is concern for SNHL as and AEFI.

1.15.5. Differentiation from other similar disorders

Conductive hearing loss is the most important differential diagnosis to consider to establish a diagnosis of SNHL. The key elements to establish these diagnoses are included in Table 7.

1.16. Guidelines for data collection, analysis and presentation

The case definition is accompanied by guidelines which are structured according to the steps of conducting a clinical trial, i.e. data collection, analysis and presentation. (Appendix B and C) Neither case definition nor guidelines are intended to guide or establish criteria for management of ill infants, children, or adults. Both were developed to improve data comparability.

1.17. Periodic review

Similar to all Brighton Collaboration case definitions and guidelines, review of the definition with its guidelines is planned on a regular basis and as needed.

2. Case definition of SNHL

The working group recommends to utilize the standard definition of SNHL endorsed by the American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS), the National Institute of Deafness and Other Communication Disorders (NIDCD), and the American Speech-Language-Hearing Association (ASHA), as follows:

SNHL is hearing loss of at least 30 dB in three sequential frequencies in the standard pure tone audiogram. SNHL results from dysfunction of the inner ear, the vestibulocochlear nerve, or the central processing centers of the brain.

The definitive diagnosis of SNHL requires:

A physical examination to exclude conductive hearing loss

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AND

An audiometric evaluation consistent with SNHL

The definition can be applied to any subject, regardless of age or clinical presentation. While some subjects may present with self-recognized hearing loss or other clinical symptoms such as tinnitus, or because of concerns from contacts who have observed difficulty understanding everyday conversation, frequently asking others to repeat things, social avoidance, difficulty hearing with background noise, or turning up the volume of sound equipment, some individuals with SNHL might have no clinical symptoms or concerns. This is more likely to occur with milder severity or unilateral SNHL.

A key element of the definition of SNHL is the differentiation between conductive hearing loss and SNHL. A careful physical examination and a properly conducted audiometry test are considered essential to establish a definitive diagnosis of SNHL (definite case). The criteria for ascertainment of a case of SNHL based on level of diagnostic certainty are described in Table 8.

A physical examination that excludes possible causes of hearing loss includes the clinical observation and inspection of the ears to demonstrate that there are no anomalies or obstruction of the ear canal, and that the tympanic membrane is visible, intact and mobile, with no evidence of middle ear disease. The physical examination must include otoscopy, which is necessary to evaluate the patency of the ear canal and the condition and movement of the tympanic membrane. In addition to otoscopy, a tympanogram, if available, can help identify middle ear disease, and could be included as part of the physical examination to exclude conductive hearing loss, but it is not considered essential, as long as proper physical exam is conducted.

An audiometry consistent with SNHL is one that shows 30 dB or more hearing loss over 3 consecutive frequencies.

The audiometry can be a limiting factor for a definitive diagnosis when adequate equipment and appropriately trained personnel are not available. However, the diagnosis of SNHL may be established at a lower level of certainty (probable case), with a physical examination that excludes conductive hearing loss and by performing standard tests that can differentiate conductive vs. SNHL utilizing a an ABR or Tuning fork test, as described in this document.

An auditory brainstem response (ABR) test is considered equivalent to standard audiometry in infants under 6 months of age and in individuals older than 6 months of age, who are unable to be tested by audiometry because of inability to respond to auditory stimuli, such as in persons with cognitive impairment. In older persons the ABR does not provide as complete data compared to standard audiometry, it requires a prolonged testing period, and is more costly.

Other tests such otoacoustic emissions (OAE), behavioral questionnaires, and remote testing using telehealth technologies, are not able to establish a specific diagnosis of SNHL, but can be used to determine hearing loss, when used in conjunction with a physical examination that excludes conductive hearing loss (possible case). Understanding the proper utilization, limitations, and interpretation of these tests is important. Other indirect tests (finger rub, whisper test) are not recommended by the working group due to the lack of data on their reliability, sensitivity or specificity.

Table 8
Levels of diagnostic certainty (LOC) in the ascertainment of a case of SNHL.

Case definition of SNHL
SNHL is hearing loss of $\geq$ 30 dB in three sequential frequencies in the standard pure tone audiogram
Levels of Diagnostic Certainty
LEVEL 1 (Definite case)
A physical examination excluding conductive hearing loss
AND
Audiometry consistent with SNHL
LEVEL 2 (Probable case)
A physical examination excluding conductive hearing loss
AND
Auditory Brainstem Response (ABR) test consistent with SNHL
OR
Tuning fork exam consistent with SNHL
LEVEL 3 (Possible case)
A physical examination excluding conductive hearing loss
AND
Otoacoustic Emissions (OAE) test consistent with hearing loss
OR
Behavioral or neurodevelopmental testing questionnaire concerning for hearing loss
OR
Remote screening using telehealth technology concerning for hearing loss

Disclaimer

The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university, or corporation). Specifically, the findings and conclusions in this paper are those of the authors and do not necessarily represent the views of their respective institutions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data (Appendix A, B and C) to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.05.019.

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