Safety Platform for Emergency vACcines

AESI Case Definition Companion Guide

Sensorineural Hearing Loss

Work Package: WP2 Standards and tools

V1.0 – [28 Feb 2023]

Authors: Barbara Law, Marta Rojo Villaescusa

Nature: Report | Diss. level: Public

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THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

DOCUMENT INFORMATION

SPEAC Project Lead	Robert Chen	E-mail: robert.chen@cepi.net
Scientific Coordinator	Miriam Sturkenboom	E-mail: miriam.sturkenboom@cepi.net

Main Author(s)	Barbara Law Marta Rojo Villaescusa	E-mail: Barbara.law@cepi.net E-mail: martusred@gmail.com
WP Leader	Barbara Law	E-mail: barbara.law@cepi.net

Description of the deliverable	This deliverable collates into a single document the SPEAC Sensorineural Hearing Loss resources (ICD9/10-CM, MedDRA & SNOMEDCT codes, global background incidence data, risk factors), tools (data abstraction & interpretation form, tabular summary of key case definition criteria and algorithm for level of certainty determination, pictorial level of certainty algorithm) and guidance (key caveats from the published case definition, real time investigation, data collection, analysis and presentation). This guide can be used by stakeholders to assess the occurrence of Sensorineural Hearing Loss in several settings including as an adverse event following immunization.
Key words	Sensorineural Hearing Loss, Brighton case definition, risk factors, background rates, ICD-9-CM, ICD-10-CM, MedDRA, SNOMEDCT, case definition level of certainty.

DOCUMENT HISTORY

NAME OF DOCUMENT	DATE	VERSION	DESCRIPTION
D2.2.1 Sensorineural Hearing Loss Companion Guide	28Feb2023	1.0	Review and approval

DEFINITIONS & ACRONYMS

ABR	Auditory brainstem response
AEFI	Adverse Event Following Immunization
AESI	Adverse Events of Special Interest
AIED	Autoimmune inner ear disease
BC	Brighton Collaboration
CD	Case Definition
CDCP	Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness and Innovation
CHL	Conductive hearing loss
CI	Confidence Interval
CISA	Clinical Immunization Safety Assessment (project initiated by CDCP)
CMV	Cytomegalovirus
CUI	Concept Unique Identifier
dB	Decibel
DNA	Deoxyribonucleic acide
DTaP	Diptheria Tetanus acelluar Pertussis vaccine
DTaP-IPV	Diphtheria Tetanus acellular pertussis with inactivated polio combo vaccine
EBV	Epstein Barr Virus
ENT	Ear Nose and Throat
HIV	Human Immunodeficiency Virus
HL	Hearing loss
HPV	Human Papilloma Virus
HPV4	Human Papilloma Virus Quadrivalent Vaccine
HSV	Herpes Simplex Virus
Hz	Hertz
ICAM-1	Intercellular adhesion molecule 1
ICD-9-CM	International Classification of Diseases-9th Revision-Clinical Modification
ICD-10-CM	International Classification of Diseases-10th Revision-Clinical Modification
ICPC-2	International Classification for Primary Care Version 2
IOM	Institute of Medicine (now the National Academy of Medicine)
IPV	Inactivated Polio Vaccine
ISSNHL	Idiopathic sudden sensorineural hearing loss
LAIV	Live attenuated influenza vaccine
lang	Language (relevant to literature search instructions)
LMIC	Lower- or Middle-Income Country
LOC	Level of Certainty
MCV4	Quadrivalent meningococcal conjugate vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings (used for indexing articles for PubMed)
MHL	Mixed hearing loss
MMR	Measles Mumps Rubella vaccine
MRI	Magnetic Resonance Imaging
N	No

noexp	Literature search term to turn off automatic explosion of MeSH headings
NOS	Not otherwise stated
NSAID	Non-steroidal anti-inflammatory drug
OAE	Otoacoustic emissions
OR	Odds Ratio
ORL	Otorhinolaryngology
Read-CTv3	READ Clinical Terminology version 3
RNA	Ribonucleic acid
SARS-CoV-2	Reporting Odds Ratio
SD	Reactive oxygen species
SHL	Sudden hearing loss
SNHL	Sensorineural hearing loss
SNOMEDCT	SNOMED Clinical Terminology
SOSNHL	Sudden onset sensorineural hearing loss
SSNHL	Sudden sensorineural hearing loss
SPEAC	Safety Platform for Emergency Vaccines
TB	Tuberculosis
Tdap	Tetanus diphtheria acellular pertussis vaccine (formulated for ≥7-year-olds)
ti	Title (used for literature search)
tiab	Title & abstract (used for literature search)
TM	Tympanic membrane (ear drum)
U	Unknown
UMLS	Unified Medical Language System
URTI	Upper Respiratory Tract Infection
VAERS	Vaccine Adverse Event Reporting System
VCAM-1	Vascular cellular adhesion molecule - 1
VZV	Varicella Zoster Virus
Y	Yes

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INTRODUCTION

1. Background

CEPI has contracted with the Brighton Collaboration (BC), through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

SPEAC Work Package 2 is creating resources and tools for the AESI including:

1. Tabular summaries of ICD9/10, MedDRA and SNOMEDCT codes for each AESI.
2. Spreadsheet and tabular summaries of global AESI incidence data.
3. Tabular summaries of risk factors and evidence on vaccine – AESI association.
4. Guidance on AESI real time investigation, data collection, analysis and presentation.
5. Tools to facilitate capturing the specific clinical data needed to meet AESI case definitions across a variety of settings applicable to clinical trials, epidemiologic studies and individual case causality assessment. These include:
    a. Data abstraction and interpretation forms to facilitate capturing data from medical charts and applying it to determine a given AESI case definition level of certainty.
    b. Tabular logic and pictorial decision tree algorithms, keyed to the data abstraction form case definition criteria to facilitate harmonized assessment of the level of diagnostic certainty for each AESI.
    c. Glossary of terms relevant to anaphylaxis and the neurologic AESI.

All tools and resources noted above are compiled together into a companion guide for each Brighton AESI case definition. That is the purpose of this deliverable, which focuses on Sensorineural Hearing Loss.

2. Objective of this deliverable

To collate SPEAC & BC tools and resources that have been developed for Sensorineural Hearing Loss.

3. Methods

The methods for developing each of the tools included in this guide were detailed in previously completed SPEAC deliverables as follows:

- Sensorineural Hearing Loss Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- Sensorineural Hearing Loss background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Sensorineural Hearing Loss Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- Sensorineural Hearing Loss Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation

The methods are briefly described in Appendix 6 of this Guide along with links to source documents which have more detailed methodology. A new feature of this and future Companion Guides is that a systematic search was done for risk

factors and background rates. The methods section in Appendix 6 has been amended to include the new approach and specific search strategy used.

4. Results

4.1 Systematic Search for Background incidence and Risk Factors

A total of 41 articles were retrieved of which 9 were screened out for the following reason: 1 duplicate, 6 focused on treatment, diagnosis or prevention and 2 were non-contributory to risk factors or general population background incidence. Of 32 articles screened in for full text review: none had data on background incidence; 3 were studies cited by the SNHL working group[11, 20, 21]; and 12 provided risk factor information beyond what was included in the case definition publication.[22, 23, 25-29, 31, 32, 42] The remaining 17 articles did not provide any new data on risk factors. In addition, several articles, cited in the SNHL CD publication were also reviewed in depth to provide more specific detail on risk factors. [12, 14, 15, 17-21]

The citations of all retrieved articles were carefully searched for studies of background incidence. This identified the 7 studies included in the Appendix 2, Background Incidence Table.[7-13]

4.2 Systematic Search for Vaccine / vaccination as a risk factor for Sensorineural Hearing Loss

A total of 166 articles were retrieved from the search strategy as shown in Appendix 6. Of these 99 were excluded based on title or abstract including 2 duplicates, 84 judged to be non-contributory over and above what was already found in the screened in publications, 12 which focused on treatment, diagnosis, or prevention of hearing loss and 1 that focused on healthcare. After full text review of the remaining 67 articles, 47 were excluded as being non-contributory to SNHL occurring in an immunization context, leaving 19 case reports and 1 data link study of SNHL following immunization. Of these 9 had been cited in the case definition publication[45, 46, 48-50,54-56, 59] and 11 [47, 51, 58, 60-66, 68] were not. Hand search of the included report references yielded an additional 8[52, 53, 57, 67, 69-71, 74] publications of which 6 were case reports [52, 53, 57, 67, 69, 70], 1 was a summary of VAERS reports of SNHL after COVID-19 vaccination[71] and 1 was a data-link study of SNHL following the Pfizer mRNA vaccine in Israel, compared to historical incidence in 2018 and 2019.[74]

The case reports and data link study results are summarized in Appendix 3 Tables 3.1 and 3.3. The case reports documented temporal but not causal association with SNHL following: measles/mumps[45-47], influenza[48, 49, 50], Hepatitis B[51-54], tetanus / diphtheria[55, 56] meningococcal[56], rabies[57, 58] vaccines and tetanus antitoxin.[59] A Northern California Kaiser Permanente electronic datalink study of all vaccines used from 2007 through 2014 did not find evidence for an increased risk of post-immunization SNHL.[50]

Most SNHL case reports were for single vaccines, 41 in total, followed COVID-19 vaccines: 32 mRNA [61-63, 66, 68, 70] (16 Pfizer, 15 Moderna, 1 not specified); 7 adenoviral vector[60, 64, 65, 68, 69] (3 ChAdOx1, 4 Vaxzevria); and 2 inactivated virus [67] (Sinovac). With respect to dose, 20 occurred after dose 1, 15 after dose 2, 3 after dose 3 and 3 after each of dose 1 and dose 2.

Table 1 classifies the case reports according to dose and interval from immunization to onset, following the recommended intervals by the SNHL working group. The 3 cases where SNHL occurred after each of dose 1 and dose 2 are not included in the table because the timing after each dose was not specified in the report.

Table 1. Timing of SNHL onset following COVID-19 vaccine by dose.

	Interval from immunization to onset of SNHL		
Vaccine dose (total cases)	< 1 week (% cases)	1 to <4 weeks (% cases)	4 to 12 weeks (% cases)
Dose 1 (20 cases)	9 (45%)	10 (50%)	1 (5%)
Dose 2 (15 cases)	4 (27%)	9 (60%)	2 (13%)
Dose 3 (3 cases)	2 (67%)	1 (33%)	0

A ~~reporting incidence~~ cross-sectional study using VAERS data identified a total of 2170 possible cases of SSNHL. [71] Of these, 555 reports met their definition of probable SSNHL (onset within 21 days after vaccination and a report that referenced an audiographic report confirming hearing loss or specific physician diagnosis of SSNHL, or otolaryngologist evaluation resulting in specific treatment for SSNHL or MRI investigation). They calculated a minimum annualized incidence of vaccine-associated SSNHL of 0.6/100,000 people per year including only the probable cases and based on the assumption that the population size included 1 vaccine dose/person and all cases that occurred following vaccination were reported to VAERS. They also calculated a maximum vaccine-associated SSNHL incidence of 28.0 cases/100,000 using all 2170 possible cases and assuming a population size that included 2 vaccine doses/person and that there was 50% underreporting of SSNHL cases to VAERS. They compared these rates to the USA 2005-2006 study by Alexander et al[7] which estimated an age-related range of 11-77 cases of idiopathic SSNHL/100,000/year and concluded that there was no population-level association between COVID-19 vaccination and SSNHL. In contrast, an Israeli datalink study found a slightly increased risk of SNHL within 3 weeks following Pfizer mRNA vaccine relative to the incidence in historical cohorts (2018 and 2019) with an attributable risk of 0.91/100,000 for first doses and 0.61/100,000 for second doses. No conclusion can yet be drawn as to a causal association between COVID-19 vaccination and SNHL and further research is needed. In their discussion of the VAERS data, Formeister et al concluded that while there did not appear to be a population-based risk, it was not possible to rule out causality in individual cases, and underscored this with post-mortem findings in fatal COVID-19 cases of SARS-CoV-2 viral RNA in the middle ear[72] and experimental evidence that SARS-CoV-2 can directly infect human vestibular hair and Schwann cells.[73]

Perhaps the risk factor data that are most relevant to Lassa Fever vaccine developers planning clinical trials in West Africa are the many prevalent risks for sensorineural hearing loss in the population from birth due to congenital CMV[24, 25] in particular, as well as from viral (including Lassa Fever[34,35] itself as well as Zika and Ebola infection[35]), bacterial and parasitic infections suffered during childhood or later, the increased risk of SNHL in individuals with Sickle Cell Disease[31, 32] or iron deficiency anemia[33], the impact of parental consanguinity on risk of genetic causes of SNHL and potential for SNHL following exposure to ototoxic drugs. While history of possible exposure to risk factors or family history of SNHL is important, objective measurement of hearing function is also highly recommended. Audiologic assessment of clinical trial subjects should be done prior to administration of each scheduled vaccine dose and repeated 3 to 4 weeks later as well as at the end of the clinical trial follow-up.

All outputs are provided in separate appendices as shown below:

1. Sensorineural Hearing Loss Diagnostic Codes: ICD-9-CM, ICD-10-CM and MedDRA
2. Sensorineural Hearing Loss background rates
3. Sensorineural Hearing Loss risk Factors
4. Sensorineural Hearing Loss case definition key caveats for diagnosis, data analysis and presentation plus recommendations for real time investigation.
5. Sensorineural Hearing Loss data abstraction and interpretation forms with algorithms for assessing level of certainty.

6. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion

This guide brings together many resources and tools related to the AESI of Sensorineural Hearing Loss including: ICD-9/10-CM, SNOMED and MedDRA codes for data entry or database searching; background rates; risk factors; guidance for real time investigation; and tools for collecting and interpreting clinical data to apply the Brighton Sensorineural Hearing Loss case definition and determine the level of diagnostic certainty.

The choice of tabular or pictorial algorithm is up to the user in terms of what is best suited to the situation and the assessor. SPEAC recommends that the tools be used to assign level of certainty for all identified AEFI with features of Sensorineural Hearing Loss. This standard, harmonized approach will facilitate signal detection and assessment, epidemiologic studies of background incidence, hypothesis testing for causality and capacity to combine data across trials for meta-analyses. Further in the context of clinical phase I, II and III trials of Lassa Fever vaccine in West Africa, SPEAC recommends that audiologic assessment of all clinical trial subjects be done prior to each scheduled dose and 3-4 weeks after each dose and at the end of the planned study follow-up.

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APPENDIX 1

Sensorineural Hearing Loss Diagnostic Codes: ICD-9/10-CM, MedDRA and SNOMED

4.1 Sensorineural Hearing Loss Diagnostic Codes: ICD-9/10-CM and MedDRA

TABLE 1. NARROW TERMS FOR Sensorineural Hearing Loss (note, the abbreviation SNHL is used for UMLS concept name and code Term when it matches sensorineural hearing loss. Variations are written out in full)

UMLS Concept		Diagnostic Coding Systems Terms and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0018784	SNHL (disorder)	SNHL	10040016	389.1		60700002
		SNHL, unilateral		389.15		
		SNHL, asymmetrical		389.16		428887009
		SNHL, bilateral		389.18		194424005
		Sudden SNHL				715239002
		Profound SNHL				700454004
		High frequency SNHL of bilateral ears				1083811000119108
		SNHL of right ear				1119386008
		SNHL of right ear with normal hearing left side				1010441004
		SNHL of left ear				1119387004
		SNHL of left ear with normal hearing right side				1010442006
		Unspecified SNHL			H90.5	
		SNHL, unspecified	10040018	389.10		
		Sensorineural deafness	10040015			
		Neurosensory deafness	10029253			
		Neurosensory hypoacusis	10067587			
		Sensory hearing loss, bilateral		389.11		430985005
		Sensory hearing loss, unilateral		389.17		
		Neural hearing loss, bilateral		389.12		430977001
		Neural hearing loss, unilateral		389.13		
		Neural hearing loss of right ear				1010230003
		Neural hearing loss of left ear				1010229008
		Central hearing loss		389.14		
		Deafness neurosensory	10011891			
		Perceptive deafness	10034375			194421002

		Perceptive deafness [diagnos]				155256000
		Perceptive hearing loss NOS				194427003
C0452138	SNHL, bilateral				H90.3	
C0452139	SNHL, unilateral with unrestricted hearing on the contralateral side SNHL, unilateral with unrestricted hearing on the contralateral side, right ear SNHL, unilateral with unrestricted hearing on the contralateral side, left ear				H90.4 H90.41 H90.42	194425006
C2229503	SNHL in right ear					23641000119100
C3863312	High frequency SNHL in right ear					1091541000119108
C1691779	Sensory hearing loss		10040029			

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C1955773	Unilateral neural hearing loss					425601005
C1955774	Unilateral sensory hearing loss					425980006
C0155550	Neural hearing loss	Neural hearing loss	10029222			
		Neural deafness	10029221			
		Nerve deafness	10029178			
		Deafness nerve	10011889			
		Deafness nerve type	10011890			
		Cochlear nerve deafness	10009833			
		Nerve conduction deafness				80695003
C0001163	Vestibulocochlear Nerve Diseases	Disorders of acoustic nerve	10013292	388.5	H93.3, H93.3X	
		Disorders of right acoustic nerve			H93.3X1	
		Disorders of left acoustic nerve			H93.3X2	
		Disorders of bilateral acoustic nerves			H93.3X3	
		Disorders of unspecified acoustic nerves			H93.3X9	
		Disorder of acoustic nerve Acoustic neuroma	 10000523			77949003 126949007
		Acoustic nerve disorder NOS	10000521			194402005
		Auditory nerve disorder Auditory nerve disorders Auditory neuropathy spectrum disorder	10078784 10003788 10072198			
		VIIIth cranial nerve disorders	10047408			
		VIIIth nerve injury	10047409			
		VIIIth nerve lesion Deafness neurosensory Deafness permanent Deafness transitory Neurosensory hypoacusis Mumps deafness	10062177 10011891 10011894 10011900 10067587 10075137			

UMLS Concept		Diagnostic Coding Systems Terms and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0494559	Diseases of inner ear	Inner ear disorder Inner ear disorder NOS Disorder of inner ear [X]Diseases of inner ear Otosclerosis	10061524 10049276		 H80	 232297009 194690003
		Otosclerosis involving oval window, nonobliterative			H80.0	
		Otosclerosis involving oval window, nonobliterative, unspecified ear			H80.00	
		Otosclerosis involving oval window, nonobliterative, right ear			H80.01	
		Otosclerosis involving oval window, nonobliterative, left ear			H80.02	
		Otosclerosis involving oval window, nonobliterative, bilateral			H80.03	
		Otosclerosis involving oval window, obliterative			H80.1	
		Otosclerosis involving oval window, obliterative, unspecified ear			H80.10	
		Otosclerosis involving oval window, obliterative, right ear			H80.11	
		Otosclerosis involving oval window, obliterative, left ear			H80.12	
		Otosclerosis involving oval window, obliterative, bilateral			H80.13	
		Cochlear otosclerosis			H80.2	
		Cochlear otosclerosis, unspecified ear			H80.20	
		Cochlear otosclerosis, right ear			H80.21	
		Cochlear otosclerosis, left ear			H80.22	
		Cochlear otosclerosis, bilateral			H80.23	
		Other otosclerosis			H80.8	
		Other otosclerosis, unspecified ear			H80.80	
		Other otosclerosis, right ear			H80.81	
		Other otosclerosis, left ear			H80.82	
		Other otosclerosis, bilateral			H80.83	
		Unspecified otosclerosis			H80.9	

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		Unspecified otosclerosis, unspecified ear			H80.90	
		Unspecified otosclerosis, right ear			H80.91	
		Unspecified otosclerosis, left ear			H80.92	
		Unspecified otosclerosis, bilateral			H80.93	

UMLS Concept		Diagnostic Coding Systems Terms and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0494559	Diseases of inner ear (continued)	Ménière's disease Ménière's disease Ménière's disease Ménière's disease Ménière's disease			H81.0 H81.01 H81.02 H81.03 H81.09	
		Other diseases of inner ear			H83	
		Labyrinthitis Labyrinthitis, right ear Labyrinthitis, left ear Labyrinthitis, bilateral Labyrinthitis, unspecified ear			H83.0 H83.01 H83.02 H83.03 H83.09	
		Labyrinthine fistula Labyrinthine fistula, right ear Labyrinthine fistula, left ear Labyrinthine fistula, bilateral Labyrinthine fistula, unspecified ear			H83.1 H83.11 H83.12 H83.13 H83.19	
		Labyrinthine dysfunction Labyrinthine dysfunction, right ear Labyrinthine dysfunction, left ear Labyrinthine dysfunction, bilateral Labyrinthine dysfunction, unspecified ear			H83.2/H83.2X H83.2X1 H83.2X2 H83.2X3 H83.2X9	
		Noise effects on inner ear Noise effects on right inner ear			H83.3, H83.3X H83.3X1	

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		Noise effects on left inner ear Noise effects on inner ear, bilateral Noise effects on inner ear, unspecified ear			H83.3X2 H83.3X3 H83.3X9	

APPENDIX 2.

Sensorineural Hearing Loss Background Rates

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TABLE 2.1. SENSORINEURAL HEARING LOSS BACKGROUND RATES. All studies focused on sudden sensorineural hearing loss. Case ascertainment methodology: *Administrative data with cases found using specified codes for SSNHL as well as the co-morbidity listed; ** Specialty referral patients in a defined catchment area; #SNHL confirmed by audiology.

Author/Country	Study years	Population (Age in years)		Incidence rate per 100,000 person years [95% confidence interval] (total cases) All	Males	Females
AFRICA – None						
AMERICAs						
Alexander[7] * USA National data	2006-2007	<18		8	9	7
		18-34		12	12	13
		35-44		19	19	19
		45-54		30	30	31
		55-64		47	53	42
		65+		70	81	62
		All ages		**27**	**28**	**36**
Byl[8] ** # California, USA	1973	0-14		4.6 (2)		
		15-44		7.6 (6)		
		45-64		14.5 (5)		
		65+		47.2 (5)		
		All ages		**10.7 (18)**		
ASIA						
Lin[9] * Taiwan	2000-2004	No Chronic Kidney Disease	0-35	22.0 (10)		
			35-49	57.6 (35)		
			50-64	98.6 (66)		
			≥65	67.2 (62)		
			All	**65.2 (173)**	**74.7 (99)**	**55.7 (74)**
		With Chronic Kidney Disease	0-35	46.6 (21)		
			35-49	86.2 (51)		
			50-64	142.1 (90)		
			≥65	114.5 (90)		
			All	**102.4 (252)**	**116.1 (141)**	**89.1 (111)**
Wang[10] *#, Taiwan			20-34	22 (21)		

	2000 – 2010	No End Stage Renal Disease	35-49	41 (95)		
			≥50	62 (232)		
			Overall	**49 (348)**		
		With End Stage Renal Disease	20-34	197 (22)		
			35-49	244 (68)		
			≥50	244 (97)		
			Overall	**237 (187)**		
Lin[11] * Taiwan	1996 – 2010	No HIV Infection	18-35	19.9 (26)	19.5 (23)	22.9 (3)
			≥36	44.5 (39)	40.9 (32)	74.5 (7)
		With HIV infection	18-35	43.2 (11)	43.7 (10)	39.3 (1)
			≥36	32.2 (5)	21.7 (3)	117.6 (2)

Country reference (case ascertainment method)	Study years	Population (Age in years)		Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
				All	Males	Females
Chen[12] * Taiwan	2002-2010	Without Hepatitis B or C infection	**20-29**	**49.04 (14)**		
			30-39	41.54 (53)		
			40-49	71.71 (160)		
			50-59	79.13 (294)		
			60-69	55.28 (256)		
			≥70	26.12 (201)		
			Total	**49.31 (978)**	**50.57 (640)**	**47.08 (338)**
		With Hepatitis B or C infection	20-29	511.14 (33)		
			30-39	347.83 (71)		
			40-49	325.37 (111)		
			50-59	357.76 (176)		
			60-69	249.94 (125)		
			≥70	191.81 (131)		
			Total	**283.17 (647)**	**272.56 (395)**	**301.57 (252)**
Kim[13] * # South Korea	2011	All ages		11.6 (5855)		
	2012			14.7 (7458)		

	2013		17.9 (9132)		
	2014		20.3 (10382)		
	2015		24.2 (12450)		
AUSTRALIA/OCEANIA	NONE				
EUROPE	NONE				
MIDDLE EAST	NONE				

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APPENDIX 3.

Sensorineural Hearing Loss Risk Factors

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Although as much as 70% of sensorineural hearing loss is idiopathic, there are a plethora of possible causes and risk factors. It was beyond the scope of developing the Companion Guide to systematically review the original publications for each purported cause. Table 4 in the case definition publication[1] listed the major categories of SNHL causes but then only gave examples for each. In the table below a more complete listing of causes is provided based on the review articles cited by the case definition working group.[14-21] In addition the literature review identified several relevant articles published after the case definition as well as some others that were not cited in the case definition but provided relevant information on risk factors. These are cited within the table as pertinent to the specific risk factor. The distribution of etiologic groups for SNHL vary according to whether it is unilateral or bilateral (see Table 3.2 below)

TABLE 3.1. Sensorineural Hearing Loss RISK FACTORS

Age	• Increased frequency with aging (see appendix 2 for specific variation in background incidence by age) especially for ≥65 years where 33% have disabling hearing loss. Presbycusis is age-related hearing loss due to loss of hair cells, degeneration of the organ of Corti and cells of the spiral ganglia.

Genetic	• Syndromic SNHL: over 400 syndromes with associated hearing loss have been identified and make up 30% of inherited SNHL; of the more frequent types and the basis of inheritance are listed below: [22]
	  ○ Autosomal dominant inheritance: Wardenberg, Branchio-oto-renal, Crouzon syndromes; neurofibromatosis type 2
	  ○ Autosomal recessive inheritance: Pendred syndrome, Usher syndrome
	  ○ X-linked inheritance: Alport syndrome, Kearns-Sayre syndrome, X-linked hypophosphatemia, STAR syndrome (Syndactyly, Telecanthus, Anogenital and Renal malformations), JS-X syndrome
	• Non-syndromic SNHL: singular abnormality without involving other systems; account for 70% of inherited SNHL; may be autosomal dominant, autosomal recessive or X-linked inheritance[22]. 5.7% of idiopathic non-syndromic SNHL due to point mutations in mitochondrial DNA [23] These vary in age of onset from early onset in childhood to first presenting in the 2nd or 3rd decade.

Pre-, peri- or post-natal Insult	• Congenital infection: Rubella, Cytomegalovirus, Toxoplasmosis, Syphilis and Herpes Simplex • CMV has replaced rubella as the most frequent cause of hearing loss due to congenital infection; A systematic review of hearing loss due to congenital CMV[24] identified 10 cohort studies done in developed countries where populations had universal newborn screening for congenital CMV; the pooled prevalence of congenital CMV infection was 0.58% (95% CI 0.41-0.79). Longitudinal follow up for hearing loss identified an average affected proportion of 12.6% (10.2-16.5). Among the 90% of congenitally infected infants who were asymptomatic at birth, 10% were found to have hearing loss; Among the 10% of congenitally infected infants who had symptomatic congenital CMV at birth (defined as ≥ 3 of: petechiae, jaundice with conjugated hyperbilirubinemia, hepatosplenomegaly, thrombocytopenia, chorioretinitis, seizures, microcephaly, intracranial calcifications), 33% had hearing loss. The prevalence of congenital CMV infection in developing countries is up to 2%[25] • Prenatal exposure to ototoxins • Birth asphyxia • Neonatal jaundice, kernicterus

	• Neonatal infection: cerebral malaria, Lymphocytic Choriomeningitis Virus[20]
Primary Otologic conditions	• Ménière disease[26] • Otosclerosis • Perilymphatic fistula – found in 11% of series of 90 SSNHL undergoing tympanotomy[27] • Enlarged vestibular aqueduct • Inner ear anomaly (demonstrable on MRI; found in 2.5% of 366 patients with SNHL • Primary autoimmune inner ear disease (not associated with systemic disease)
Medical conditions associated with SNHL	• Autoimmune or inflammatory disorders: antiphospholipid syndrome, Behcet's syndrome, Cogan syndrome, Crohn's disease, Goodpasture syndrome, Kawasaki syndrome[28], Langerhans cell histiocytosis, polyarteritis nodosa, polymyositis/dermatomyositis, relapsing polychondritis, rheumatoid arthritis, sarcoidosis, scleroderma, Sjogren's syndrome, Susac's syndrome (small blood vessel vasculitis), systemic lupus erythematosus, systemic sclerosis, Takayasu's arteritis, temporal arteritis, temporal bone histiocytosis[29] , ulcerative colitis, Vogt-Koyanagi-Harada syndrome, Waldenstrom's macroglobulinemia, Wegeners' granulomatosis, • Cancer: cerebellopontine angle (CPA) tumors (most common - vestibular schwannoma (or acoustic neuroma), meningioma, meningeal carcinomatosis, intravascular lymphomatosis, metastatic lesions to internal auditory canal; haematologic malignancies[30] (multiple myeloma, acute myelogenous leukemia, malignant lymphoma, T-cell lymphoma, B cell lymphoblastic leukemia) • Cardiovascular disease: Hyper- or hypotension; ischemic cardiomyopathy; myocardial infarction; cardiopulmonary bypass, cerebrovascular accident, migraine-associated vasospasm, • Endocrine-metabolic disorders: diabetes mellitus, hypothyroidism, thyrotoxic hypokalemia, Hashimoto's thyroiditis • Hematologic disorders: Sickle cell disease[31, 32], iron deficiency anemia[33] • Neurologic disorders: demyelinating disorders including multiple sclerosis
Trauma including surgery	• Excessive noise (barotrauma): defined as acute exposure to >130dB or chronic exposure to >85dB (personal listening devices can generate >100dB[20]) • Temporal bone fractures • Whiplash, cliff jumping, diving decompression sickness, blast injury, fl in unpressurised aircraft • Post general anesthetic or surgical micro-embolic or other haemodynamic complications
Infection	• Viruses: Lassa Fever[34, 35], Ebola and Zika viruses[35], HIV, HSV, measles (bilateral SNHL in 5-10% of cases), mumps (about 4% of cases with short term high-frequency deafness; 1/20,000 cases with permanent hearing loss, usually unilateral), VZV, EBV, enteroviruses, influenza and other viral URTIs; COVID-19[36], Creutzfeldt-Jakob disease, ○ Animal models have been developed to study Lassa Fever associated SNHL in cynomolgus macaques[37] and mice[38] • Bacteria: bacterial meningitis; syphilis; Lyme disease, mycoplasma, TB, Group A streptococcus, • Fungi: cryptococcal meningitis • Parasites: toxoplasmosis, Plasmodium falciparum

Ototoxic drugs or poisonings or radiation	• Antimicrobial agents: aminoglycosides; penicillin; ribavirin, macrolides[39]: oral or intravenous erythromycin; azithromycin; only 2 case reports following clarithromycin; chlorquine and hydroxychloroquine[40], mefloquine[41]. • Chemotherapeutic agents and immunosuppressive drugs: alkalizing agents, cisplatin cyclosporin, pegylated interferon • Lead poisoning • Loop diuretics • NSAIDs, salicylates • Snakebite • Substance abuse: alcohol, cocaine, ecstasy, heroin, opioids • Other purported agents: benzodiazepine, synthetic prostacyclin, retinoid, phosphodiesterase-5 inhibitors • Radiation for head and neck cancers[42]

Vaccine	• IOM 2012 review of events associated with childhood vaccines (MMR, VZV, Influenza, Hepatitis A, Hepatitis B, HPV, Meningococcal, Diphtheria Toxoid, Tetanus Toxoid and Acellular Pertussis containing vaccines) [43]. MMR was the only vaccine with data for hearing loss. None of the evidence was epidemiologic. Of 11 publications reporting hearing loss after MMR combined or individual vaccines 8 were judged to contribute to the weight of mechanistic evidence. These were 5 single case reports, a case series of 202 VAERS reports and 2 experimental studies. The IOM concluded that there was low-intermediate mechanistic evidence for an association between measles or mumps vaccine and hearing loss based on the reviewed evidence and the known association between natural infection and hearing loss. They did not think the evidence adequate to accept or reject a causal relationship.
	• Dudley et al[44] published an updated review of causal associations for the same vaccines as IOM in 2020. They concluded, as per IOM, there was no demonstrated causal association for hearing loss.
	• Case reports cited by the Working Group as well as additional ones found in the literature review done for this guide noted temporally associated sudden onset deafness following: measles/mumps[45-47], influenza[48, 49, 50], Hepatitis B[51-54], tetanus / diphtheria Mair[55, 56] meningococcal[56], rabies[57, 58] vaccines and tetanus antitoxin.[59]
	• After referring a case of sudden SNHL to CISA, Baxter et al[50] did a case-centered analysis using the Northern California Kaiser Permanente database to study a possible association between vaccination and sudden onset SNHL. First ever cases were identified using ICD-9 codes but in addition a random selection of 25 cases that occurred within 2 weeks after immunization and 25 cases that occurred outside the risk interval were reviewed in detail to ensure that each was a new case and was a diagnosis made by a clinician. The study period was 2007 to 2014 and all vaccines were analyzed provided over 20,000 doses were administered during the study interval. A total of 1929 new cases of SNHL occurring within 9 months after any vaccine were identified.
	  ○ Odds ratios, OR (95% Confidence Interval) were determined for all vaccines as follows:
	  ▪ 1-7 days after vaccination: OR 0.965 (0.61-1.50)
	  ▪ 1-14 days after vaccination: OR 1.235 ().80-1.69)

- 1-25 days after vaccination: OR 1.026 (0.80-1.31)
- 15-28 days after vaccinatioin: OR 0.870 (0.63-1.18)

- There were 0 cases of SNHL in the week following immunization for MMR, IPV, MCV4, Rabies, DTaP, VZV, oral typhoid, Yellow Fever, Hepatitis A, LAIV or Td vaccines. From 1-8 cases occurred in the week following immunization for Hepatitis A/B combined, Tdap, Zostavax, Pneumovax, injectable typhoid, HPV4, monovalent H1N1, and Hepatitis B but Odds Ratios did not indicate an increased risk.

- COVID-19 vaccines: the literature search identified publications reporting 41 cases of temporally associated sudden SNHL including 6 single case reports[60-65], 2 each reporting two cases[66, 67], 2 each reporting three cases[68, 69] and an ENT specialty clinic series of 25 cases.[70] Table 3.3 summarizes the features of the case reports in terms of vaccine type, dose, age, sex, and time to onset of SNHL.
  - Formeister et al [71], used VAERS reports of SSNHL post COVID-19 vaccination from Dec 14, 2020 through July 16, 2021 to estimate a minimum to maximum incidence of SNHL following vaccination. Only credible reports were included which were defined as: onset within 3 weeks after vaccination, audiology confirmed HL with evaluation by an ORL or audiology specialist with evaluation leading to appropriate threrapy or an MRI examination. Any reports that identified an alternate cause (e.g., schwannoma or stroke) were excluded. Among 2170 reports of hearing loss, 555 met the study definition of probable sudden SNHL.
    - Number of cases and calculated incidence/100,000 doses given were:
      - Pfizer mRNA: 305 cases; 0.16
      - Moderna mRNA: 222 cases; 0.16
      - Janssen/Johnson & Johnson adenoviral vector: 28 cases; 0.22
    - The estimated minimum to maximum range of incidence was 0.6-28.0/100,000/yr which was within the expected range of 11-77 cases/100,000/yr.[7]
    - The authors concluded that there was no association between the three COVID-19 vaccines and SNHL at the population level but could not exclude causality in individual cases without further research. Of relevance to the possible link between COVID-19 vaccination and SNHL was demonstrated recovery of SARS-CoV-2 RNA in the middle ear of COVID-19 fatalities[72] and demonstration that SARS-CoV-2 can directly infect human vestibular hair and Schwann cells.[73]
  - Yanir et al [74] used an Israeli electronic health database that provides health care to over 50% of the population to look for an association between Pfizer mRNA vaccine and sudden SNHL. ICD-9 codes were used to identify cases for 2018 and 2019 (as a non-concurrent comparative group) and from Dec 20 2020 to Apr 30 2021 focusing on those aged ≥16 years. Observed cases were identified within 21 days after each of the first two doses. Separate analyses were done using 2018 or 2019 as the comparator group. The incidence rate of SSNHL after dose 1 was 60.77 (95% CI 48.29-73.26)/100,000 person years; after dose 2 it was 56.24 (43.83-68.64)/100,000 person years. The respective attributable risk was 0.91 (0.29-1.8) and 0.61 (-

	.07=1.12) per/100,000 vaccinees. They concluded that there was a possible association between Pfizer mRNA vaccine and SSNHL, but the effect was very small.
Miscellaneous risk factors	• Sedentary lifestyle; high levels of: cholesterol, fibrinogen, homocysteine, ICAM-1, VCAM-1; low levels of Vitamin A, folate, plasma Coenzyme Q; insufficient sleep (<7 hrs/day) • Hypercholesterolemia, low serum coenzyme Q10, low nervonic acid.[74]

TABLE 3.2 Distribution of etiologic groups for sudden SNHL based ear involvement.

The data in the table are from systematic reviews of unilateral and bilateral sudden SNHL.

Etiology	Unilateral[18] (95% of all sudden SNHL) Based on 686 reported cases	Bilateral[15] (5% of all sudden SNHL) Based on 103 reported cases
Idiopathic	71%	5.8%
Infection	12.8%	10.7%
Otologic disease	4.7%	Not mentioned
Vascular or haematologic disease	2.8%	16.5%
Neoplasm	2.3%	16.5%
Autoimmune	Not mentioned	16.5%
Toxic	0.1%	29.1%
Iatrogenic	0.6%	3.9%
Traumatic	4.2%	1%
Pregnancy related	0.7%	Not mentioned
Other	0.7% (Rabies vaccine, other CNS disease)	Not mentioned

TABLE 3.3. Case reports of sensorineural hearing loss following COVID-19 vaccination.

Author	Vaccine type	Dose	Age years	Sex	Time from vaccine to onset of hearing loss	Comment
Tsetsos[60]	ChAdOx1	2	61	F	2 days	
Li[61]	mRNA not specified	2	20s	M	1 day	Proven labyrinthine schwannoma; authors suggest vaccine may have been a trigger
Kahn[62]	mRNA, Pfizer	1	20	M	2 hours	
Jeong[63]	mRNA, Pfizer	3	61	F	Same day	
Chen[64]	ChAdOx1	1	48	F	8 weeks	Susac's syndrome; visual loss onset 4 weeks after vaccine
Pisani[65]	Vaxzevria	1	57	M	2 days	
Zoccali[66]	mRNA, Pfizer	3	40	M	5 days	
	mRNA, Moderna	3	67	F	7 days	
Zhao[67]	Sinovac	1	30	M	4 days	
	Sinovac	1	64	F	4 days	
Jeong[68]	ChAdOx	1	64	F	2 days	
	mRNA, Pfizer	1	42	M	Same day	
	mRNA, Pfizer	2	18	M	2 days	
Canales-Medina [69]	Vaxzevria	2	44	M	18 days	
	Vaxzevria	1	39	M	11 days	
	Vaxzevria	2	43	M	14 days	
Wichova[70]	mRNA, Pfizer	1	53	F	10 days	
			51	M	14 days	
			69	M	7 days	
			55	M	10-14 days	
			61	F	12 days	
			58	F	10 days	
		2	60	M	7-14 days	
			86	M	42 days	
			78	F	1-2 days	
			66	F	7-10 days	
		1 & 2	67	F	8 days	
	mRNA, Moderna	1	74	F	7 days	

			49 43 59 48 39	M M M M M	4-5 days 14 days 6 days 2-3 days 10-14 days	
		2	83 77 54 76 67 64	M F F M M M	10 days 30 days 14-21 days 14 days 7 days 7-10 days	
		1 & 2	73 51	M F	2-3 days 21 days	

APPENDIX 4

Sensorineural Hearing Loss Key Caveats for Real Time Investigation and Case Definition Working Group Guidance for Data Analysis and Presentation

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

4.1. Sensorineural Hearing Loss Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

4.1.1 Key elements of Case Definition (CD)

- Hearing loss is the most prevalent sensory deficit and by adulthood the 5th leading cause of disability. WHO estimates that 6.1% of the world population have disabling hearing loss. Conductive hearing loss, due to middle ear disease (otitis media with effusion; chronic suppurative otitis media) are the most common causes.
- In the absence of routine screening at birth and in schools, hearing loss may go undetected. Thus, in areas like West Africa where there is a high prevalence of conductive hearing loss as well as sensorineural hearing loss it is essential to objectively assess hearing with audiometry during clinical trials where SNHL is a potential adverse outcome.
- **For SNHL all 3 CD levels of certainty require that conductive hearing loss be ruled out by physical examination.**
- **Audiometry is the only testing required (as opposed to laboratory or radiologic testing) to reach level 1 – Definite case. Specifically, there must be hearing loss of ≥30 dB in three consecutive frequencies.**
- In the absence of audiometric testing, level 2 – Probable case – can be met by doing a tuning form exam (Rinne and Weber tests) or an Auditory Brainstem Response test.
- A level 3, possible case, requires evidence of hearing loss via remote or behavioural screening questionnaire or an abnormal otoacoustic emissions test. Clearly this is a sensitive, but very non-specific definition for SNHL.
- It is possible to rule out SNHL (Level 5) if an Audiogram OR ABR OR Tuning form examination is not consistent with an SNHL diagnosis.

4.2.2 Recommendations for real time assessment

- **Healthy, clinical trial subjects prior to enrolment: a complete medical history and physical examination is essential, paying particular attention to:**
  - Family history of hearing loss; parental consanguinity
  - Pre/perinatal history of congenital infection (CMV, rubella, toxoplasmosis in particular), positive screen for CMV infection at birth, hearing screen at birth, birth trauma, need for neonatal intensive care with time spent in an incubator (potential barotrauma)
  - Childhood history of speech, language, motor, or global delayed development
  - Immunization history
  - Medical history of frequent ear infections, exposure to ototoxic drugs (in particular aminoglycosides, macrolides), sickle cell disease, iron deficiency anemia, diabetes mellitus, hypertension, renal disease, autoimmune disease, stroke episode(s), head or ear trauma, acute or chronic exposure to loud noise.
  - Physical examination for:
    - Possible syndrome: abnormalities if the outer ear (e.g., tags, pits, misshapen ears); position of ear lobes in reference to each other and rest of face.
    - External auditory canal obstruction (wax, foreign object, tumor, otitis externa edema/inflammation)

- Visual inspection of the tympanic membrane: normal cone of light, any ventilation tubes/perforations or retraction, appearance of middle ear fluid
- Pneumatic otoscopy to assess mobility of tympanic membrane
- Tympanometry may help to identify presence of middle ear fluid or tumor; TM perforation; or eustachian tube dysfunction
- Tuning Fork examination (using a 512 Hz fork): normal results if
  - Weber test – with fork placed on middle of the forehead, the sound should be perceived equally in both ears
  - Rinne test – able to perceive sound through the air (when fork vibrating near but not touching the ear or skull) and bone (when vibrating fork place on the mastoid bone.
- Audiogram – to demonstrate normal hearing in both ears

- Individual complaining of hearing loss
  - All the above points for healthy subjects are also important to follow where there is a hearing loss concern
  - Ask about recent trauma, exposure to loud noise, ear surgery, possible stroke
  - Characterize the type and temporal pattern of hearing loss:
    - Unilateral or bilateral
    - Fluctuating (more likely in ménière disease),
    - Rapid (more likely in autoimmune conditions) or gradual (more likely in neoplastic, neuro-degenerative and bony (osseous) disease)
    - Date and time of: symptom onset; first observation by a health professional; diagnosis by a health professional; specialist examination.
  - Obtain a complete description of symptoms and signs other than hearing loss including:
    - Evidence of vestibular disorder: tinnitus, dizziness, nystagmus, vertigo.
    - Concurrent acute (may indicate infectious process) and chronic (may indicate neurologic, cardiovascular, endocrine or haematologic risk factors) symptoms and signs.
  - The findings of the tuning fork exam that are consistent with SNHL are:
    - Weber test (fork on mid-forehead): the sound will be heard best in the unaffected, hearing ear (in contrast, in CHL the sound seems to be louder in the affected ear)
    - Rinne test: in the affected ear, sound is conducted better by air than bone – but this is true for normal hearing as well. (If bone conduction is better than air conduction, CHL is present).
  - Sudden hearing loss, where onset is rapid over <72 hours:
    - **Bilateral onset,** involving both ears, is rare (5% of cases) but should be considered a medical emergency requiring specialty assessment and investigation for exposure to ototoxins, neoplasms especially acoustic neuroma (brain MRI), vascular or haematologic disease, autoimmune conditions (antinuclear antibody, anticardiolipin antibody, lupus anticoagulant, antineutrophil cytoplasmic antibody, clotting factors) or recent infection (see risk factor table, appendix 3 for etiologic possibilities in context of local endemic disease or behavioral risk factors (HIV, syphilis).

- **Unilateral onset** is more likely to be idiopathic (71% of cases) but a careful history for recent infection, and risk factors for vascular or hematologic disease should be taken. Screening for multiple infectious or autoimmune diseases as well as imaging are less likely to be helpful but should be considered in appropriate contexts: e.g., in areas where Lyme disease is endemic, it could be reasonable to do appropriate serology. Specialty consultation for assessment and treatment should be done. In many cases of unilateral SNHL, rapid and sometimes complete recovery may occur within days to weeks.

4.2.3 Duration of Surveillance

- The risk window for onset of sensorineural hearing loss following vaccination is unknown. Cases observed after Lassa Fever infection occured both within the acute phase and the convalescent phase.[34, 35] In the mouse and macaque animal models of SNHL in Lassa Fever hearing loss was identified within 45 days after infection.[37, 38] Based on these data a minimum risk interval, and thus period of follow-up would be 6 weeks after each dose of vaccine.

4.2.3 Data Collection Guidelines – document all the following

- History and physical examination findings as noted in 4.2.2
- Audiometry: document the method of measurement including type of test, type of audiometer, conditions of testing
- Radiologic evaluations: if brain or head MRI, CT or angiography – note if done with or without contrast and specify type of contrast
- Laboratory investigations if done, for infection, haematologic abnormality, autoimmune disease
- Treatment given for SNHL, specifying drug(s), route(s), dosing with start and stop dates if repeated courses

4.2.4 Data Analysis and Presentation Guidelines:

- Classify each case as:
  - Meeting SNHL case definition level of certainty:
    - Level 1 – Definite case
    - Level 2 – Probable case
    - Level 3 – Possible case
  - Not meeting the SNHL case definition because:
    - Insufficient evidence to meet level 1, 2 or 3 of certainty
    - Not a case of SNHL because 1 of the following was documented: Physical exam findings of conductive hearing loss were present; Audiology was inconsistent with SNHL; ABR or tuning fork exam were inconsistent with SNHL
- Classify case(s) according to the interval from immunization to onset of hearing loss:
  - < 1 week after immunization
  - 1 to <4 weeks after immunization
  - 4 to 12 weeks after immunization
  - >12 weeks after immunization

APPENDIX 5

Sensorineural Hearing Loss Data Abstraction and Interpretation Forms

With Algorithms for Assessing Level of Certainty

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

5.1. Sensorineural Hearing Loss Data Abstraction and Interpretation Form for Medical Chart Review

This appendix provides tools for gathering data pertinent to SNHL and assessing level of certainty based on the published Brighton case definition.[1] The tools can be used in a variety of settings including: medical chart review to validate SNHL cases; record case information from an AEFI report and identify what supplemental information would be needed to reach a level of certainty; guide data collection and case investigation during a clinical vaccine trial or as part of active surveillance; and to guide data collection for epidemiologic studies of background incidence or to assess causality. Five tables, each with brief usage instructions and 1 figure are included in this appendix:

- **Table 5.1** lists all Brighton case definition[1] criteria for SNHL and identifies likely sources of information for each.
- **Table 5.2** is the main data abstraction form that can be used to record data pertinent to SNHL
- **Table 5.3** provides a guide for assigning a '**Y**es', '**N**o' or '**U**nknown' status to each case definition criterion based on data entered into table 5.2.
- **Table 5.4** enables a summary of the final value for each criterion, as determined using table 5.3
- **Table 5.5** provides formulae used to assign SNHL level of certainty based on criterion values summarized in Table 5.4.
- **Figure 5.1** shows a pictorial algorithm for determining SNHL level of certainty.

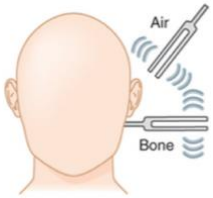
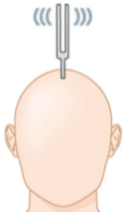
TABLE 1. Sensorineural Hearing Loss KEY CASE DEFINITION CRITERIA AND LIKELY SOURCES OF INFORMATION. *Use 4th column to record actual sources.*

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Exclusion of Conductive Hearing Loss by Physical Examination	Admitting, emergency or outpatient clinic physical examination; Specialty consultation reports	
B	Audiometry consistent with SNHL	ENT or Audiology consultation; Audiology test reports in hospital or outpatient clinic records	
C	Auditory Brainstem Response test consistent with SNHL	ENT, Audiology or Neurology consultation; ABR test reports	`
D	Tuning fork exam consistent with SNHL	Admitting, emergency or outpatient clinic physical examination; Specialty consultation reports	
E	Otoacoustic Emissions test consistent with hearing loss	ENT/Audiology consult or Specialty clinic notes or reports	
F	Behavioral or neurodevelopmental test questionnaire concerning for hearing loss		
G	Remote Telehealth Screening that is concerning for hearing loss		

TABLE 5.2. Sensorineural Hearing Loss DATA ABSTRACTION FORM: Record specific information, to the extent possible, for all rows in the table below. The red font identifies specific criteria related to the SNHL case definition. NOTE: SNHL can be bilateral or unilateral. Data as specified in the table should be gathered for both ears if bilateral and the affected ear if unilateral.

1. Date of illness onset		
2. Hospital admission?		
3. Admitting diagnosis:		
4. Discharge diagnosis:		
5. Criterion A Exclusion of conductive hearing loss by physical examination	**A-1 Otoscopy of external ear canals**	**Check all that apply but note that 1 is mutually exclusive with 2 – 6. Otoscopic examination of the affected external ear canal(s) showed:** ☐ 1. Patent external ear canal(s) with healthy mucosa and no evidence of obstruction by cerumen (ear wax), foreign body or ear canal neoplasm (such as exostosis, osteoma) ☐ 2. Obstruction by cerumen (ear wax) ☐ 3. Obstruction by foreign body ☐ 4. Obstruction by bony growth or ear canal neoplasm (Specify:) ☐ 5. Otitis externa (edematous and inflamed ear canal) ☐ 6. Unknown because otoscopic exam not done, or unknown if done, or done but results unrecorded.
	A-2 Tympanic membrane (TM)	**Check all that apply but note that 1 is mutually exclusive with 2 – 6. Visual examination of TM(s) by otoscopy showed:** ☐ 1. Normal TM(s) (translucent in appearance, reflects light and anatomic landmarks visible) with no evidence of bulging, retracted or perforated TM or middle ear effusion or cholesteatoma ☐ 2. Perforation of the TM(s) on the affected side(s) ☐ 3. Middle ear effusion on the affected side(s) ☐ 4. ≥ 1 of the following, which would be consistent with the presence of cholesteatoma: ○ A. TM retraction pocket ○ B. Otorrhea ○ C. Pearly white mass in the middle ear ☐ 5. Reddish mass behind the TM, consistent with Glomus tumor ☐ 6. Unknown because TM(s) not visualized or condition not described

	A-3 Pneumatic otoscopy	**Check the one most correct response. Pneumatic otoscopy:** ☐ 1. was done and showed normally mobile TM(s) ☐ 2. was done and showed immobile TM(s) on the affected side(s) ☐ 3. was not done or unknown if done or done but results not recorded.
	A-4 Tympanometry *(Record result if available since may help identify middle ear disease, but not required to meet CD)*	**Check the one most correct response. Tympanometry** ☐ 1. Was done and showed normal TM(s) pressure responses (Type A tympanogram) ☐ 2. Was done and showed abnormal TM(s) pressure responses due to middle ear effusion or tumor (Type B tympanogram). ☐ 3. Was done and showed abnormal TM(s) pressure responses due to Eustachian tube dysfunction with negative pressure in middle ear and TM retraction (Type C tympanogram) ☐ 4. Was not done or unknown if done or done but results not recorded.
6. Criterion B Audiometry consistent with SNHL	**B-1 Audiometry testing**	Check all that apply. Note multiple options can be chosen for 1-6, but 7 implies none of 1-6 were done. ☐ **1. Behavioral audiometry** was performed with an audiometer in a sound booth in a quiet location. The patient presses a button in the booth, indicating that a sound was heard. ☐ **2. Behavioral Observation Audiometry** was done where tonal and speech stimuli presented by audiologist and child (typically <6mo old or developmentally delayed) watched for responses to stimuli ☐ **3. Visual Reinforcement Audiometry** was done, where earphones are used to transmit sound and a child (typically 6-24mo old or developmentally delayed) is trained to respond to a heard sound by turning right or left depending on which ear the sound is heard in. Initially the sound is paired with lighting up a 'favorite' object (e.g., plush toy) to the right or left when a sound is heard. Subsequently only the sound is used and if the child turns in the correct direction, it indicates the sound was heard. ☐ **4. Conditioned Play Audiometry** was done where the child (typically 2-5yrs old or developmentally delayed) is trained to perform a task (e.g., drop a block in a bucket) when a sound is heard. ☐ **5. Audiometer program on a tablet computer** was used. ☐ **6. A Smartphone with a hearing screening app** was used ☐ **7. None of the above was done, or unknown if any were done, or audiometry done but no result**

	B-2 **Audiometry test results**	☐ **1.** Audiometry showed ≥30dB hearing loss over ≥3 consecutive frequencies ☐ **2.** Audiometry showed no hearing loss, or the loss was <30dB or was not seen over at least 3 consecutive frequencies. ☐ **3.** Audiometry results unavailable or uninterpretable.
7. Criterion C **Auditory Brainstem Response (ABR) test consistent with SNHL**	ABR tests how well the acoustic nerve transmits information to the brain. Typically, it is used for infants <6mos old or for pats unable or unwilling to respond consistently to acoustic stimuli used in audiometry testing. Choose the one best answer: ☐ 1. An ABR test was done with the patient sedated and was consistent with SNHL ☐ 2. An ABR test was done with the patient not-sedated and was consistent with SNHL. ☐ 3. An ABR test was done but unknown if patient sedated or not-sedated and was consistent with SNHL. ☐ 4. An ABR test was done with the patient sedated and was inconsistent with SNHL. ☐ 5. An ABR test was done with the patient not-sedated and was inconsistent with SNHL. ☐ 6. An ABR test was done but unknown if the patient was sedated or not-sedated and was inconsistent with SNHL. ☐ 7. An ABR test was not done, or unknown if done, or done but results unknown.	
8. Criterion D **Tuning fork exam consistent with SNHL** *Test usually done with the 512 Hz tuning fork; Record the type of tuning fork used if known here:*	**D-1 Rinne test**  	**Check the one most correct response. The Rinne tuning fork test** *(compares how well sound is heard when the tuning fork is struck and: i) held by the ear, without touching it; ii) placed on the mastoid bone behind the ear):* ☐ 1. Showed that the tuning fork sound was transmitted better through the air than via bone on the affected side(s), indicating SNHL. ☐ 2. Showed that the tuning fork sound was transmitted better via bone than through the air on the affected side(s), indicating a conductive type of hearing loss. ☐ 3. Was not done, or unknown if done, or done but no results recorded or the results were unclear
	D-2 Weber test 	**Check the one most correct response. The Weber tuning fork test** *(tuning fork struck and placed on the center of the forehead or midline skull on top of the head):* ☐ 1. Showed that the sound localized to the side of the normal hearing ear, indicating SNHL. ☐ 2. Showed that the sound localized to the side of the affected ear, indicating conductive hearing loss. ☐ 3. Was not done, or unknown if done, or done but no results recorded or the results were unclear.

9. Criterion E **Otoacoustic Emissions (OAE) test consistent with hearing loss**	**Check the one most correct response:** ☐ 1. An OAE was done and was consistent with hearing loss. ☐ 2. An OAE was not done, or unknown if done, or done but results unavailable or not interpretable.	
10. Criterion F **Behavioral or neurodevelopmental testing questionnaire concerning for hearing loss**	**F-1 Hearing loss questionnaire**	**Choose the one best answer:** A validated questionnaire to assess hearing loss: ☐ 1. Was done. Indicate the result in **F-2, and if known, specify the questionnaire that was used**: ☐ 2. Was not done. ☐ 3. Unknown if done or done but results unknown or unavailable.
	F-2 Hearing loss questionnaire result	**Check the one most correct response: The hearing loss questionnaire answers were:** ☐ 1. Consistent with hearing loss. ☐ 2. Unknown, unavailable or not interpretable.
11. Criterion G **Remote screening using telehealth technology concerning for hearing loss**	**G-1 Remote screening for hearing loss**	**Check the one most correct response: Remote screening for hearing loss:** ☐ 1. Was done. Indicate result in **G-2, and if known describe the remote screening method used**: ☐ 2. Was not done. ☐ 3. Unknown if done or done but results unavailable or uninterpretable.
	G-2 Result of remote screening	**Check the one most correct response: Remote screening for hearing loss showed:** ☐ 1. Hearing loss a concern. ☐ 2. Unknown because results unavailable or uninterpretable.

TABLE 5.3. INTERPRETATION FORM FOR SNHL CRITERION VALUES: Based on Table 2 data, assign a value to each criterion using rules in Criterion Options columns.

CRITERIA	CRITERION OPTIONS			Criterion Value
	Criterion = YES (Y) IF:	Criterion = NO (N) IF:	Criterion = UNKNOWN (U) IF:	
A. Exclusion of conductive hearing loss by physicalexamination	__ (A-1 AND A-2 AND A-3) = 1	__ A-1=≥1 of (2, 3, 4 OR 5) OR __ A-2 = 1 of (2, 3, 4 OR 5) OR __ A-3 = 2	__ (A-1 OR A-2) = 6 OR A-3 = 3	A = Y N U
B. Audiometry consistent with SNHL	__ B-2 = 1	__ B-2 = 2	__ B-1 = 7 OR __ B-2 = 3	B = Y N U
C. Auditory Brainstem Response consistent with SNHL	__ C = (1, 2 OR 3)	__ C = (4, 5 OR 6)	__ C = 7	C = Y N U
D. Tuning fork exam consistent with SNHL	__ (D-1 AND D-2) = 1	__ (D-1 AND D-2) = 2	__ (D-1 OR D-2) = 3	D = Y N U
E. Otoacoustic Emissions test consistent with hearing loss	__ E = 1	NA	__ E = 2	E = Y U
F. Behavioral or neurodevelopmental testing questionnaire concerning for hearing loss	__ F-2 = 1	NA	__ F-1 = (2 OR 3) OR __ F-2 = 2	F = Y U
G. Remote screening using telehealth technology concerning for hearing loss	__ G-2 = 1	NA	__ G-1 = (2 OR 3) OR __ G-2 = 2	G = Y U

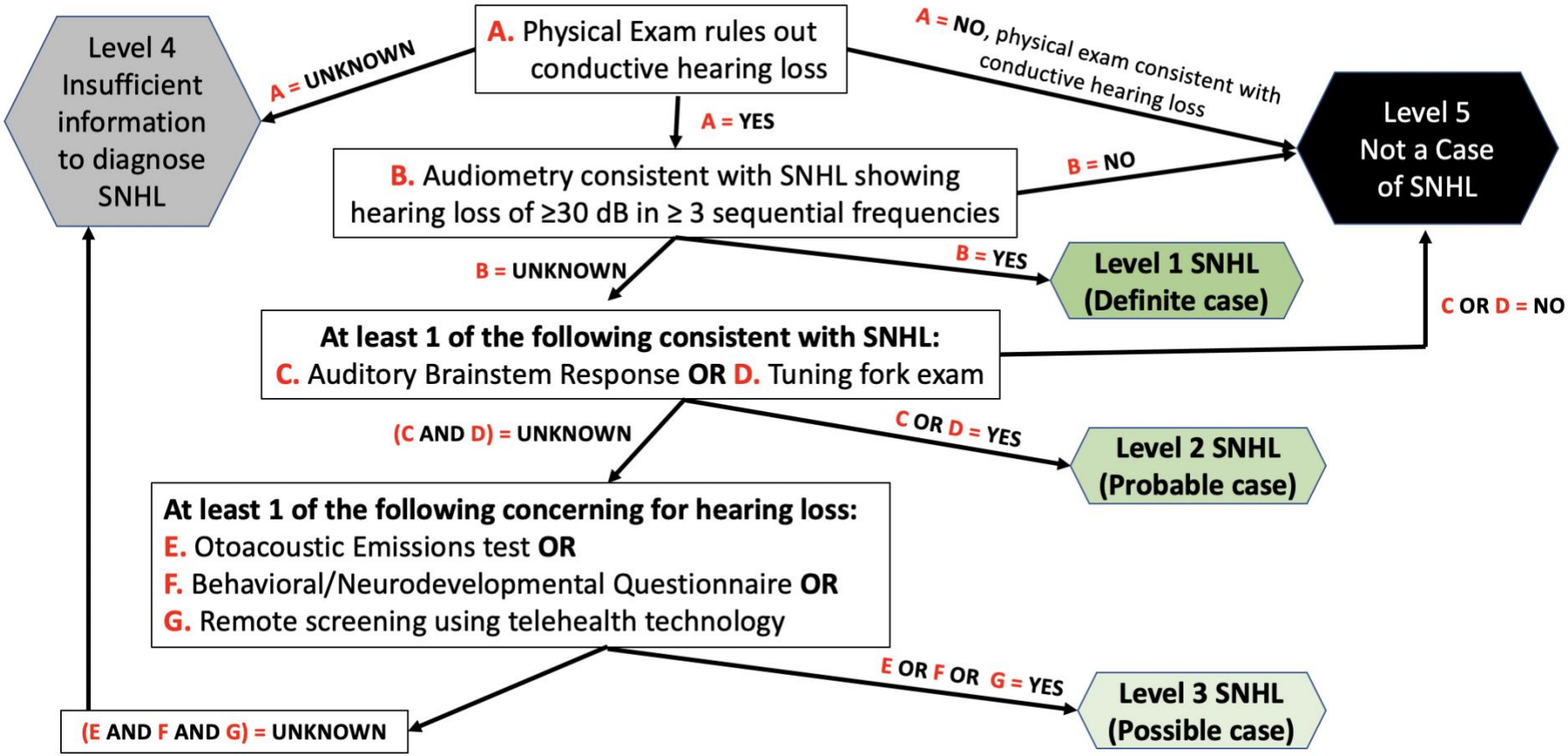
TABLE 5.4. SUMMARY OF Sensorineural Hearing Loss CRITERION VALUES Record the final value for each Criterion from Table 5.3.

Criterion	A	B	C	D	E	F	G
Final Value							

TABLE 5.5 TABULAR ALGORITHM TO DETERMINE SNHL LEVEL OF CERTAINTY BASED ON CRITERION VALUES Use final values of all criteria recorded in Table 5.4 to determine LOC based on the formulae below. Highest row in the table where **all criteria are met** = Level of Certainty.

Level of Certainty	Sensorineural Hearing Loss
Level 1	A = YES AND B = YES
Level 2	A = YES AND (C OR D) = YES
Level 3	A = YES AND (E OR F OR G) = YES
Level 4	A = UNKNOWN OR (B AND C AND D AND E AND F AND G) = UNKNOWN
Level 5	A = NO OR B = NO) OR [B = Unknown AND (C OR D = NO)]

FIGURE 5.1 PICTORIAL ALGORITHM FOR DETERMINING SNHL LEVEL OF CERTAINTY



APPENDIX 6.

Methodology: Brief Summary

6.1. Sensorineural Hearing Loss ICD-9/10-CM, MedDRA and SNOMEDCT Codes [2-6]

An initial set of codes were retrieved through the Codemapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper[2] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[3] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, MedDRA.[4,5] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[6] Of note, while the Companion Guide provides ICD-9/10-CM, MedDRA and SNOMEDCT codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including MeSH, ICPC-2 and Read-CTv3.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the targeted vocabulary of the column. The codes are displayed when the names are hovered over with the mouse. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.
3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

Codemapping was conducted by MS. The output of the Codemapper concepts was reviewed by a medical expert (BL) familiar with the SNHL Brighton case definitions. The concepts identified for SNHL were considered relevant for background incidence rate determination as well as to study hypotheses related to SNHL as a vaccine-product related reaction.

For a more detailed description of methodology see SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes which is available in the CEPI Developers' Toolbox and at the Brighton Collaboration website.

6.2. Sensorineural Hearing Loss Background Incidence

A PubMed search for articles on incidence or risk factors of acute SNHL in the population was conducted on Dec 22, 2022 using the following search strategy:

("Sensorineural hearing loss"[Mesh] OR "Sensorineural hearing loss"[ti]) AND ("Incidence"[Mesh:noexp] OR "incidence"[tiab])

AND English[lang]

AND ("2000/01/01"[PDAT]: "3000/12/31"[PDAT])

AND ("Observational Study"[Publication Type] OR "Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type])

NOT ("animals"[Mesh] NOT "humans"[Mesh])

NOT ("Coronavirus"[Mesh] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti])

NOT ("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR "trial"[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti])

Articles had to meet the following criteria:

1. Original research/meta-analysis
2. Population-based study (selecting the entire population or using probability-based sampling methods)
3. Reported an incidence estimate (or raw numbers that allowed the calculation of an estimate).

If multiple articles reported data from the same study population, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), efforts to include all nonoverlapping data were made. Age, sex, study location, sources of ascertainment, and definitions/diagnostic criteria for SNHL were extracted. SNHL incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

Articles were screened by a Barbara Law. Marta Rojo Vallaescusa reviewed all screened in articles and abstracted data into an excel spreadsheet. The citations were also hand searched for additional data that would meet the inclusion criteria. Key data from the spreadsheet were summarized in the background incidence table in Appendix 2. The spreadsheet with all extracted background incidence data and Forest plots is available in the CEPI Developers' Toolbox and on the Brighton Collaboration website.

6.3. Sensorineural Hearing Loss Risk Factors

A risk factor is "an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor". According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related

condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:
1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.
2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

Risk factors can include infection, medication, diet, surgical or medical procedure, environmental location, stress, toxins, trauma and vaccine. Attribute includes genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for each AESI. Risk factors are only included if there is evidence for an association with the AESI.

The published SNHL Brighton Case definition[1] was reviewed for evidence related to associated risk factors. In addition, a systematic search was conducted to identify evidence for risk factors using the same search strategy shown for background incidence in section 6.2 above. The same expert (BL) screened all retrieved articles and set aside and reviewed all that pertained to the epidemiology of SNHL. Additional articles were retrieved by a hand search of the article citations. The included articles were used not only to inform the Risk factor table(s) in Appendix 3, but also guidance on real time investigation in Appendix 4.

A PubMed search for articles reporting SNHL following vaccination was conducted on Dec 22, 2022 using the following search strategy:
(“Vaccines” [Mesh] OR “vaccine”[tiab] OR “vaccines”[tiab] OR “vaccination” [Mesh] OR “vaccination”[tiab] OR “vaccinations”[tiab] OR “vaccinate”[tiab] OR “vaccinated”[tiab] OR “immunization” [mesh] OR “immunization”[tiab] OR “immunizations”[tiab] OR “immunisation”[tiab] OR “immunisations”[tiab] OR “immunize”[tiab] OR “immunized”[tiab] OR “immunise”[tiab] OR “immunised”[tiab])

AND ("Sensorineural hearing loss"[Mesh] OR "Sensorineural hearing loss"[tw] OR "Hearing Impairment"[tw] OR "Hypoacusis"[tw] OR "Hypoacuses"[tw] OR "Deafness"[tw])

AND ("1900/01/01"[PDAT]: "3000/12/31"[PDAT])

NOT (Comment[ptyp] OR Editorial[ptyp] OR Letter[ptyp] OR News[ptyp] OR Newspaper Article[ptyp])

NOT ("animals"[Mesh] NOT "humans"[Mesh])

AND ("Observational Study"[Publication Type] OR "Clinical trial"[Publication Type] OR "Case report*"[Publication Type] OR "Case series"[Publication Type] OR "Causality assessment"[Publication Type] OR "Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "Protocol"[Publication Type])

AND English[lang].

A single reviewer (BL) screened the articles first on title and abstract to identify case reports, case series, reviews, descriptive and research studies focused on humans. For COVID-19 vaccines commentaries and letters to the editor were reviewed to

identify case reports and studies Otherwise editorials, letters to the editor, other commentaries, erratum, guidelines and articles focused only on management or therapy were excluded. A full text review was conducted for all screened in articles. Articles were judged to be contributory or non-contributory for the purpose of the Companion guide which was to identify vaccine as a risk factor for SNHL and to describe up to date information related to any SNHL safety signal associated with specific vaccines. Hypothesis-testing studies as well as descriptive datalink or other epidemiologic studies that provided risk analyses (Incidence Rate, Incidence Reporting Ratio, Incidence Rate Difference) or disproportionality analyses (Reporting Odds Ratio, Information Component) or that systematically reviewed published case reports and case series or that provided relevant histopathology were considered contributory. Additional relevant articles were found by a hand search of the included article reference list.

6.4. Sensorineural Hearing Loss Case Definition key caveats for diagnosis, data analysis and presentation [1]

The published SNHL Brighton case definition was reviewed for key caveats relevant to real time assessment of SNHL in the context of a clinical trial where it occurs as an AEFI. In addition, the case definition guidelines, published as a supplement to the case definition publication, were reviewed, and key recommendations identified for data collection, analysis and presentation.

For a more detailed description of methodology see SO1-D2.7 Guidance for CEPI Developers which is available in the CEPI Developers' Toolbox.

6.5. Data Abstraction Form and Tabular Checklist and Algorithms for Level of Certainty Determination

The Brighton Collaboration SNHL case definition[1] was thoroughly and repeatedly reviewed by one individual (BL) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each level of certainty.

The SNHL criteria were displayed in a tabular format to enable recording of all relevant clinical data (based on history, physical examination and audiological or other investigations) needed to meet each criterion. A guide was included to help with interpretation and translation of the data into a Yes, No or Unknown value for each criterion.

Algorithms were developed for each level of diagnostic certainty based on the values of each criterion as described in the published case definition. Two types of algorithms were developed for SNHL: a tabular presentation of formulae based on the logic in the case definition with each row representing a level of certainty (Appendix 5, Table 5.5); and a more visual decision tree algorithm (Appendix 5, Figure 5.1).

For a more detailed description of methodology see Tabular Checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation which is available in the CEPI Developers' Toolbox.