Title:

Estimation of symptomatic respiratory syncytial virus infection incidence in adults in multiple countries: a time-series model-based analysis protocol

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Suppl Table 1. Primary outcomes

All cardiorespiratory disease (broad)	ICD-9-CM codes: 460-519, 390-459 or ICD-10-CM codes: J00-J99, I00-I99[a] in hospital, outpatient/GP or death registries
All cardiorespiratory disease (narrow)	ICD-9-CM codes: 460-519, 410, 426-428, 430-432 or ICD-10-CM codes: J00-J99, I21, I48-I50, I63-I64 in hospital, outpatient/GP or death registries
All respiratory diseases	ICD-9-CM codes: 460-519 or ICD-10-CM codes: J00-J99[a] in hospital, outpatient/GP or death registries
All cardiovascular diseases	ICD-9-CM codes: 390-459 or ICD-10-CM codes: I00-I99[a] in hospital, outpatient/GP or death registries

ICD-9-CM: International Classification of Diseases Ninth Revision; ICD-10: Clinical Modification. International Classification of Diseases, Tenth Revision, Clinical Modification.
[a] On October 1, 2015, the ICD codes changed from its 9th to its 10th version; therefore, depending on the study period assessed, the use of these codes changed.

Suppl Table 2. Outcome subcategories

Outcome subcategory	ICD-10[a]	ICD-10 nomenclature	ICD-9[a]	ICD-9 nomenclature
Influenza or Pneumonia	J09	Influenza due to identified zoonotic or pandemic influenza virus	488	Influenza due to certain identified influenza viruses
	J10	Influenza due to identified seasonal influenza virus	487	Influenza
	J11	Influenza, virus not identified	**	
	J12	Viral pneumonia, not elsewhere classified	480	Viral pneumonia
	J13	Pneumonia due to *Streptococcus pneumoniae*	481	Pneumococcal pneumonia [*Streptococcus pneumoniae pneumonia*]
	J14	Pneumonia due to *Hemophilus influenzae*	482.2	Pneumonia due to *Hemophilus influenzae* (*h. influenzae*)
	J15	Bacterial pneumonia, not elsewhere classified	482	Other bacterial pneumonia
	J16	Pneumonia due to other infectious organisms, not elsewhere classified	483	Pneumonia due to other specified organism
	J17	Pneumonia in diseases classified elsewhere	484	Pneumonia in infectious diseases classified elsewhere
	J18	Pneumonia, organism unspecified	486	Pneumonia, organism unspecified
			485	Bronchopneumonia, organism unspecified
Bronchitis or bronchiolitis	J20	Acute bronchitis	466	Acute bronchitis and bronchiolitis
	J21	Acute bronchiolitis		
	J22	Unspecified acute lower respiratory infection	**	
Chronic lower respiratory diseases	J40	Bronchitis, not specified as acute or chronic	490	Bronchitis, not specified as acute or chronic
	J41	Simple and mucopurulent chronic bronchitis	491	Chronic bronchitis
	J42	Unspecified chronic bronchitis	**	
	J43	Emphysema	492	Emphysema
	J44	Chronic obstructive pulmonary disease	496	Chronic airway obstruction, not elsewhere classified
	J45	Asthma	493	Asthma
	J46	Status asthmaticus	**	
	J47	Bronchiectasis	494	Bronchiectasis
	**		495	Extrinsic allergic alveolitis
Upper respiratory disease	J00	Acute nasopharyngitis [common cold]	460	Acute nasopharyngitis [common cold]
	J01	Acute sinusitis	461	Acute sinusitis
	J02	Acute pharyngitis	462	Acute pharyngitis
	J03	Acute tonsillitis	463	Acute tonsillitis
	J04	Acute laryngitis and tracheitis	464	Acute laryngitis and tracheitis
	J05	Acute obstructive laryngitis [croup] and epiglottitis	464.3	Epiglottitis
			464.4	Croup
	J06	Acute upper respiratory infections of multiple and unspecified sites	465	Acute upper respiratory infections of multiple or unspecified sites
	J30	Vasomotor and allergic rhinitis	477	Allergic rhinitis
	J31	Chronic rhinitis, nasopharyngitis and pharyngitis	472	Chronic pharyngitis and nasopharyngitis
	J32	Chronic sinusitis	473	Chronic sinusitis
	J33	Nasal polyp	471	Nasal polyps
	J34	Other and unspecified disorders of nose and nasal sinuses	470	Deviated nasal septum
	J35	Chronic diseases of tonsils and adenoids	474	Chronic disease of tonsils and adenoids
	J36	Peritonsillar abscess	475	Peritonsillar abscess

Outcome subcategory	ICD-10[a]	ICD-10 nomenclature	ICD-9[a]	ICD-9 nomenclature
	J37	Chronic laryngitis and laryngotracheitis	476	Chronic laryngitis and laryngotracheitis
	J38	Diseases of vocal cords and larynx, not elsewhere classified	**	
	J39	Other diseases of upper respiratory tract	478	Other diseases of upper respiratory tract
Chronic heart failure exacerbations	I42	Cardiomyopathy	425	Cardiomyopathy
	I43	Cardiomyopathy in diseases classified elsewhere	425.8	Cardiomyopathy in other diseases classified elsewhere
	I50	Heart failure	428	Heart failure
	I51.7	Cardiomegaly	429.3	Cardiomegaly
Ischemic heart diseases	I20	Angina pectoris	413	Angina pectoris
	I21	Acute myocardial infarction	410	Acute myocardial infarction
	I22	Subsequent myocardial infarction	**	
	I23	Certain current complications following acute myocardial infarction	**	
	I24	Other acute ischemic heart diseases	411	Other acute and subacute forms of ischemic heart disease
	I25	Chronic ischemic heart disease	412	Old myocardial infarct
			414	Other forms of chronic ischemic heart disease
Arrhythmias	I44	Atrioventricular and left bundle-branch block,	426	Conduction disorders
	I45	Other conduction disorders	427	Cardiac dysrhythmias
	I46	Cardiac arrest	427.5	Cardiac arrest
	I47	Paroxysmal tachycardia	427.0	Paroxysmal supraventricular tachycardia
			427.1	Paroxysmal ventricular tachycardia
			427.2	Paroxysmal tachycardia unspecified
	I48	Atrial fibrillation and flutter	427.3	Atrial fibrillation and flutter
	I49	Other cardiac arrhythmias	427.8	Other specified cardiac dysrhythmias
Cerebrovascular diseases	I60	Subarachnoid hemorrhage	430	Subarachnoid haemorrhage
	I61	Intracerebral hemorrhage	431	Intracerebral hemorrhage
	I62	Other nontraumatic intracranial hemorrhage	432	Other and unspecified intracranial hemorrhage
	I63	Cerebral infarction	**	
	I64	Stroke, not specified as haemorrhage or infarction	**	
	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	433	Occlusion and stenosis of precerebral arteries
	I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	434	Occlusion of cerebral arteries
	I67	Other cerebrovascular diseases	436	Acute but ill-defined cerebrovascular disease
	I68	Cerebrovascular disorders in diseases classified elsewhere	437	Other and ill-defined cerebrovascular disease
	**		435	Transient cerebral ischemia
Myocarditis	I40	Acute myocarditis	422	Acute myocarditis
	I41	Myocarditis in diseases classified elsewhere	422.0	Acute myocarditis in diseases classified elsewhere
	I51.4	Myocarditis, unspecified	429.0	Myocarditis, unspecified
	I51.5	Myocardial degeneration	429.1	Myocardial degeneration

ICD-9-CM: International Classification of Diseases Ninth Revision; ICD-10: Clinical Modification. International Classification of Diseases, Tenth Revision, Clinical Modification. RSV: respiratory syncytial virus.

[a] On October 1, 2015, the ICD codes changed from its 9th to its 10th version; therefore, depending on the study period assessed, the use of these codes changed.

Suppl Table 3. Risk factors for RSV

Risk group category	ICD-9-CM*	ICD-9-CM nomenclature	ICD-10-CM*	ICD-10-CM nomenclature
Chronic cardiac disease	393	Chronic rheumatic pericarditis	I09.2	Chronic rheumatic pericarditis
	394	Diseases of mitral valve	I05	Rheumatic mitral valve diseases
	395	Diseases of aortic valve	I06	Rheumatic aortic valve diseases
	396	Diseases of mitral and aortic valves	I08.0	Rheumatic disorders of both mitral and aortic valves
	397	Diseases of other endocardial structures	***	Not equivalent code in ICD-10
	398	Other rheumatic heart disease	I09	Other rheumatic heart diseases
	402	Hypertensive heart disease	I11	Hypertensive heart disease
	404	Hypertensive heart and chronic kidney disease	I13	Hypertensive heart and chronic kidney disease
	410	Acute myocardial infarction	I21-I23	I21: ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction I22: Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction I23: Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within 28 day period)
	411	Other acute and subacute forms of ischemic heart disease	I24	Other acute ischemic heart diseases
	412	Old myocardial infarction	I25.2	Old myocardial infarction
	413	Angina pectoris	I20	Angina pectoris
	414	Other forms of chronic ischemic heart disease	I25.8	Other forms of chronic ischemic heart disease
	416	Chronic pulmonary heart disease	I27	Other pulmonary heart diseases
	V45.00	Unspecified cardiac device in situ	Z95.9	Presence of cardiac and vascular implant and graft, unspecified
	V45.81	Aortocoronary bypass status	Z95.1	Presence of aortocoronary bypass graft
	424	Other diseases of endocardium	I34-I39	I34: Nonrheumatic mitral valve disorders I35: Nonrheumatic aortic valve disorders I36: Nonrheumatic tricuspid valve disorders I37: Nonrheumatic pulmonary valve disorders I38: Endocarditis, valve unspecified I39: Endocarditis and heart valve disorders in diseases classified elsewhere
	425	Cardiomyopathy	I42	Cardiomyopathy
	426	Conduction disorders	I45	Other conduction disorders
	427	Cardiac dysrhythmias	I49	Other cardiac arrhythmias
	428	Heart failure	I50	Heart failure
	429	Ill-defined descriptions and complications of heart disease	I51	Complications and ill-defined descriptions of heart disease

Risk group category	ICD-9-CM*	ICD-9-CM nomenclature	ICD-10-CM*	ICD-10-CM nomenclature
	440	Atherosclerosis	I70	Atherosclerosis
	745	Bulbus cordis anomalies and anomalies of cardiac septal closure	Q21	Congenital malformations of cardiac septa
	746	Other congenital anomalies of heart	Q24	Other congenital malformations of heart
	747	Other congenital anomalies of circulatory system	Q28	Other congenital malformations of circulatory system
	427.5	Cardiac arrest	I46	Cardiac arrest
	***	Not equivalent code in ICD-9	I97.1	Other postprocedural cardiac functional disturbances
Chronic respiratory diseases	490	Bronchitis, not specified as acute or chronic	J40	Bronchitis, not specified as acute or chronic
	491	Chronic bronchitis	J41, J42	J41 Simple and mucopurulent chronic bronchitis, J42: Unspecified chronic bronchitis
	492	Emphysema	J43	Emphysema
	493	Asthma	J45	Asthma
	494	Bronchiectasis	J47	Bronchiectasis
	495	Extrinsic allergic alveolitis	***	Not equivalent code in ICD-10
	496	Chronic airway obstruction, not elsewhere classified	J44	Other chronic obstructive pulmonary disease
	500	Coal workers' pneumoconiosis	J60	Coal workers' pneumoconiosis
	501	Asbestosis	J61	Pneumoconiosis due to asbestos and other mineral fibers
	502	Pneumoconiosis due to other silica or silicates	J62	Pneumoconiosis due to dust containing silica
	503	Pneumoconiosis due to other inorganic dust	J63	Pneumoconiosis due to other inorganic dust
	504	Pneumonopathy due to inhalation of other dust	***	Not equivalent code in ICD-10
	505	Pneumoconiosis, unspecified	J64	Pneumoconiosis, unspecified
	506	Respiratory conditions due to chemical fumes and vapors	J68	Respiratory conditions due to inhalation of chemicals, gases, fumes and vapors
	507	Pneumonitis due to solids and liquids	J69	Pneumonitis due to solids and liquids
	508	Respiratory conditions due to other and unspecified external agents	J70	Respiratory conditions due to other external agents
	277	Cystic fibrosis	E84	Cystic fibrosis
	513	Abscess of lung and mediastinum	J85	Abscess of lung and mediastinum
	514	Pulmonary congestion and hypostasis	J81	Hypostatic pneumonia, unspecified organism; Chronic pulmonary edema
	515	Post inflammatory pulmonary fibrosis	J84.10, J84.89	Pulmonary fibrosis, unspecified; Other specified interstitial pulmonary diseases
	516	Other alveolar and parietoalveolar pneumonopathy	J84.09	Other alveolar and parieto-alveolar conditions
	517	Lung involvement in conditions classified elsewhere	***	Not equivalent code in ICD-10
	518	Other diseases of lung	J98.4	Other disorders of lung
Diabetes mellitus	250	Diabetes mellitus	E08-E13	Diabetes mellitus
	251	Other disorders of pancreatic internal secretion	E16	Other disorders of pancreatic internal secretion

Risk group category	ICD-9-CM*	ICD-9-CM nomenclature	ICD-10-CM*	ICD-10-CM nomenclature
	357.2	Polyneuropathy in diabetes	E08.42, E09.42, E10.42, E11.42, E13.42	E08.42 Diabetes mellitus due to underlying condition with diabetic polyneuropathy; E09.42 Drug or chemical induced diabetes mellitus with neurological complications with diabetic polyneuropathy; E10.42 Type 1 diabetes mellitus with diabetic polyneuropathy; E11.42 Type 2 diabetes mellitus with diabetic polyneuropathy E13.42 Other specified diabetes mellitus with diabetic polyneuropathy
	362.0	Diabetic retinopathy	E10.31, E11.31	Type 1 diabetes mellitus with unspecified diabetic retinopathy; Type 2 diabetes mellitus with unspecified diabetic retinopathy
	362.11	Hypertensive retinopathy	H35.039	Hypertensive retinopathy, unspecified eye
	366.41	Diabetic cataract	E08.36, E09.36, E10.36, E11.36, E13.36	E08.36 Diabetes mellitus due to underlying condition with diabetic cataract; E09.36 Drug or chemical induced diabetes mellitus with diabetic cataract; E10.36 Type 1 diabetes mellitus with diabetic cataract; E11.36 Type 2 diabetes mellitus with diabetic cataract; E13.36 Other specified diabetes mellitus with diabetic cataract
	648	Diabetes mellitus complicating pregnancy childbirth or the puerperium	O24	Diabetes mellitus in pregnancy, childbirth, and the puerperium
Chronic liver disease	570-573	570 Acute and subacute necrosis of liver; 571 Chronic liver disease and cirrhosis; 572 Liver abscess and sequelae of chronic liver disease; 573 Other disorders of liver	K70-K77	Diseases of liver
	751.62	Congenital cystic disease of liver	Q44.6	Cystic disease of liver
Chronic kidney disease	403	Hypertensive chronic kidney disease	I12	Hypertensive chronic kidney disease
	580	Acute glomerulonephritis	N00	Acute nephritic syndrome
	581	Nephrotic syndrome	N04	Nephrotic syndrome
	582	Chronic glomerulonephritis	N03	Chronic nephritic syndrome
	583	Nephritis and nephropathy not specified as acute or chronic	N05	Unspecified nephritic syndrome
	584	Acute kidney failure	N17	Acute kidney failure
	585	Chronic kidney disease (ckd)	N18	Chronic kidney disease (ckd)
	586	Renal failure, unspecified	N19	Unspecified kidney failure
	587	Renal sclerosis, unspecified	N26.9	Renal sclerosis, unspecified
	588	Disorders resulting from impaired renal function	N25	Disorders resulting from impaired renal tubular function
	589	Small kidney of unknown cause	N27	Small kidney of unknown cause
	590	Infections of kidney	***	Not equivalent code in ICD-10
	591	Hydronephrosis	N13.30	Unspecified hydronephrosis
	593.8	Other specified disorders of kidney and ureter	N28.8	Other specified disorders of kidney and ureter
	V42.0	Kidney replaced by transplant	V42.0, Z94.0	Kidney replaced by transplant; Kidney transplant status
	V45.1	Postsurgical renal dialysis status	***	Not equivalent code in ICD-10
	V56	Encounter for dialysis and dialysis catheter care	Z49	Encounter for care involving renal dialysis

Risk group category	ICD-9-CM*	ICD-9-CM nomenclature	ICD-10-CM*	ICD-10-CM nomenclature
Immunosuppression	042	Human immunodeficiency virus [HIV] disease	B20	Human immunodeficiency virus [HIV] disease
	079.5	Retrovirus in conditions classified elsewhere and of unspecified site	***	Not equivalent code in ICD-10
	279	Disorders involving the immune mechanism	***	Not equivalent code in ICD-10
	288.0	Neutropenia	***	Not equivalent code in ICD-10
	288.1	Functional disorders of polymorphonuclear neutrophils	D71	Functional disorders of polymorphonuclear neutrophils
	288.2	Genetic anomalies of leukocytes	D72.0	Genetic anomalies of leukocytes
	446	Polyarteritis nodosa and allied conditions	M30	Polyarteritis nodosa and related conditions
	710	Systemic lupus erythematosus	M32	Systemic lupus erythematosus (SLE)
	710.2	Sicca syndrome	M35.00, M35.1	M35.00 Sjögren syndrome, unspecified; M35.01 Sjögren syndrome with keratoconjunctivitis
	710.4	Polymyositis	M33.2	Polymyositis
	714	Rheumatoid arthritis and other inflammatory polyarthropathies	M06	Other rheumatoid arthritis
	V08	Asymptomatic human immunodeficiency virus [HIV] infection status	Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
	V42.0	Kidney replaced by transplant	Z94.0	Kidney transplant status
	V42.1	Heart replaced by transplant	Z94.1	Heart transplant status
	V42.2	Heart valve replaced by transplant	Z95.3	Presence of xenogenic heart valve
	V42.6	Lung replaced by transplant	Z94.2	Lung transplant status
	V42.7	Liver replaced by transplant	Z94.4	Liver transplant status
	V42.8	Other specified organ or tissue replaced by transplant	Z94.81, Z94.84, Z94.83, Z94.82, Z94.89	Z94.81 Bone marrow transplant status, Z94.84 Stem cells transplant status, Z94.83 Pancreas transplant status; Z94.82 Intestine transplant status, Z94.89 Other transplanted organ and tissue status
	V42.9	Unspecified organ or tissue replaced by transplant	Z94.9	Transplanted organ and tissue status, unspecified
	V58.0	Encounter for radiotherapy	Z51.0	Encounter for antineoplastic radiation therapy
	V58.1	Encounter for antineoplastic chemotherapy and immunotherapy	Z51.11, Z51.12	Z51.11 Encounter for antineoplastic chemotherapy; Z51.12 Encounter for antineoplastic immunotherapy
	235-239	235-238 Neoplasms Of Uncertain Behavior; 239 Neoplasms Of Unspecified Nature	D37-D48	Neoplasms of uncertain or unknown behaviour
	140-149	Malignant Neoplasm Of Lip, Oral Cavity, And Pharynx	C00-C14	Malignant neoplasms of lip, oral cavity and pharynx
	150-159	Malignant Neoplasm Of Digestive Organs And Peritoneum	C15-C26	Malignant neoplasms of digestive organs
	160-165	Malignant Neoplasm Of Respiratory And Intrathoracic Organs	C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
	170-176	Malignant Neoplasm Of Bone, Connective Tissue, Skin, And Breast	C40-C41, C43-C44, C45-C49, C50-C50	Malignant neoplasms of bone and articular cartilage, Melanoma and other malignant neoplasms of skin, Malignant neoplasms of mesothelial and soft tissue, Malignant neoplasms of breast

Risk group category	ICD-9-CM*	ICD-9-CM nomenclature	ICD-10-CM*	ICD-10-CM nomenclature
	179-189	Malignant Neoplasm Of Genitourinary Organs	C51-C58, C60-63, C64-C68	Malignant neoplasms of female genital organs, Malignant neoplasms of male genital organs, Malignant neoplasms of urinary tract
	190-192	Malignant neoplasm of eye, Malignant neoplasm of brain, Malignant neoplasm of other and unspecified parts of nervous system	C69-C72	Malignant neoplasms of eye, brain and other parts of central nervous system
	193, 194	Malignant neoplasm of thyroid gland, Malignant neoplasm of other endocrine glands and related structures	C73-C75	Malignant neoplasms of thyroid and other endocrine glands
	195, 199	Malignant neoplasm of other and ill-defined sites, Malignant neoplasm without specification of site	C76-C80	Malignant neoplasms of ill-defined, other secondary and unspecified sites
	200-202	200 Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue; 201 Hodgkin's disease; 202 Other malignant neoplasms of lymphoid and histiocytic tissue	C81-C88	C81 Hodgkin lymphoma, C82 Follicular lymphoma, C83 Non-follicular lymphoma, C84 Mature T/NK-cell lymphomas, C85 Other specified and unspecified types of non-Hodgkin lymphoma, C86 Other specified types of T/NK-cell lymphoma, C88 Malignant immunoproliferative diseases and certain other B-cell lymphomas,
	203.1, 204-208	203.1 Plasma cell leukemia, 204 Lymphoid leukemia, 205 Myeloid leukemia, 206 Monocytic leukemia, 207 Other specified leukemia, 208 Leukemia of unspecified cell type	C90.1; C91-C95	C90.1 Plasma cell leukemia, C91 Lymphoid leukemia, C92 Myeloid leukemia, C93 Monocytic leukemia, C94 Other leukemias of specified cell type, C95 Leukemia of unspecified cell type
	235-238	Neoplasms Of Uncertain Behavior	D37-D48	Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes
	279	Disorders involving the immune mechanism	D80-D84 and D89	D80 Immunodeficiency with predominantly antibody defects D81 Combined immunodeficiencies D82 Immunodeficiency associated with other major defects D83 Common variable immunodeficiency D84 Other immunodeficiencies D89 Other disorders involving the immune mechanism, not elsewhere classified
	***	No equivalent in ICD-9	T86	Complications of transplanted organs and tissue
	V42	Organ or tissue replaced by transplant	Z94.6	Solid organ transplantation
	710.0	Systemic lupus erythematosus	M32	Systemic lupus erythematosus
	714.0	Rheumatoid arthritis	M05; M06; M08	Rheumatoid arthritis
	696.0, 696.1, 696.8	Psoriatic arthropathy, Other psoriasis, Other psoriasis and similar disorders	L40	Psoriasis
		No equivalent in ICD-9	M07	Enteropathic arthropathies
	446.5	Giant cell arteritis	M31.5; M31.6	Giant cell arteritis with polymyalgia rheumatica, Other giant cell arteritis
Neurological disorders	742	Other congenital anomalies of nervous system	Q00-Q07	Congenital malformations of the nervous system
	320-327 , 330-337	Inflammatory Diseases Of The Central Nervous System, Hereditary And Degenerative Diseases Of The Central Nervous System	G10-G39	G10-G09 Inflammatory diseases of the central nervous system, G10-G14 Systemic atrophies primarily affecting the central nervous system,

Risk group category	ICD-9-CM*	ICD-9-CM nomenclature	ICD-10-CM*	ICD-10-CM nomenclature
	435	Transient cerebral ischemia	G45-G46	G45 Transient cerebral ischemic attacks and related syndromes, Vascular syndromes of brain in cerebrovascular diseases
	340, 341, 347-349,	340 Multiple sclerosis 341 Other demyelinating diseases of central nervous system347 Cataplexy and narcolepsy 348 Other conditions of brain 349 Other and unspecified disorders of the nervous system	G70-G99	G70-G73 Diseases of myoneural junction and muscle, G80-G83 Cerebral palsy and other paralytic syndromes, G89-G99 Other disorders of the nervous system

ICD-9-CM: International Classification of Diseases Ninth Revision; ICD-10: Clinical Modification. International Classification of Diseases, Tenth Revision, Clinical Modification.
RSV: respiratory syncytial virus.
*On October 1, 2015, the ICD codes changed from its 9th to its 10th version; therefore, depending on the study period assessed, the use of these codes changed.

Suppl Table 4. Shell table: outcome data

Year	Time: unit	Time: value[a]	Age group (years)	Risk group (when applicable)	Event count[b]
2010	Week / Month	1	18-44	Yes	
2010	Week / Month	1	45-64	Yes	
2010	Week / Month	1	65-79	Yes	
2010	Week / Month	1	≥80	Yes	
2010	Week / Month	1	18-44	No	
2010	Week / Month	1	45-64	No	
2010	Week / Month	1	65-79	No	
2010	Week / Month	1	≥80	No	
2010	Week / Month	2	18-44	Yes	
2010	Week / Month	2	45-64	Yes	
2010	Week / Month	2	65-79	Yes	
2010	Week / Month	2	≥80	Yes	
2010	Week / Month	2	18-44	No	
2010	Week / Month	2	45-64	No	
2010	Week / Month	2	65-79	No	
2010	Week / Month	2	≥80	No	
…	…	…	…	…	…
2019	Week / Month	52 / 12 [a]	18-44	Yes	
2019	Week / Month	52 / 12 [a]	45-64	Yes	
2019	Week / Month	52 / 12 [a]	65-79	Yes	
2019	Week / Month	52 / 12 [a]	≥80	Yes	
2019	Week / Month	52 / 12 [a]	18-44	No	
2019	Week / Month	52 / 12 [a]	45-64	No	
2019	Week / Month	52 / 12 [a]	65-79	No	
2019	Week / Month	52 / 12 [a]	≥80	No	

[a] ranging from week 1 to 52 (or 53 for leap year) if time unit is week; ranging from 1 to 12 if time unit is month.
[b] Events refer to one column for each event type and outcome. Planned event types include general practitioner visits, emergency department visits, hospitalizations, and deaths. Planned outcomes include all cardiorespiratory (broad), selected cardiorespiratory (narrow), all respiratory, all cardiovascular, influenza or pneumonia, bronchitis or bronchiolitis, chronic lower respiratory diseases, upper respiratory diseases, chronic heart failure exacerbations, ischemic heart diseases, arrhythmias, cerebrovascular diseases, and myocarditis.

Suppl Table 5. Shell table: weekly viral proxy data

Year	Time: unit	Time: value [a]	RSV					Influenza				
			Lag 0	Lag 1	Lag 2	Lag 3	Lag4	Lag 0	Lag 1	Lag 2	Lag 3	Lag4
2010	Week	1										
2010	Week	2										
2010	Week	3										
…	…	…	…									
2019	Week	51										
2019	Week	52										

Suppl Table 6. Shell table: monthly viral proxy data

Year	Time: unit	Time: value [a]	RSV	Influenza
2010	Month	1		
2010	Month	2		
2010	Month	3		
…	…	…	…	
2019	Month	11		
2019	Month	12		

Respiratory syncytial virus (RSV) model-based study: Statistical Analysis Plan – SPAIN

Model-based approach to estimate RSV disease incidence, including hospitalizations, and deaths.

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Explanation
ARI	Acute respiratory tract infection
CVA	Cerebrovascular accident
COPD	Chronic obstructive pulmonary disease
ED	Emergency department
EMR	Electronic medical record
GP	General practitioner
ICD	International Classification of Disease
LRTI	Lower respiratory tract infection
RSV	Respiratory syncytial virus
SAP	Statistical analysis plan

1 BACKGROUND

Respiratory syncytial virus (RSV) is a common cause of respiratory tract infections in children and adults. In children, the disease presentation ranges from sinusitis to bronchiolitis and pneumonia. In adults, the clinical presentation typically ranges from mild disease to severe lower respiratory tract infection (LRTI) or exacerbation of chronic respiratory and cardiac disease. Annual RSV epidemics occur seasonally, primarily in colder months in temperate climates [1].

In young children, RSV is a leading cause of hospitalization for respiratory tract infection. It is estimated that in children under 5 years of age, approximately 40 million cases of RSV occur annually, of which 10% are hospitalized [2]. In older adults, RSV burden was estimated at 1.5 million episodes of acute respiratory infections (ARIs) in industrialized countries, of which 14,5% required hospitalization. In 2016, RSV was the second leading cause of death from LRTI overall, and 54% of deaths from LRTI attributable to RSV occurred in children under 5 years of age [3]. Morbidity and mortality in older adults (≥65 years old) with underlying medical conditions is high, including those with chronic lung and heart disease, long-term care facility residents and immunocompromised patients [4].

The incidence and burden of RSV disease in adults are difficult to measure since RSV cases do not have a specific symptomatology that could distinguish them from cases of influenza and other respiratory viruses. Additionally, the incidence of RSV is underestimated due to resolution of symptoms before reaching medical attention, lack of standard-of-care testing for RSV when presenting to medical care facilities with ARI, the low diagnostic capacity and high cost of polymerase chain reaction testing. In addition, the use of RSV-specific International Classification of Diseases (ICD) codes dramatically underestimates the incidence due to the infrequency of standard-of-care testing [5]. As a result, several alternative “model-based” approaches are used to retrospectively assess RSV incidence. These approaches model claims/electronic medical record (EMR) data and apply the expected proportion of events that would be due to RSV to the events with clinical syndromes consistent with RSV (e.g., bronchitis, chronic obstructive pulmonary disease [COPD] exacerbation, pneumonia).

The aim of this statistical analysis plan (SAP) is to define a statistical model-based approach to estimate RSV disease incidence, including hospitalizations and mortality, from recorded RSV circulation in the population. This SAP focuses on the country-specific analysis for Spain.

2 OBJECTIVES

The aim of the study is to estimate the population-based epidemiologic burden of RSV. To answer this research question, a set of objectives has been set out revolving around two types of events: hospitalization and mortality (Section 4.1).

2.1 Primary objectives

The primary objectives, depending on availability of the required data within the databases, include for each event type in adults:

1. To estimate RSV-attributable incidence of cardiorespiratory events.
    1.1. To estimate RSV-attributable incidence of respiratory events.
    1.2. To estimate RSV-attributable incidence of circulatory events.

In children, objective 1.1 is investigated for each event type.

These objectives are assessed stratified by age group (Section 4.5).

2.2 Secondary objectives

In addition, nine secondary objectives are investigated for adults. Depending on availability of the required data within the databases, these include for each event type:

1.1.1. To estimate RSV-attributable incidence of influenza or pneumonia events.
1.1.2. To estimate RSV-attributable incidence of bronchitis or bronchiolitis events.
1.1.3. To estimate RSV-attributable incidence of chronic lower respiratory disease events.
1.1.4. To estimate RSV-attributable incidence of upper respiratory disease events.

1.2.1. To estimate RSV-attributable incidence of chronic heart failure exacerbation events.
1.2.2. To estimate RSV-attributable incidence of ischemic heart disease events.
1.2.3. To estimate RSV-attributable incidence of arrhythmia events.
1.2.4. To estimate RSV-attributable incidence of cerebrovascular events.
1.2.5. To estimate RSV-attributable incidence of myocarditis events.

These objectives are assessed stratified by age group (Section 4.5).

3 STUDY DESIGN

The objectives are assessed through a retrospective analysis of healthcare data (Section 3.3). Data are analysed with a Quasi-Poisson model adjusting for seasonality and viral activity (Section 7.2).

3.1 Study population

Individuals (male or female) residing in Spain captured by the selected databases that are registered in national registries (Section 3.3) with one of the studied event types (Section 4.1).

3.2 Study period

Data are captured from 2015 until 2019, hence excluding 2020 (COVID-19 pandemic), which is expected to distort RSV surveillance and/or incidence.

3.3 Data sources

The study is conducted using healthcare data that are available online or reside in administrative databases with Pfizer Spain (Table 1).

Table 1. Characteristics of healthcare databases used in this study.

Variable	Data source	Description	Data owner	Coverage	Granularity
Event type: hospitalization	Conjunto Mínimo de Datos Básicos (CMBD) National	National hospital discharge register	Ministry of Health	National	Daily
Event type: mortality	Base de datos de mortalidad	National mortality register	National Statistical Office	National	Monthly
Viral activity: RSV	Vigilancia centinela de IRAs y de IRAG: Gripe, Covid-19 y otros virus respiratorios	National sentinel surveillance	Instituto de Salud Carlos III	National	Weekly
Viral activity: influenza	Vigilancia centinela de IRAs y de IRAG: Gripe, Covid-19 y otros virus respiratorios	National sentinel surveillance	Instituto de Salud Carlos III	National	Weekly
Viral activity: RSV – HB	Conjunto Mínimo de Datos Básicos (CMBD) National	National hospital discharge register	Ministry of Health	National	Daily
Viral activity: influenza - HB	Conjunto Mínimo de Datos Básicos (CMBD) National	National hospital discharge register	Ministry of Health	National	Daily

RSV: Respiratory syncytial virus; HB: hospital-based.

The hospitalization data file, obtained from the national hospital discharge register, includes the following variables of interest for this study: hospital code (for 2015 only), patient code (within the hospital for 2015, across hospitals for 2016-2019), year, date of birth, gender, principal diagnosis, secondary diagnosis and date of admission.

The mortality data file, obtained from the national mortality register, includes the following variables of interest for this study: year and month of death, age (in years) and principal diagnosis (cause of death).

The surveillance data file, obtained by extracting surveillance data from the national sentinel surveillance, includes the following variables of interest for this study: ISO calendar week of testing, number of positive tests (for RSV or influenza), number of tests taken (for RSV or influenza).

4 OPERATIONAL DEFINITIONS

In this study, two event types are of interest (Section 4.1). They are assessed through a set of objectives (Section 2) revolving around a set of primary and secondary outcomes (Section 4.2). The analysis of these outcomes accounts for seasonality, viral proxies (Section 4.4) and other variables (Section 4.5).

4.1 Event types

The event types of interest in this study include hospitalization and mortality. A hospitalization (including at least one overnight stay at a hospital) is defined by the date of admission. Mortality is defined by the month and year of death.

For hospitalization, a readmission for the same outcome (Section 4.2) within 30 days from the preceding hospital admission is considered as part of the preceding hospitalization. When readmission occurs more than 30 days after the preceding hospitalization it is considered as an independent hospitalization.

4.2 Outcomes

The outcomes, primary and secondary, are defined by occurrence of selected ICD codes (9th revision before October 1, 2015, and 10th revision afterwards). For hospitalization, any mentioning of the selected

ICD codes qualifies a record as an event. For mortality, only the primary diagnosis is considered for event qualification.

4.2.1 Primary outcomes

The main outcomes of interest for each event type in adults are cardiorespiratory events, respiratory events and circulatory events (Table 2). These outcomes have been selected based on a literature review to balance sensitivity and specificity of the ICD diagnosis for identification of RSV disease and to approximate estimates reported from observational studies. In children, the outcome of interest for each event type is respiratory events (Table 2).

Table 2. Definition of primary outcomes.

Outcome	ICD-9-CM	ICD-10-CM
1. Cardiorespiratory event	460-519 390-459	J00-J99 I00-I99
1.1 Respiratory event	460-519	J00-J99
1.2 Circulatory event	390-459	I00-I99

ICD: International Classification of Diseases.
Note that on October 1, 2015 the ICD codes changed from its 9th revision to its 10th revision. Therefore, depending on the study period, different ICD nomenclature is to be used for the classification of events.

4.2.2 Secondary outcomes

In addition, nine secondary outcomes are of interest for each studied event type in adults (Table 3). These outcomes have been selected to give more detailed information relevant for use in economic evaluations.

Table 3. Definition of secondary outcomes.

Outcome subcategory	ICD-10-CM	ICD-10-CM nomenclature	ICD-9-CM	ICD-9-CM nomenclature
1.1.1 Influenza or pneumonia	J09	Influenza due to identified zoonotic or pandemic influenza virus	488	Influenza due to certain identified influenza viruses
	J10	Influenza due to identified seasonal influenza virus	487	Influenza
	J11	Influenza, virus not identified	**	
	J12	Viral pneumonia, not elsewhere classified	480	Viral pneumonia
	J13	Pneumonia due to Streptococcus pneumoniae	481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]
	J14	Pneumonia due to Hemophilus influenzae		482.2 - Pneumonia due to hemophilus influenzae (h. influenzae)
	J15	Bacterial pneumonia, not elsewhere classified	482	Other bacterial pneumonia
	J16	Pneumonia due to other infectious organisms, not elsewhere classified	483	Pneumonia due to other specified organism
	J17	Pneumonia in diseases classified elsewhere	484	Pneumonia in infectious diseases classified elsewhere
	J18	Pneumonia, organism unspecified	486	Pneumonia, organism unspecified
			485	Bronchopneumonia, organism unspecified
1.1.2 Bronchitis or bronchiolitis	J20	Acute bronchitis	466	Acute bronchitis and bronchiolitis
	J21	Acute bronchiolitis		
	J22	Unspecified acute lower respiratory infection	**	
1.1.3 Chronic lower respiratory diseases	J40	Bronchitis, not specified as acute or chronic	490	Bronchitis, not specified as acute or chronic
	J41	Simple and mucopurulent chronic bronchitis	491	Chronic bronchitis
	J42	Unspecified chronic bronchitis	**	
	J43	Emphysema	492	Emphysema
	J44	Chronic obstructive pulmonary disease	496	Chronic airway obstruction, not elsewhere classified
	J45	Asthma	493	Asthma
	J46	Status asthmaticus	**	
	J47	Bronchiectasis	494	Bronchiectasis
	**		495	Extrinsic allergic alveolitis
1.1.4 Upper respiratory diseases	J00	Acute nasopharyngitis [common cold]	460	Acute nasopharyngitis [common cold]
	J01	Acute sinusitis	461	Acute sinusitis
	J02	Acute pharyngitis	462	Acute pharyngitis
	J03	Acute tonsillitis	463	Acute tonsillitis
	J04	Acute laryngitis and tracheitis	464	Acute laryngitis and tracheitis
	J05	Acute obstructive laryngitis [croup] and epiglottitis		464.3 Epiglottitis
				464.4 Croup

	J06	Acute upper respiratory infections of multiple and unspecified sites	465	Acute upper respiratory infections of multiple or unspecified sites
	J30	Vasomotor and allergic rhinitis	477	Allergic rhinitis
	J31	Chronic rhinitis, nasopharyngitis and pharyngitis	472	Chronic pharyngitis and nasopharyngitis
	J32	Chronic sinusitis	473	Chronic sinusitis
	J33	Nasal polyp	471	Nasal polyps
	J34	Other and unspecified disorders of nose and nasal sinuses	470	Deviated nasal septum
	J35	Chronic diseases of tonsils and adenoids	474	Chronic disease of tonsils and adenoids
	J36	Peritonsillar abscess	475	Peritonsillar abscess
	J37	Chronic laryngitis and laryngotracheitis	476	Chronic laryngitis and laryngotracheitis
	J38	Diseases of vocal cords and larynx, not elsewhere classified	**	
	J39	Other diseases of upper respiratory tract	478	Other diseases of upper respiratory tract
1.2.1 Chronic heart failure exacerbations	I42	Cardiomyopathy	425	Cardiomyopathy
	I43	Cardiomyopathy in diseases classified elsewhere		425.8 Cardiomyopathy in other diseases classified elsewhere
	I50	Heart failure	428	Heart failure
	I51.7	Cardiomegaly	429.3	Cardiomegaly
1.2.2 Ischemic heart diseases	I20	Angina pectoris	413	Angina pectoris
	I21	Acute myocardial infarction	410	Acute myocardial infarction
	I22	Subsequent myocardial infarction	**	
	I23	Certain current complications following acute myocardial infarction	**	
	I24	Other acute ischemic heart diseases	411	Other acute and subacute forms of ischemic heart disease
	I25	Chronic ischemic heart disease	412	Old myocardial infarct
			414	Other forms of chronic ischemic heart disease
1.2.3 Arrhythmias	I44	Atrioventricular and left bundle-branch block,	426	Conduction disorders
	I45	Other conduction disorders	427	Cardiac dysrhythmias
	I46	Cardiac arrest		427.5 Cardiac arrest
	I47	Paroxysmal tachycardia		427.0 Paroxysmal supraventricular tachycardia, 427.1 Paroxysmal ventricular tachycardia, 427.2 Paroxysmal tachycardia unspecified
	I48	Atrial fibrillation and flutter		427.3 Atrial fibrillation and flutter
	I49	Other cardiac arrhythmias		427.8 Other specified cardiac dysrhythmias
1.2.4 Cerebrovascular diseases	I60	Subarachnoid hemorrhage	430	Subarachnoid haemorrhage
	I61	Intracerebral hemorrhage	431	Intracerebral hemorrhage

	I62	Other nontraumatic intracranial hemorrhage	432	Other and unspecified intracranial hemorrhage
	I63	Cerebral infarction	**	
	I64	Stroke, not specified as haemorrhage or infarction	**	
	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	433	Occlusion and stenosis of precerebral arteries
	I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	434	Occlusion of cerebral arteries
	I67	Other cerebrovascular diseases	436	Acute but ill-defined cerebrovascular disease
	I68	Cerebrovascular disorders in diseases classified elsewhere	437	Other and ill-defined cerebrovascular disease
	**		435	Transient cerebral ischemia
1.2.5 Myocarditis	I40	Acute myocarditis	422	Acute myocarditis
	I41	Myocarditis in diseases classified elsewhere		422.0 Acute myocarditis in diseases classified elsewhere
	I51.4	Myocarditis, unspecified	429.0	Myocarditis, unspecified
	I51.5	Myocardial degeneration	429.1	Myocardial degeneration

ICD: International Classification of Diseases.
Note that on October 1, 2015 the ICD codes changed from its 9th revision to its 10th revision. Therefore, depending on the study period, different ICD nomenclature is to be used for the classification of events.

In order to obtain the RSV-specific hospitalization and mortality rates, we extracted data provided in Table 4.

Table 4. RSV-specific data definition

RSV specific	B97.4	Respiratory syncytial virus as the cause of diseases classified to other chapters	079.6	Respiratory syncytial virus (RSV)
	J21.0	Acute bronchiolitis due to respiratory syncytial virus	466.11	Acute bronchiolitis due to respiratory syncytial virus (RSV)
	J12.1	Respiratory syncytial virus pneumonia	480.1	Pneumonia due to respiratory syncytial virus
	J20.5	Acute bronchitis due to respiratory syncytial virus	**	No equivalent

4.3 Alternative outcomes

An expert panel (in France) identified nine cardiac diagnoses as potentially associated with RSV: acute myocardial infarction, pulmonary embolism, acute pericarditis, acute myocarditis, myocarditis in disease classified elsewhere, atrial fibrillation and flutter, heart failure, cerebral infarction, and stroke, not specified as haemorrhage or infarction. To ensure these diagnoses were accounted for, several alternative definitions of cardiorespiratory hospitalizations will be included as a sensitivity analysis for adults (Table 5).

Table 5. Definition of alternative outcomes.

Outcome	Definition
Selected cardiorespiratory hospitalization	ICD-10 codes: I21, I48-50, I63-64 and J00-99
Combined cardiorespiratory hospitalization	Outcomes: 1.1, 1.2.1, 1.2.2, 1.2.3 and 1.2.4

ICD: International Classification of Diseases.

4.4 Viral proxies

Circulation of selected pathogens in the population can be accounted for by standardized surveillance-based viral proxies or by hospital-based viral proxies.

Surveillance-based viral proxies are defined as the weekly (or monthly) number of positive tests for a pathogen out of the total reported number of tests performed for the respective pathogen in the corresponding year. Note that the number of tests taken is only reported during influenza season.

Hospital-based viral proxies are defined as hospitalizations with a pathogen-specific ICD code in patients of a specific age (Table 6).

Table 6. Definition of hospital-based viral proxies.

Viral proxy	Age	ICD-9-CM	ICD-10-CM
RSV – all models	<2 years	079.6, 466.1, 466.11, 480.1	B97.4, J21.0, J12.1, J20.5, J21.9
Influenza – adult models	≥60 years	487, 488	J09, J10, J11
Influenza – pediatric models	<2 years	487, 488	J09, J10, J11

ICD: International Classification of Diseases.
Note that on October 1, 2015 the ICD codes changed from its 9th revision to its 10th revision. Therefore, depending on the study period, different ICD nomenclature is to be used for the classification of events.

Selected pathogens of interest in this study include RSV and influenza.

4.5 Other variables

Other variables of interest in this study include time and age.

The definition of time depends on the event type. For hospitalization, time is defined as running ISO calendar week (of hospital admission). For mortality, time is defined as running Gregorian calendar month (of death).

Age is defined as the age at the time of the event, categorized as one of four age groups of interest. The categorization of age depends on the event type. For hospitalization, age is categorized as 0-5 months, 6-11 months, 12-23 months, 2-5 years, 6-17 years, 18-49 years, 50-59 years, 60-79 years and ≥80 years. If the observed number of respiratory hospitalizations is too low (<5 in >20% of the weeks), age groups 12-23 months and 2-5 years are concatenated (1-5 years). For mortality, age is categorized as 0-11 months, 1-5 years, 6-17 years, 18-49 years, 50-59 years, 60-79 years and ≥80 years. If the observed number of

respiratory deaths is too low (<5 in >20% of the months), age groups 0-11 months and 1-5 years are concatenated (0-5 years).

5 SAMPLE SIZE CONSIDERATIONS

This is a descriptive study without any a priori hypothesis tests specified. As such, sample size calculations are not applicable.

6 DATA TRANSFORMATIONS

Initial data transformations are conducted on the hospitalization data file (Section 6.1), the mortality data file (Section 6.2) and the surveillance data file (Section 6.3), resulting in cleaned data files. Then, viral proxies based on the surveillance and the hospitalization data files are compared and one set is selected for use in the analysis (Section 6.4). Afterwards, the cleaned data files are merged together to obtain one analysis file for each event type (Section 6.5). This process is visualized in Figure 1 and elaborated in subsequent subsections.

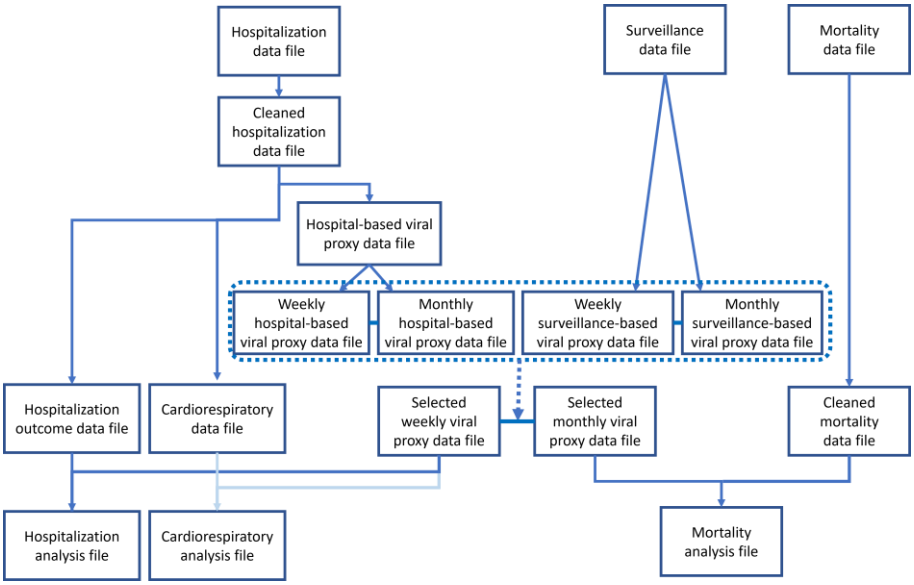

Figure 1. Visualization of data transformation process.

6.1 Hospitalization data file

Entries with admission dates outside of the study period or with identical admission and discharge dates (i.e. no overnight stay included) are dropped from the hospitalization data file. Afterwards, a unique patient ID is generated using the information available in the hospitalization data file. For 2015, the patient ID consists of a concatenation of hospital code, patient code and date of birth. For 2016-2019, the patient ID is represented by the National health system's patient identification number (CIP SNS). To avoid all entries with missing CIP SNS to be considered as one patient in analyses, a missing CIP SNS is

replaced by a substitute patient ID constructed from the information available in the data file (i.e. a concatenation of year, date of birth and gender).

Duplicate entries are removed from the hospitalization data file. For entries which differ only in diagnosis codes, the entry with the highest number of diagnosis codes is retained, assuming this is the most updated record. If only the diagnosis codes differ but the number of codes is equal, a random entry is retained. For entries which differ only in diagnosis codes and date of discharge, the entry with the latest discharge date is retained, assuming this is the most updated record.

For each of the remaining entries in the hospitalization data file, the presence of each of the studied outcomes and viral proxies is assessed based on the outcome and proxy definitions (Sections 4.2, 4.3 and 4.4). Age is determined as time between date of admission and date of birth in years (floored) or months (floored) when <1 year of age. Patients with age missing or date of birth reported as 1JAN1900 are dropped from the hospitalization data file. Afterwards, the patient's age is categorized in the study age groups (Section 4.5).

For each of the outcomes and hospital-based viral proxies, a similar approach is followed. Individual patients' records are sorted from the start of the study period to the end of the study period. For the records that are considered to be a readmission, the presence of the respective outcome or viral proxy during the preceding hospitalization and the time (in days) since this hospitalization are obtained. If readmission for the same outcome or proxy occurs within 30 days of the preceding hospitalization, only the initial hospitalization is retained (for the respective outcome or proxy).

The cleaned hospitalization data file is then used to generate three data files: the hospitalization outcome data file, the cardiorespiratory data file and the hospital-based viral proxy data file. The former are constructed by retaining the admission date, age group and outcomes, with the hospitalization outcome data file containing all outcomes (Section 4.2) and the cardiorespiratory data file containing all alternative outcomes (Section 4.3). The hospital-based viral proxy file is constructed by retaining the admission date, age and viral proxies.

6.1.1 Hospitalization outcome data file

Time is determined as ISO calendar week and ISO calendar year from the date of hospital admission. The records for each outcome are aggregated to number of events per ISO week (within ISO year) for each age group.

A shell table showing the layout of the hospitalization outcome data file is shown in Annex Table A1. Because the first ISO week for 2015 spans dates in 2014, for which no hospitalization information is available, the timeline for the hospitalization data file runs from 2015 week 2 until 2019 week 52.

6.1.2 Cardiorespiratory data file

Time is determined as ISO calendar week and ISO calendar year from the date of hospital admission. The records for each outcome are aggregated to number of events per ISO week (within ISO year) for each age group. Because alternative outcomes were ICD-10 coded, only entries for 2016 to 2019 are selected.

A shell table showing the layout of the cardiorespiratory data file is shown in Annex Table A2.The timeline for the cardiorespiratory data file runs from 2016 week 1 until 2019 week 52.

6.1.3 Hospital-based viral proxy data file

In the hospital-based viral proxy data file, three additional columns are created: a hospital-based RSV indicator and two hospital-based influenza indicators. The first identifies records for patients which are <2 years of age and hospitalized with RSV-specific ICD codes. The second identifies records for patients which are ≥60 years of age and hospitalized with influenza-specific ICD codes. The third identifies records for patients which are <2 years of age and hospitalized with influenza-specific ICD codes (Table 6).

Because information on viral proxies needs to match the aggregation level of the event data files (Sections 6.1.1 and 6.2), the hospital-based viral proxy data file is duplicated and data transformations are conducted on both files separately resulting in one weekly hospital-based viral proxy data file (Section 6.1.3.1) and one monthly hospital-based viral proxy data file (Section 6.1.3.2).

6.1.3.1 Weekly hospital-based viral proxy data file

Time is determined as ISO calendar week and ISO calendar year from the date of hospital admission. The records for each indicator are aggregated to number of events per ISO week (within ISO year). Afterwards, four variables (for each indicator) reflecting the indicator levels in the week preceding the index week with 1, 2, 3 or 4 week(s) are appended to the weekly hospital-based viral proxy data file.

A shell table showing the layout of the resulting weekly hospital-based viral proxy data file is shown in Annex Table A3. To match available hospitalization information, the timeline for the data file runs from 2015 week 2 until 2019 week 52. Note however that complete lagged proxies (up to 4 weeks back) will only be available as of 2015 week 6.

6.1.3.2 Monthly hospital-based viral proxy data file

Time is determined as Gregorian calendar month and Gregorian calendar year from the date of hospital admission. The records for each indicator are aggregated to number of events per Gregorian calendar month (within Gregorian calendar year).

A shell table showing the layout of the resulting monthly hospital-based viral proxy data file is shown in Annex Table A4. To match mortality information, the timeline for the data file runs from 2015 month 1 until 2019 month 12.

6.2 Mortality data file

For each individual patient record, the presence of each of the studied outcomes is assessed based on the outcome definitions (Section 4.2). The recorded age groups are categorized in the study age groups (Section 4.5). The records for each outcome are aggregated to number of events per month (within the year) for each age group.

A shell table showing the layout of the cleaned mortality data file is shown in Annex Table A5. The timeline for the mortality data file runs from 2015 month 1 until 2019 month 12.

6.3 Surveillance data file

For each pathogen, the number of positive tests in the aggregated off-season weeks (e.g., weeks 21-25) is evenly spread across the contained weeks to obtain weekly surveillance data. Once even spreading results in non-integer counts, the remaining number of positive tests is spread randomly across the contained weeks.

Because surveillance information needs to match the aggregation level of the event data files (Sections 6.1 and 6.2), the surveillance data file is duplicated and data transformations are conducted on both files separately resulting in one weekly surveillance data file (Section 6.3.1) and one monthly surveillance data file (Section 6.3.2).

6.3.1 Weekly surveillance-based viral proxy data file

For each pathogen, the reported number of samples tested is summed over the corresponding year. For each week, the number of samples testing positive for a pathogen is standardized by dividing by the total reported number of samples tested for the respective pathogen in the corresponding ISO calendar year. Afterwards, four variables (for each pathogen) reflecting the computed numbers in the week preceding the index week with 1, 2, 3 or 4 week(s) are appended to the weekly surveillance data file.

A shell table showing the layout of the cleaned weekly surveillance data file is shown in Annex Table A6. To match available hospitalization information, the timeline for the cleaned weekly surveillance data file runs from 2015 week 2 until 2019 week 52.

6.3.2 Monthly surveillance-based viral proxy data file

For each pathogen, the number of positive tests and the number of tests taken in the weeks (when available) is evenly spread across the contained seven days to achieve daily surveillance data for all pathogens of interest in this study. Once even spreading results in non-integer counts, the remaining number of positive tests is spread randomly across the contained days. Time indicators to map these daily surveillance data to the Gregorian calendar month and the Gregorian calendar year are deducted from the combination of the day of the week, the ISO calendar week and the ISO calendar year.

For each pathogen, the reported number of samples tested is summed over the corresponding year. For each month, the number of samples testing positive for a pathogen is summed and standardized by dividing by the total reported number of samples tested for the respective pathogen in the corresponding year.

A shell table showing the layout of the resulting surveillance datafile is shown in Annex Table A7. To match mortality information, the timeline for the cleaned monthly surveillance data file runs from 2015 month 1 until 2019 month 12.

6.4 Comparison of viral proxy data files

Two sources of viral proxy data, a national surveillance system and a hospital discharge register, are considered for generating analysis files (Section 6.5). While the surveillance-based viral proxy data are extracted from a tool that is well-known to the public for monitoring influenza surveillance, they are expected to be less stable when sampling practices are suboptimal. In order to compare, weekly hospital-based viral proxies and weekly surveillance-based viral proxies are plotted over running ISO

weeks. The proxy with less weekly fluctuation over time will be considered representative and coherent of the viral epidemic and therefore selected.

6.5 Generation of analysis files

After initial data transformations and comparisons, selected data files are merged to obtain one analysis file for each event type (Sections 6.5.1 and 6.5.3).

6.5.1 Hospitalization analysis file

The hospitalization outcome data file is merged with the selected weekly viral proxy data file on ISO week and year. For weeks in which no hospitalizations are reported for specific outcomes and/or age groups, zeros are entered to avoid gaps in the analysis timeline. Afterwards, weeks, each consisting of seven days, are sorted from the start to the end of the study period and a unique indicator variable showing running weeks is added to the analysis file. Note that the running week indicator starts from 2 instead of 1 to reflect the exclusion of 2015 ISO week 1 from the analysis. Because hospital-based viral proxies are not available as of 2015 week 6, analyses will run as of week 6 when the hospitalization analysis file was constructed using the hospital-based viral proxy data file and as of week 2 when the file was constructed using the surveillance-based viral proxy data file.

Consistency between 2015 and 2016-2019 hospitalization outcomes (Section 4.2) will be evaluated by plotting the observed events over time. In case of major inconsistencies between 2015, for which ICD-9 coding is used, and 2016-2019, for which ICD-10 coding is used, the first year of the hospitalization analysis file will be dropped.

6.5.2 Cardiorespiratory analysis file

The cardiorespiratory data file is merged with the selected weekly viral proxy data file on ISO week and year. For weeks in which no hospitalizations are reported for specific outcomes and/or age groups, zeros are entered to avoid gaps in the analysis timeline. Afterwards, weeks, each consisting of seven days, are sorted from the start to the end of the study period and a unique indicator variable showing running weeks is added to the analysis file.

Note that the timeline for this analysis file will follow the timeline of the cardiorespiratory analysis file, not the viral proxy data file.

6.5.3 Mortality analysis file

The cleaned mortality data file is merged with the selected monthly viral proxy data file on Gregorian calendar month and year. For months in which no deaths are reported for specific outcomes and/or age groups, zeros are entered to avoid gaps in the analysis timeline. Afterwards, months are sorted from the start to the end of the study period and a unique indicator variable showing running months is added to the analysis file.

7 STATISTICAL ANALYSIS

7.1 Descriptive analysis

Descriptive statistics are used to summarize the yearly number of events for each outcome (Section 4.2, within each event type (Section 4.1) and Section 4.3) stratified by age group (Annex Table A8 and Table A9). The number of tests taken and tests positive for each pathogen (Section 4.4) is summarized per year (Annex Table A10). The number of virus-specific hospitalizations (Section 4.4) is summarized per year (Annex Table A11).

Note that for hospitalization outcomes and pathogen surveillance, years reflect ISO years while for mortality outcomes, years reflect Gregorian calendar years.

7.2 Main analysis

There are different models that can be used to estimate the incidence of RSV. The statistical method most frequently used in recent literature was regression, which has the advantage that seasonal trends and cocirculation of other pathogens can be adjusted for [7]. Among regression models used in recent literature, the most frequently used outcome distribution was a Poisson distribution, which is recommended as the studied events generally occur according to a Poisson process. To account for expected overdispersion, a Quasi-Poisson distribution was selected for this study.

For each subgroup (one event type – one outcome – one age group), the observed number of events is plotted over time (Figure A1). For subgroups in which a trend can be observed (instead of random noise), a Quasi-Poisson regression model is used to model the number of events (Section 4.2) as a function of periodic time trends, aperiodic time trends and viral activity, while allowing for potential overdispersion. To reflect the most plausible biological link between viral circulation and the occurrence of events, the identity link function is used.

The periodic time trend, which reflects the seasonal variation in the weekly (or monthly) number of events, is represented by sine and cosine terms with weekly (or monthly) periodicity (period = 52.143, or 12, respectively)). The aperiodic time trend, which reflects subtle trends in the weekly (or monthly) number of events over time, is represented by a polynomial up to the 4th order.

Viral activity is represented by selected viral proxies for RSV and influenza (Section 6.4). To reflect delays between an increase in viral proxy detection (e.g., testing in children) and an increase in the weekly number of events (e.g., death in older adults), appropriate lags (0 to 4 weeks) are considered when incorporating the viral proxies into the model for weekly data.

The following general model for hospitalization is used:

$$Nr\_events_t \sim Poisson(\lambda_t, \theta)$$

$$\lambda_t = \beta_0 + \sum_{k=1}^{4} \beta_k . t^k + \beta_5 . \sin\left(\frac{2\pi . t}{52.143}\right) + \beta_6 . \cos\left(\frac{2\pi . t}{52.143}\right) + \beta_7 . \sin\left(\frac{4\pi . t}{52.143}\right) + \beta_8 . \cos\left(\frac{4\pi . t}{52.143}\right) + \sum_{l=1}^{L} \beta_{(8+l)} . VP_{l_{(t-m_l)}}$$

where λ_t is the expected number of events in week *t* with *t* representing the running week index in the study period, and θ is the overdispersion parameter. Parameter β_0 is the coefficient associated with the baseline number of events, β_1 to β_4 are coefficients associated with the aperiodic time trend, β_5 to β_8 are coefficients associated with the periodic time trend, and β_9 to $\beta_{(8+L)}$ are coefficients associated with appropriately lagged activity of pathogen VP_1 to VP_L, with $m_l = 0, 1, \ldots, M$ reflecting the pathogen-specific time lag. All models use $L = 2$ (RSV and influenza) and $M = 4$.

The following general model for mortality is used:

$$Nr\_events_t \sim Poisson(\lambda_t, \theta)$$

$$\lambda_t = \beta_0 + \sum_{k=1}^{4} \beta_k . t^k + \beta_5 . \sin\left(\frac{2\pi . t}{12}\right) + \beta_6 . \cos\left(\frac{2\pi . t}{12}\right) + \sum_{l=1}^{L} \beta_{(6+l)} . VP_{l_t}$$

where λ_t is the expected number of events in month *t* with *t* representing the running month index in the study period, and parameters θ, and β_0 to β_6 are defined as before. Parameters β_7 to $\beta_{(6+L)}$ are coefficients associated with activity of pathogen VP_1 to VP_L, with $L = 2$ (RSV and influenza).

For each subgroup, a final model is constructed using a step-by-step approach. First, a model containing only the periodic and aperiodic time trends is fitted, and the polynomial order is reduced when possible (significance level 0.05). Next, the model for the weekly data is expanded step-by-step. In each step, all possible lags of all pathogens not yet included in the model are considered for inclusion to the constructed model (one at a time), with the one with the highest test statistic selected for inclusion. By using the value of the test statistic in model selection instead of the p-value, priority is given to significant positive associations over non-significant positive associations, over non-significant negative associations, over significant negative associations. This process is followed as it is biologically implausible for the viral pathogens (RSV and influenza) to protect against hospitalization or death [8, 9]. This step is repeated, until all pathogens are included in the final model once.

General model fit of all final subgroup-specific models is inspected visually by plotting observed and model-based number of events over time (Annex Figure A2).

The weekly (or monthly) number of events (within the study period, Section 3.2) that are attributable to RSV is calculated as the difference between the total model-predicted number of events (using the final

model) and the model-predicted number of events under the hypothetical absence of RSV circulation (by setting the parameter associated with RSV to zero). The yearly age-specific number of RSV-attributable events is obtained by summing over the included years (Annex Table A12 and Table A13). Confidence intervals are obtained through residual bootstrapping.

The yearly proportion of RSV-attributable events, for each age group, is obtained by dividing the yearly number of RSV-attributable events by the yearly number of observed events.

Note that for hospitalization outcomes, years reflect ISO years while for mortality outcomes, years reflect Gregorian calendar years.

7.3 Extrapolation to population-level

Age-specific incidence rates of RSV-attributable events per year are obtained by dividing the yearly model-based age-specific number of RSV-attributable events by the age- specific population at risk of the event (from yearly July 1st national census data [10]). Incidence rates are obtained for each outcome, within each event type, and expressed as number of events per 100,000 person-years (Annex Table A14).

8 DISSEMINATION OF STUDY RESULTS

It is planned that two conference abstracts (one for adults and one for children) and one peer-reviewed manuscript (covering adults and children) will result from this study.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

9 SOFTWARE

All data management will be conducted in SAS version 9.4 or later, or R version 4.1.2 or later. All statistical analysis, including double programming, will be conducted in R version 4.1.2 or later.

10 LIMITATIONS

The selected approach shows some limitations which are mainly linked to the data sources. For example, when obtaining data from a hospital, the fixed number of beds may affect the hospitalization rates. In this same scenario there may also be inaccuracy in laboratory reports indicating RSV circulation [11]. Working with administrative data comes with the risk of both over- and underestimating the actual number of events, with overestimation resulting from e.g., ICD codes printed as rule-out diagnosis, and underestimation resulting from e.g., involuntary omission of ICD codes.

The hospitalization data used in this study hold the additional limitation that a unique patient identifier is not always provided. In the absence of a unique identifier, the remainder of the patient identifying data (e.g. date of birth, gender, …) can be used to construct an artificial patient identifier. Although this remedial measure is required to proceed with the study as outlined in this SAP, it comes with the risk of underestimating the number of events when the patient identifying data is unable to uniquely identify each patient. The models used to estimate RSV-attributable number of events include viral proxies for RSV and influenza, which implicitly assumes that these are the only two pathogens that show a relevant association with the outcome of interest. If relevant associations between other, currently not included, pathogens and the outcome of interest come to light for which robust time series data are available, they could be accounted for in the model through viral proxies (as for RSV and influenza). However, even without explicitly modelling these potentially relevant pathogens, they would to a great extent be indirectly accounted for in the proposed model through the periodic component and the overdispersion parameter.

These limitations should be taken into consideration when interpreting results obtained from conducting the study described in this SAP.

11 QUALITY CONTROL

The hospital and mortality registries and surveillance data will be verified and validated accordingly to reliability. When potential quality risks are identified, the corrective measures will be applied through hard coding. The cleaned data will be retained prior to analysis in accordance with Spain's regulatory authority's retention policy. The data will be securely stored. Before the results obtained from analysing the data are released, the analytical scripts will undergo quality control (double programming), which will be documented and retained.

12 ETHICAL CONSIDERATIONS

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients is not required.

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the Good Epidemiological Practice guidelines issued by the International Epidemiological Association.

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ANNEXES

Year	Week	Age group	Primary outcome: number of events			Secondary outcome: number of events								
			All cardio-respiratory events	All respiratory events	All circulatory events	Influenza or Pneumonia events	Bronchitis or bronchiolitis events	chronic lower respiratory disease events	Upper respiratory disease events	Chronic heart failure exacerbation events	Ischemic heart disease events	Arrhythmia events	cerebrovascular events	Myocarditis events
2015	2	0-5 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	2	6-11 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	2	12-23 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	2	2-5 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	2	6-17 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	2	18-49 years												
2015	2	50-59 years												
2015	2	60-79 years												
2015	2	>=80 years												
2015	3	0-5 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	3	6-11 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	3	12-23 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	3	2-5 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	3	6-17 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	3	18-49 years												
2015	3	50-59 years												
2015	3	60-79 years												
2015	3	>=80 years												
...	...	....												
...	...	....												
2019	52	0-5 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	52	6-11 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	52	12-23 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	52	2-5 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	52	6-17 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	52	18-49 years												
2019	52	50-59 years												
2019	52	60-79 years												
2019	52	>=80 years												

Table A1. Shell table for the hospitalization outcome data file.

Year	Week	Age group	Selected cardiorespiratory hospitalizations	Combined cardiorespiratory hospitalizations
2016	1	18-49 years		
2016	1	50-59 years		
2016	1	60-79 years		
2016	1	>=80 years		
2016	2	18-49 years		
2016	2	50-59 years		
2016	2	60-79 years		
2016	2	>=80 years		
...	...	....		
...	...	....		
2019	52	18-49 years		
2019	52	50-59 years		
2019	52	60-79 years		
2019	52	>=80 years		

Table A2. Shell table for the cardiorespiratory data file.

Year	Week	Hospitalizations for			Lagged (1 week) hospitalizations for			Lagged (2 weeks) hospitalizations for			Lagged (3 weeks) hospitalizations for			Lagged (4 weeks) hospitalizations for		
		RSV	Influenza (≥60 years)	Influenza (<2 years)	RSV	Influenza (≥60 years)	Influenza (<2 years)	RSV	Influenza (≥60 years)	Influenza (<2 years)	RSV	Influenza (≥60 years)	Influenza (<2 years)	RSV	Influenza (≥60 years)	Influenza (<2 years)
2015	2				NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	3							NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	4										NA	NA	NA	NA	NA	NA
2015	5													NA	NA	NA
2015	6															
...	...															
...	...															
2019	52															

Table A3. Shell table for the weekly hospital-based viral proxy data file.
RSV: respiratory syncytial virus; NA: not available

Year	Month	Number of hospitalizations for		
		RSV	Influenza (≥60 years)	Influenza (<2 years)
2015	1			
2015	2			
2015	3			
....	....			
....	....			
2019	12			

Table A4. Shell table for the monthly hospital-based viral proxy data file.
RSV: respiratory syncytial virus.

Year	Month	Age group	Primary outcome: number of events			Secondary outcome: number of events								
			All cardio-respiratory events	All respiratory events	All circulatory events	Influenza or Pneumonia events	Bronchitis or bronchiolitis events	chronic lower respiratory disease events	Upper respiratory disease events	Chronic heart failure exacerbation events	Ischemic heart disease events	Arrhythmia events	cerebrovascular events	Myocarditis events
2015	1	0-5 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	1	6-11 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	1	12-23 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	1	2-5 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	1	6-17 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	1	18-49 years												
2015	1	50-59 years												
2015	1	60-79 years												
2015	1	>=80 years												
2015	2	0-5 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	2	6-11 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	2	12-23 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	2	2-5 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	2	6-17 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2015	2	18-49 years												
2015	2	50-59 years												
2015	2	60-79 years												
2015	2	>=80 years												
...	...	....												
...	...	....												
2019	12	0-5 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	12	6-11 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	12	12-23 months	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	12	2-5 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	12	6-17 years	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2019	12	18-49 years												
2019	12	50-59 years												
2019	12	60-79 years												
2019	12	>=80 years												

Table A5. Shell table for the cleaned mortality data file.

Year	Week	Number of tests positive for		Standardized number of positive tests for		Lagged (1 week) standardized number of positive tests for		Lagged (2 weeks) standardized number of positive tests for		Lagged (3 weeks) standardized number of positive tests for		Lagged (4 weeks) standardized number of positive tests for	
		RSV	Influenza	RSV	Influenza	RSV	Influenza	RSV	Influenza	RSV	Influenza	RSV	Influenza
2015	2												
2015	3												
2015	4												
....	....												
....	....												
2019	52												

Table A6. Shell table for the weekly surveillance-based viral proxy data file.
RSV: respiratory syncytial virus.

Year	Month	Number of tests positive for		Standardized number of positive tests for	
		RSV	Influenza	RSV	Influenza
2015	1				
2015	2				
2015	3				
....	....				
....	....				
2019	12				

Table A7. Shell table for the monthly surveillance-based viral proxy data file.
RSV: respiratory syncytial virus.

Year	Hospitalization				Mortality[c]			
	18-49 years	50-59 years	60-79 years	≥80 years	18-49 years	50-59 years	60-79 years	≥80 years
2015[b]								
2016								
2017								
2018								
2019								

Table A8. Number of events[a] reported for adults in Spain, 2015-2019[b].

[a] events refers to one outcome per table.

List of outcomes: cardiorespiratory events, respiratory events, circulatory events, influenza or pneumonia, bronchitis or bronchiolitis, chronic lower respiratory disease, upper respiratory disease, chronic heart failure exacerbation, ischemic heart disease, arrhythmia, cerebrovascular disease, or myocarditis, and alternative outcomes: selected cardiorespiratory hospitalizations combined cardiorespiratory hospitalizations.

[b] For alternative outcomes, the year 2015 will not be included.

[c] For alternative outcomes, mortality will not be included.

Year	Hospitalization					Mortality		
	0-5 months	6-11 months	12-23 months	2-5 years	6-17 years	0-11 months	1-5 years	6-17 years
2015								
2016								
2017								
2018								
2019								

Table A9. Number of respiratory events reported for children in Spain, 2015-2019.

Year	Number of isolates			
	Respiratory syncytial virus		Influenza	
	Tested	Positive	Tested	Positive
2015				
2016				
2017				
2018				
2019				

Table A10. Annual pathogen surveillance in Spain, 2015-2019.

Year	Respiratory syncytial virus	Influenza (≥60 years)	Influenza (<2 years)
2015			
2016			
2017			
2018			
2019			

Table A11. Annual virus-specific hospitalizations in Spain, 2015-2019.

Year	Hospitalization				Mortality[c]			
	18-49 years	50-59 years	60-79 years	≥80 years	18-49 years	50-59 years	60-79 years	≥80 years
2015[b]								
2016								
2017								
2018								
2019								

Table A12. Number of RSV-attributable events[a] for adults in Spain, 2015-2019[b].

[a] events refers to one outcome per table.

List of outcomes: cardiorespiratory events, respiratory events, circulatory events, influenza or pneumonia, bronchitis or bronchiolitis, chronic lower respiratory disease, upper respiratory disease, chronic heart failure exacerbation, ischemic heart disease, arrhythmia, cerebrovascular disease, or myocarditis, and alternative outcomes: selected cardiorespiratory hospitalizations combined cardiorespiratory hospitalizations.

[b] For hospitalization outcomes, the year 2015 will be included only when the number of observed events is consistently reported in 2015 versus 2016-2019. For alternative outcomes, the year 2015 will not be included.

[c] For alternative outcomes, mortality will not be included.

Year	Hospitalization					Mortality		
	0-5 months	6-11 months	12-23 months[a]	2-5 years[a]	6-17 years	0-11 months[b]	1-5 years[b]	6-17 years
2015[c]								
2016								
2017								
2018								
2019								

Table A13. Number of RSV-attributable respiratory events for children in Spain, 2015-2019[c].

[a] To be replaced by the concatenated age group 1-5 years if observed respiratory hospitalizations are <5 in >20% of the weeks.

[b] To be replaced by the concatenated age group 0-5 years if observed respiratory deaths are <5 in >20% of the months.

[c] For hospitalization, the year 2015 will be included only when the number of observed events is consistently reported in 2015 versus 2016-2019.

	Hospitalization					Mortality[d]				
Year	18-49 years	50-59 years	60-79 years	≥80 years	All ages[a]	18-49 years	50-59 years	60-79 years	≥80 years	All ages[a]
2015[c]										
2016										
2017										
2018										
2019										

Table A14. Incidence of RSV-attributable events[b] for adults in Spain, 2015-2019[c].

[a] standardized with January 1, 2022 census population figures for each age group.

[b] events refers to one outcome per table.

List of outcomes: cardiorespiratory events, respiratory events, circulatory events, influenza or pneumonia, bronchitis or bronchiolitis, chronic lower respiratory disease, upper respiratory disease, chronic heart failure exacerbation, ischemic heart disease, arrhythmia, cerebrovascular disease, or myocarditis, and alternative outcomes: selected cardiorespiratory hospitalizations combined cardiorespiratory hospitalizations.

[c] For hospitalization outcomes, the year 2015 will be included only when the number of observed events is consistently reported in 2015 versus 2016-2019. For alternative outcomes, the year 2015 will not be included.

[d] For alternative outcomes, mortality will not be included.

Year	Hospitalization						Mortality			
	0-5 months	6-11 months	12-23 months[a]	2-5 years[a]	6-17 years	All ages[c]	0-11 months[b]	1-5 years[b]	6-17 years	All ages[c]
2015[d]										
2016										
2017										
2018										
2019										

Table A15. Incidence of RSV-attributable respiratory events for children in Spain, 2015-2019[d].

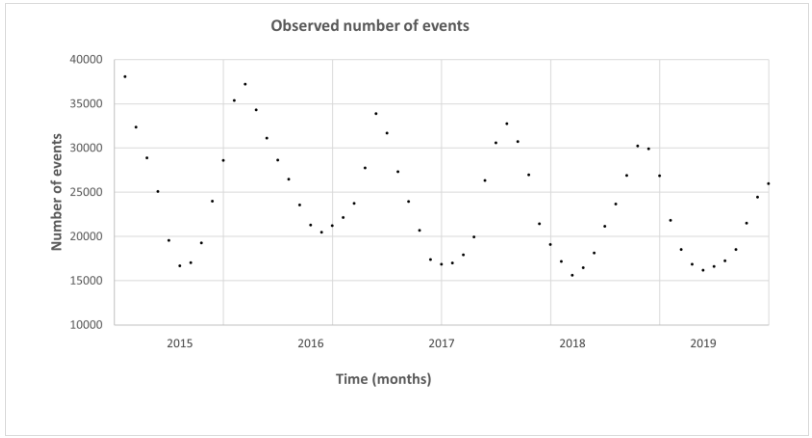
[a] To be replaced by the concatenated age group 1-5 years if observed respiratory hospitalizations are <5 in >20% of the weeks.

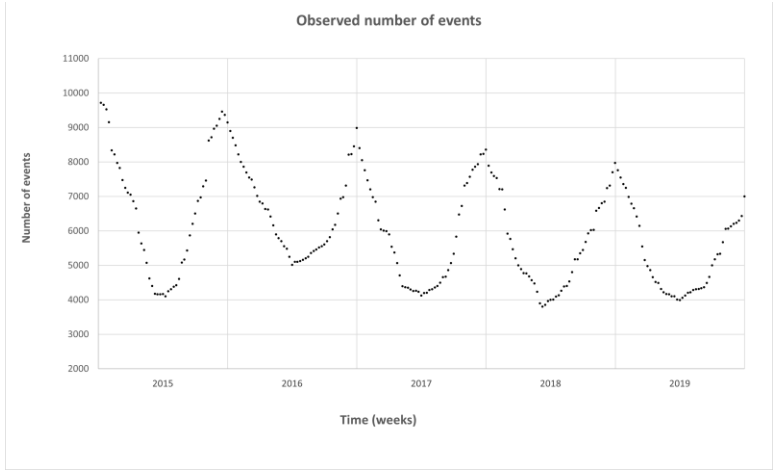
[b] To be replaced by the concatenated age group 0-5 years if observed respiratory deaths are <5 in >20% of the months.

[c] standardized with January 1, 2022 census population figures for each age group.

[d] For hospitalization, the year 2015 will be included only when the number of observed events is consistently reported in 2015 versus 2016-2019.

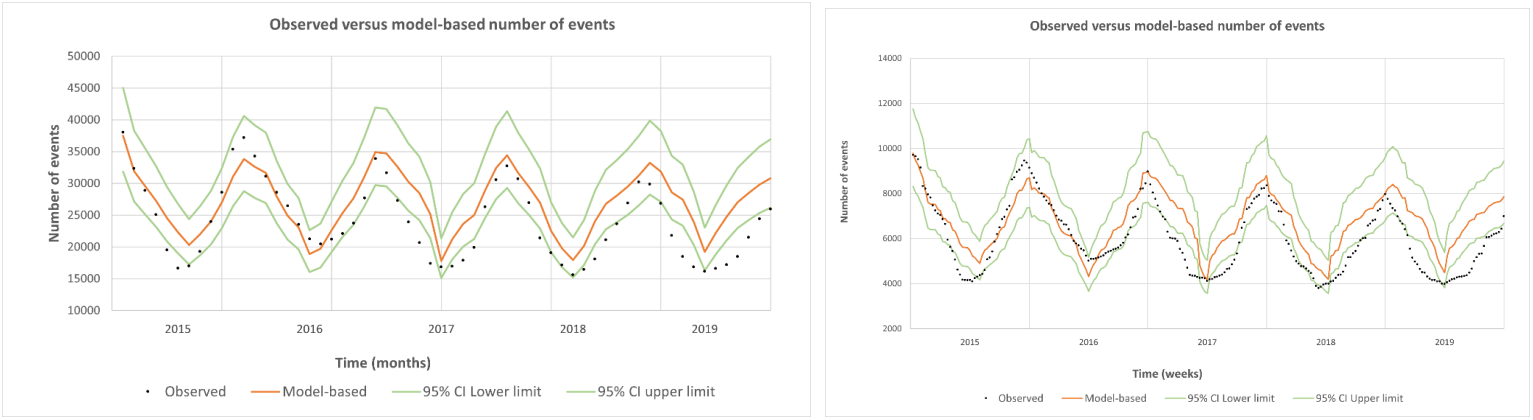
Figure A1. Monthly (left) and weekly (right) observed number of events[a] in Spain, 2015-2019[b].





[a] events refers to the combination of event type (hospitalization or death) and outcome.
List of outcomes for adults: cardiorespiratory events, respiratory events, circulatory events, influenza or pneumonia, bronchitis or bronchiolitis, chronic lower respiratory disease, upper respiratory disease, chronic heart failure exacerbation, ischemic heart disease, arrhythmia, cerebrovascular disease, or myocarditis; For children outcomes are respiratory events.
For alternative outcomes (adults only), events refers to selected cardiorespiratory hospitalizations, or combined cardiorespiratory hospitalizations.
[b] For hospitalization outcomes, the year 2015 will be included only when the number of observed events is consistently reported in 2015 versus 2016-2019. For alternative outcomes, the year 2015 will not be included.

Figure A2. Monthly (left) and weekly (right) observed and model-based number of events[a] in Spain, 2015-2019[b].



CI: confidence interval

[a] events refers to the combination of event type (hospitalization or death) and outcome.

List of outcomes for adults: cardiorespiratory events, respiratory events, circulatory events, influenza or pneumonia, bronchitis or bronchiolitis, chronic lower respiratory disease, upper respiratory disease, chronic heart failure exacerbation, ischemic heart disease, arrhythmia, cerebrovascular disease, or myocarditis; For children outcomes are respiratory events.

For alternative outcomes (adults only), events refers to selected cardiorespiratory hospitalizations, or combined cardiorespiratory hospitalizations.

[b] For hospitalization outcomes, the year 2015 will be included only when the number of observed events is consistently reported in 2015 versus 2016-2019. For alternative outcomes, the year 2015 will not be included.