



Global prevalence of varicella-associated complications: A systematic review and meta-analysis

Hiral Anil Shah¹, Anne Meiwald², Chamath Perera², Giacomo Casabona³, Peter Richmond⁴, Nicolas Jamet⁵

¹ GSK, London, United Kingdom

² Adelphi Values PROVE, Bollington, United Kingdom

³ GSK, Wavre, Belgium

⁴ University of Western Australia School of Medicine, Telethon Kids Institute and Perth Children's Hospital, Nedlands, Australia

⁵ GSK, Paris, France

Corresponding author: Hiral Shah; 90 Great West Road, Brentford, TW8 9GS; +447880459786; hiral.a.shah@gsk.com; 0000-0003-0204-451X

Running/short title:

A systematic review and meta-analysis of varicella complications

Table S1. Embase search strategy (via Ovid) (on 8 June 2020)

Search number	Search string	Hits
1	exp chickenpox/	11,308
2	exp herpes zoster/	24,402
3	1 not 2	8,889
4	(varicella or chickenpox or vzv).ti,ab.	19,979
5	3 or 4	22,967
6	(complication* or complicated or risk* or sequela* or serious or severe or mortality or morbidity).ti,ab.	6,075,734
7	5 and 6	8,686
8	(inciden* or prevalen* or epidemiolog* or surveillance or frequency or rate or burden).ti,ab.	5,910,489
9	7 and 8	3,475
10	limit 9 to (abstracts and English language)	3,089
11	limit 10 to (books or chapter or “conference review” or editorial or erratum or letter or note or short survey or tombstone)	20
12	10 not 11	3,069
13	exp “Review”/	2,614,101
14	“systematic review”/ or meta analysis/	343,328
15	(systematic or meta analysis or mixed treatment comparison or indirect treatment comparison).ti,ab.	547,121
16	14 or 15	639,556
17	13 not 16	2,302,007
18	12 not 17	2,698
19	(autoimmune or transplant* or sclerosis or arthritis or lupus).ti,ab.	1,356,129
20	18 not 19	1,953
21	limit 20 to yr=“1999-current”	1,754

ti., title; ab., abstract

Table S2. MEDLINE search strategy (via Ovid) (on 8 June 2020)

Search number	Search string	Hits
1	exp varicella zoster virus infection/	18,030
2	exp herpes zoster/	11,790
3	1 not 2	6,240
4	(varicella or chickenpox or vzv).ti,ab.	15,822
5	(complication* or complicated or risk or sequela* or side effect).ti,ab.	2,961,745
6	3 or 4	16,959
7	6 and 5	3,820
8	(inciden* or prevalen* or epidemiolog* or surveillance or frequency or rate or burden).ti,ab.	4,400,110
9	7 and 8	1,561
10	limit 8 to (address or autobiography or bibliography or biography or comment or congress or editorial or guideline or historical article or interview or lecture or legal case or legislation or letter or news or newspaper article or published erratum or technical report)	65,069
11	9 not 10	1,548
12	limit 11 to abstracts	1,544
13	limit 12 to English	1,347
14	(autoimmune or transplant* or sclerosis or arthritis or lupus).ti.	519,172
15	13 not 14	1,160
16	limit 15 to yr="1999-current"	978

ti., title; ab., abstract

Table S3. Outline of preliminary complication categories identified from the extracted studies

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
Cardiovascular (N=11)	Acute pericarditis	I30.9	1
	Deep vein thrombosis	I82.40	1
	Myocarditis/endocarditis	I51.4	5
	Other cardiovascular complications	I10.X–I15.X	5
	Pericardial effusion	I31.3	1
ENT (N=31)	Acute URT infection, unspecified	N39.0	1
	Adenoiditis	J35.02	1
	Hypertrophy adenoids and tonsils	J35.3	1
	Laryngitis	J04.0	3
	Mastoiditis	H70.0, H70.8, H70.9	4
	Nasopharyngitis	J00.X	1
	Other ENT complications	H60.X– H95.X, J00.X–J06.X	3
	Otitis media	H65.0, H65.1, H65.9, H66.9	22
	Pharyngitis/tonsillitis	J02.9	13
	Rhinitis	J30.9	2
	Sinusitis	J01.9	3
	Streptococcal anginas	J03.00	2
	Upper respiratory infection	J06.9	12
Gastrointestinal (N=35)	Abdominal infection	T81.1	1
	Abdominal pain	R10.9	3
	Appendicitis	K35.X, K37	6
	Constipation	K59.0	1
	Diarrhoea	R19.7	4
	Enteritis	K52.9	2

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
	Feeding problems	R63.0, R63.3, R63.8	2
	Gastritis	K29.0	1
	Gastroenteritis	K52.81	8
	Gingivostomatitis	K05.1	3
	Haemorrhage upper gastrointestinal	K92.2	1
	Ileus	K56.7	1
	Intussusception	K56.1	1
	Megacolon	K59.31	1
	Mouth blisters	K13.70	1
	Oesophagitis	K20	1
	Other gastrointestinal complications	K92.89	16
	Pancreatic cyst	K86.2	1
	Pancreatitis	K85.9, K87.1	4
	Peritonitis	K65.9	1
	Protein losing enteropathy	K90.4	1
	Stomatitis	K12.1	8
	Stress ulcer	K27	1
Genitourinary (N=18)	Acute glomerulonephritis	N04.2	1
	Acute renal failure	N17.X	4
	Acute renal glomerulonephritis	N04.2	1
	Epididymitis	N45.1	1
	Glomerulonephritis	N05.9	2
	Haematuria	R31.X	1
	Inappropriate anti-diuretic hormone syndrome	E22.2	2
	Nephritis/glomerulonephritis	N00, N03, N05	4
	Nephropathy	N28.9	2
	Nephrotic syndrome	N04	3
	Oedema related to UTI	T78.3	1

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
	Orchitis	N45.X	2
	Other genitourinary complications	N29.X	1
	Proteinuria	N39.1	1
	Pyelonephritis	N10, N12	2
	Urinary tract infection	N39.0	5
	Vulvovaginitis	N77. 1	2
Haematological (N=42)	Acute idiopathic thrombocytopenic purpura	D69.3	1
	Agranulocytosis	D70.1	1
	Anaemia	D64.9	8
	Angiopathy	I79.8	1
	Arthritis	M00.0, M00.1, M01.5	1
	Bleeding diathesis	D69.9	1
	Bleeding episodes	N91.3–N91.5	1
	Chronic idiopathic thrombocytopenic purpura	D69.3	3
	Clotting complication	D68.9	1
	Disseminated intravascular coagulation	D65.X	2
	Haematologic complications	D50.X– D89.X	14
	Haemato-oncologic symptoms	C95.0	1
	Haemolytic anaemia	D59.0	1
	Haemorrhage upper gastrointestinal	K92.2	1
	Haemorrhagic syndrome	R58.X	1
	Haemorrhagic varicella	B01.1	8
	Leuco- and/or erythrocytopenia/anaemia	D53.9	1
	Leucocytosis	D72.829	1
	Leucopenia	D72.819	1
	Neutropenia	D70.9	2
	Other haematological complications	D75.9	7

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
	Pancytopenia	D61.81	2
	Purpura fulminans/disseminated	D65	3
	Sickle cell crisis	D57.219	1
	Thrombocytopenia	D69.5, D69.6	22
	Thrombocytosis	D47.3	3
Infection (N=49)	Adenitis	L04.X, I88.8, I88.9	9
	Bacterial arthritis	M00.80	2
	Bacterial infection	A49.9	18
	Cervical lymphadenitis	L04.0	1
	Fever	R50.8, R50.9	8
	Infectious complications	B99.9	1
	Infectious skin complications	L08.9	1
	Multi-site infection	B99.9	1
	Other superinfections	B17.0	2
	Perirectal abscess	K61.1	1
	Salmonella spp. infection	A49.9	1
	Scarlet fever	A38	6
	Secondary infection	A49.0	1
	Sepsis	A41.9	30
	Shock	R57.9	1
	Systemic inflammatory response syndrome	R65.10	2
	Skin superinfection	L00.X–L08.X	1
	Staphylococcus infection	L00	5
	Streptococcal infection – scarlet fevers	A38.9	1
	Superinfection arthritis	B96.89	1
	Superinfection with phlegmon	L08.89	1
	Surgical scarlet fever	A38.9	1
	Toxic shock syndrome	A48.3	5
	Unspecified streptococcal infections	A49.1, B95.5	1
	Acute cholecystitis	K81.0	1

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
Liver (N=24)	Acute hepatitis	B17.9	1
	Cholecystitis	K74.3	1
	Elevated liver enzymes	R94.5	1
	Hepatic failure	K72.90	1
	Hepatitis	B17.9, B19.X, K72.0	16
	Hepatocytolysis	K76.9	1
	Necrosis liver cells	K72.9	1
	Other hepatic complications	K70.X–K77.X	5
	Acute osteomyelitis	M86.10	2
Musculoskeletal (N=35)	Arthritis	M00.0, M00.1, M01.5	11
	Arthropathy or articular pain	M12.9	1
	Bone complication	M89.X	2
	Hip synovitis	M67.359	1
	Joint complication	M20.X– M25.X	1
	Movement and stability dysfunction	M25.3	1
	Myositis	M60.0, M60.8, M60.9	3
	Necrotizing fasciitis	M72.6	16
	Osteoarticular infection	M19.9	2
	Osteolytic lesion	M89.50	1
	Osteomyelitis	M86.0, M86.1, M86.2	12
	Other musculoskeletal complications	M95.X– M99.X	2
	Pyogenic arthritis	M00.9	3

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
	Reactive arthritis	M02.1, M02.3, M02.8	5
	Sacroiliitis	M46.1	2
	Synovitis	M65.9	1
	Torticollis	M43.6	1
Neurological (N=69)	Acute disseminated encephalomyelitis	G04.0	2
	Acute transverse myelitis	G37.3	1
	Ataxia	R27.0	7
	Balance or movement disorder	G25.X	2
	Bell's palsy, Guillain-Barré syndrome or transverse myelitis	G51.0, G61.0, G37.3	1
	Cerebellar ataxia	G32.81	32
	Cerebellitis/cerebritis	G32.81	1
	Cerebral herniation	G93.5	1
	Cerebral infarction	I63.9	2
	Cerebral palsy	G80.8	1
	Cerebral vascular thrombosis	I66.X	2
	Cerebral vasculitis	I67.7	5
	Cerebritis	G04.90	2
	Coma	R40.2	1
	Convulsion	R56.9	10
	Cranial nerve palsy	G52.9	1
	Demyelinating peripheral neuropathy	G61.81	1
	Dysesthesia	R20.8	1
	Encephalitis	G05.1	39
	Epilepsy	G40.5	2
	Facial palsy	G51.0	8
	Febrile seizures	R56.01	29
	Guillain-Barré syndrome	G61. 0	7

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
	Hemiparesis, paraesthesia, myoclonus tremors ataxia Inflammation of peripheral nerves Meningitis Myelitis Neuralgia Neuritis Other neurological complications Peripheral neuropathy Polyneuropathy/radiculopathy Reye's syndrome Seizure Severe pain Stroke Syncope Transient visual loss (cortical blindness) Transverse myelitis	G80.2 T85.7 B01.0, G02.0, A87.8 G04.91 M79.2 M79.2 G60.0 G62.8, G62.9 G61.8, G61.9, G64, M54.1 G93.7 G41.X G89.1 Z82.3 R55.9 H47.619 G37.3	1 1 28 3 1 2 32 1 2 10 3 5 10 1 3
Ocular (N=23)	Blepharitis Conjunctivitis Diplopia Episcleritis Eye infection Eyelid oedema Herpetic keratitis	H01.01A, H01.01B B30.9, H10.0, H10.2, H10.3 H53. 2 H15.1 H44.009 H02.8 B00.52	11 1 1 1 1 1 2

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
	Keratitis	H16.0, H16.1, H16.3, H16.4	6
	Keratoconjunctivitis	H16.2	1
	Ophthalmic infections	H44.009	3
	Other ocular complications	H57.9	1
	Papilloedema, optic neuritis	H47.11	1
	Uveitis	H20.1X	
Other (N=37)	Anorexia	R63.0	2
	Antihistamine toxicity	Y55.5	1
	Apnoea	G47.33	1
	Cellulitis	L03.X	20
	Dehydration	E86	1
	Fluid/electrolyte disturbances	E87.X	3
	Henoch-Schönlein purpura	D69.0	1
	Mental status issues	F99.X	1
	Multi-organ failure	T86.X	1
	Multi-organ involvement	R68.8	10
	Other complications	B01.8	1
	Periorbital oedema	H05.0	1
	Permanent sequelae	Y89.X	1
	Steven-Johnson syndrome	L51.1	1
	URT, ENT, eye	J06.9	1
	Vertigo	H81.10	
Respiratory (N=70)	Respiratory	J99.0	4
	Acute respiratory distress syndrome	J80	1
	Acute respiratory failure	J96.00	3
	Asthma	J45.X	1
	Bacterial pneumonia	J15.X	10
	Bronchitis	J40, J20.2, J20.8, J20.9	2

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
	Haemorrhagic pneumonitis	J17.1	1
	Intrathoracic abscess	J85.2	10
	Lower respiratory tract infection	J20.X–J22.X, J44.0	19
	Other respiratory complications	J89.9	1
	Pleural effusion/pyothorax	J86.9	2
	Pleurisy	R09.1	55
	Pneumonia	B01.2, J171, J12.8, J12.9	1
	Pneumonia with haemato-oncologic symptoms	J18.X	1
	Pulmonary haemorrhage	J81	1
	Pulmonary oedema	R04.8	1
	Respiratory	J99.0	1
	Thoracic empyema	J86.0	1
	Tracheitis	J04.1	5
	Varicella pneumonitis	B01.2	1
	Viral croup	J05.0	1
Severe varicella (N=12)	Viral pneumonia	J12.X	
	Severe varicella	B02.8	1
	Extreme varicella (not specified/unknown complications)	B01.8	1
Skin (N=63)	Fulminant varicella	B02.8	10
	Severe varicella	B02.8	2
	Abscess	L02.X	1
	Allergic dermatitis	L23.9	7
	Bacterial skin infection	L08.9	1
	Balanitis	N48.1	25
	Cellulitis	L03.X	1
	Cellulitis and impetigo	L03.X	1
	Cellulitis of neck and groin	L03.314	2

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
	Cellulitis, erysipelas	A46.X	1
	Cutaneous overinfection	L08.9	1
	Dermatitis/eczema/skin eruption	L20–L30	1
	Ecchymotic lesion	R58	1
	Ecthymas	L08.3	3
	Erythema multiforme	L51.X	1
	Erythroderma	L53.9	1
	Eschar	R23.4	4
	Fasciitis	M72.2	1
	Focal infection of chickenpox lesions	B01.0	1
	Focal lymphadenitis	I88.9	1
	Focal purulent lesions	L98.1	1
	Folliculitis	L66.2	1
	Haemorrhagic vesicle	N50.1	1
	Haemorrhagic vesicular rash	A93.2	14
	Impetigo	L01.X	1
	Necrotizing skin lesion	M72.6	1
	Numerous skin changes	R23.8	2
	Orbital cellulitis	H05.01	1
	Orbital/preseptal cellulitis	H05.01	1
	Other skin complications	L98.9	1
	Periorbital cellulitis	L03.213	4
	Phlegmon	H04.31	1
	Preseptal cellulitis	L03.21	4
	Pyoderma	L08.0	1
	Pyogenic skin infection	L08.9	1
	Scalded skin syndrome	L00.X	1
	Scar tissue	L90.5	2
	Scarlatiniform rash	A38.9	1
	Skin and soft tissue complication	L08.9	1
	Skin and soft tissue infection	L08.8	1

Complication categories (N=) ^a	Included unique complications	ICD-10 Code ^b	Data points (n=)
	Skin haemorrhage	L76.22	20
	Skin infection	L08.8	1
	Skin rash/exanthema	B08.20	1
	Skin superinfection	L00.X–L08.X	1
	Skin vesicles	R23.8	1
	Skin/soft tissue infection	L08.9	23
	Soft tissue infection	L08.9	1
	Superinfection with abscess	A49.9	7
	Urticaria	L50.9	1
	Varicella gangrenosa	B02.8	1

ENT, ear, nose and throat; ICD-10, International Classification of Diseases 10th Revision; n, number; N, number of publications; URT, upper respiratory tract; UTI, urinary tract infection

^aThe (N=) refers to the number of unique publications that have identified complications that fall under each corresponding complication category

^bThe character string '.X' at the end of an ICD-10 code indicates that all codes within the disease category, which corresponds to the character string before the dot, are included

Table S4. Complication groups stratified by immune, vaccination and hospitalisation status, and age category

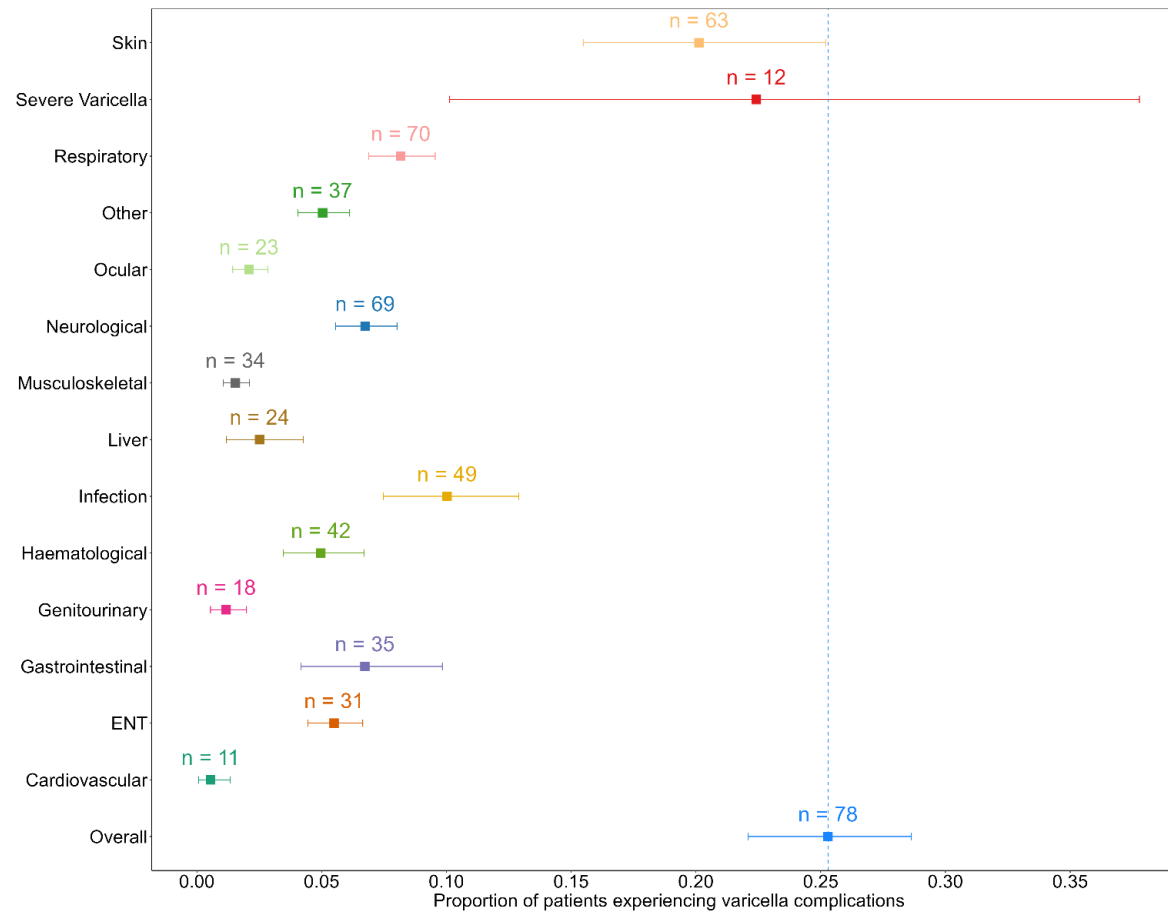
Studies (N)		Immune status		Vaccinated		Hospitalisation status		Age category	
		Immuno-competent	Immuno-compromised	No	Yes	Hospitalised	Outpatient	Adults	Children
Cardiovascular [1-11]	11	4	0	3	0	11	1	2	8
ENT [2, 4, 5, 7, 8, 10, 12-36]	31	5	1	21	2	23	8	5	27
Gastrointestinal [1, 2, 4-11, 13-15, 17, 18, 20, 21, 23-26, 28-30, 33-43]	35	10	2	22	1	30	3	6	29
Genitourinary [1-6, 8, 10, 13, 17, 20-22, 24, 26, 44-46]	18	6	0	11	0	17	2	2	14
Haematological [1-4, 6, 9, 11, 13, 14, 17, 19-21, 23, 24, 26, 28-31, 33-39, 41, 44-57]	42	12	5	23	2	40	3	6	34
Infection [1, 2, 4, 5, 7-14, 17-21, 23, 24, 26, 28, 30-39, 43-46, 49-53, 55, 56, 58-64]	49	13	6	24	1	44	6	5	42
Liver [1-3, 6, 8, 9, 11, 13, 17, 19-21, 30, 34, 37, 44-46, 48, 54-56, 60, 63]	24	8	1	12	0	24	0	5	19
Musculoskeletal [2, 4-8, 10, 13, 15-17, 19-21, 23, 24, 28, 30, 31, 33, 34, 36, 38, 39, 44-46, 49, 50, 54-56, 59, 65, 66]	35	11	2	21	1	32	4	2	31

Neurological a[1-21, 23-46, 48-60, 63, 64, 67-75]	69	17	7	36	3	62	8	10	55
Ocular [2, 4, 5, 8, 10, 15-18, 22, 26-29, 33-36, 39, 44, 54, 64, 68]	23	6	2	14	0	17	8	4	20
Other [1, 2, 4-6, 8, 10, 12, 14, 16, 18, 19, 21, 24-29, 34-36, 38, 39, 44, 46, 50, 55, 57, 58, 60, 63, 67, 68, 70, 73, 76]	37	7	3	22	1	33	4	7	31
Respiratory [1-31, 33-42, 44-46, 48-60, 62-64, 66-68, 70-72, 75-78]	70	19	9	39	2	64	11	11	54
Severe varicella [8, 10, 19, 20, 24, 26, 28, 40, 41, 45, 49, 57, 72]	13	4	1	8	0	12	0	0	9
Skin [1-11, 13-31, 33, 34, 36-46, 48, 50-56, 58-61, 63-66, 68, 70, 76, 78]	63	17	7	38	4	55	11	10	52
Overall	78	21	10	43	4	69	13	11	62

ENT: ear, nose and throat

Key: red=0 studies available, yellow=1–5 studies available, blue=6–10 studies available, green=10+ studies available

Figure S1. Pooled effects for each complication group^a



ENT, ear, nose, and throat

^aThe number of studies that included the subgroup is indicated by 'n'. The coloured box is the point estimate and the lines are the 95% confidence interval. The dashed line represents the reference line based on the pooled effect found in the overall complication group.

Table S5. Number of studies included in the meta-analysis based on study setting, study design and risk of bias

Variable	Number of studies
<i>Setting</i>	
Multicentre studies [2-5, 7-16, 18, 20-28, 32, 34-36, 38-40, 44-46, 49, 51-56, 60-66, 70, 71, 73-75, 77, 78]	55 [2-5, 7-16, 18, 20-28, 32, 34-36, 38-40, 44-46, 49, 51-56, 60-66, 70, 71, 73-75, 77, 78]
Single centre studies [1, 6, 17, 19, 29-31, 33, 37, 41, 42, 47, 48, 50, 57-59, 67-69, 72, 76]	22
No perspective [43]	1
<i>Study design</i>	
Cohort studies [6, 7, 9, 15, 16, 18, 19, 22, 24, 28, 30, 33, 35, 40, 42, 44, 47, 51, 52, 54, 59-61, 75]	24
Database analysis [2-4, 11-13, 17, 29, 32, 34, 45, 46, 50, 53, 55, 58, 67, 70-72, 74, 77, 78]	23
Surveillance [5, 8, 10, 14, 20, 21, 23, 25, 27, 31, 48, 49, 56, 63, 66, 69, 73]	17
Chart reviews [26, 36, 38, 39, 57, 64, 68, 76]	8
Cross sectional [41, 43, 62]	3 [41, 43, 62]

Case series [1, 37]	2
Case control [65]	1
<i>Risk of bias</i>	
Risk of bias quality score = poor [1-3, 6, 11-13, 16-18, 20-22, 26, 30, 32, 34-37, 39-41, 45, 47, 48, 54, 60, 62, 64, 66, 67, 69-72, 76, 77]	38
Risk of bias quality score = fair [4, 5, 7-10, 14, 15, 19, 23-25, 27-29, 31, 33, 38, 42-44, 46, 49-53, 55-59, 61, 63, 65, 68, 73-75, 78]	40

Table S6. All complications summary table excluding low quality studies

Complication	Related studies	Sample size	Complication rate, % (95% CI)	Heterogeneity				
	(reference number)			I ² , %	p value	Egger's statistic ^a	Egger's p value ^a	E-Value
Cardiovascular	6	4,668	0.76 (0.23–1.52)	77.69	p<0.01	NA	NA	20.47
ENT	16	37,667	6.47 (3.89–9.63)	99.04	p<0.01	2.63	0.02	7.16
Gastrointestinal	17	31,041	7.82 (3.86–12.99)	99.46	p<0.01	0.38	0.71	6.46
Genitourinary	7	4,469	0.93 (0.47–1.53)	55.35	0.04	NA	NA	18.49
Haematological	21	18,342	3.81 (1.87–6.36)	98.07	p<0.01	2.61	0.02	9.44
Infection	28	23,361	10.30 (3.56–19.91)	99.75	p<0.01	0.91	0.37	5.53
Liver	8	4,961	2.65 (1.00–5.01)	93.86	p<0.01	NA	NA	11.41
Musculoskeletal	20	153,512	2.11 (1.03–3.52)	97.81	p<0.01	6.97	p<0.01	12.71
Neurological	37	52,746	8.13 (5.37–11.39)	99.31	p<0.01	5.94	p<0.01	6.31
Ocular	11	16,286	1.79 (0.84–3.06)	93.81	p<0.01	3.39	p<0.01	13.70
Other	21	39,069	5.46 (3.28–8.14)	98.89	p<0.01	4.64	p<0.01	7.83
Respiratory	35	49,342	7.82 (5.20–10.90)	99.18	p<0.01	5.36	p<0.01	6.45
Severe varicella	7	1,528	24.71 (5.46–51.68)	99.14	p<0.01	NA	NA	3.24
Skin	35	191,686	18.71 (11.77–26.81)	99.88	p<0.01	4.57	p<0.01	3.89

CI, confidence interval; ENT, ear, nose and throat; I², proportion of variance

^a Egger's statistic not possible with fewer than 10 studies.

Table S7. All complications summary table excluding low evidence study designs

Complication	Related studies	Sample size	Complication rate, % (95% CI)	Heterogeneity				
	(reference number)			I ² , %	p value	Egger's statistic ^a	Egger's p value ^a	E-Value
Cardiovascular	11	68,474	0.55 (0.08–1.33)	95.27	p<0.01	3.23	0.01	23.47
ENT	29	844,810	5.51 (4.45–6.69)	99.05	p<0.01	5.00	p<0.01	7.80
Gastrointestinal	31	99,835	7.07 (4.31–10.44)	99.55	p<0.01	2.48	0.02	6.80
Genitourinary	17	70,541	1.20 (0.56–2.04)	94.14	p<0.01	0.92	0.37	16.45
Haematological	37	87,585	5.09 (3.50–6.94)	98.42	p<0.01	5.22	p<0.01	8.01
Infection	44	831,806	10.44 (7.71–13.51)	99.74	p<0.01	2.76	p<0.01	5.49
Liver	24	73,826	2.51 (1.19–4.27)	98.18	p<0.01	4.94	p<0.01	11.64
Musculoskeletal	31	218,909	1.57 (1.07–2.15)	97.53	p<0.01	6.32	p<0.01	14.50
Neurological	62	945,858	6.50 (5.31–7.81)	99.55	p<0.01	6.63	p<0.01	7.13
Ocular	18	81,399	1.43 (0.95–2.00)	92.28	p<0.01	2.13	0.05	15.36
Other	30	856,383	4.24 (3.29–5.31)	99.18	p<0.01	2.40	0.02	8.95
Respiratory	62	876,690	7.95 (6.62–9.38)	99.35	p<0.01	5.94	p<0.01	6.38
Severe varicella	11	4,521	18.38 (7.13–33.27)	99.15	p<0.01	–1.33	0.22	3.92
Skin	56	272,439	18.59 (13.87–23.82)	99.87	p<0.01	4.64	p<0.01	3.90

CI, confidence interval; ENT, ear, nose and throat; I², proportion of variance

^a Egger's statistic not possible with fewer than 10 studies.

Note: No studies were excluded for being 'poor' quality in the cardiovascular and infection groups.

Table S8. Meta-regression results

Category	Test	Term	Coefficient	SE	Statistic	P value	95% CI low	95% CI high	R ² (% heterogeneity accounted for)	I ² (% residual heterogeneity)	No. of studies
Overall	Temperature	intercept	0.492	0.042	11.715	0.000	0.410	0.574	0.000	99.876	78
		temp	0.003	0.003	0.998	0.318	-0.003	0.009	0.000	99.876	78
	GDP	intercept	0.587	0.044	13.382	0.000	0.501	0.673	0.000	99.876	78
		GDP	0.000	0.000	-1.488	0.137	0.000	0.000	0.000	99.876	78
	Healthcare system	intercept	0.654	0.179	3.647	0.000	0.302	1.005	0.000	99.833	78
		Mixed social health insurance	0.268	0.207	1.291	0.197	-0.139	0.675	0.000	99.833	78
		Mixed public-private	-0.128	0.181	-0.706	0.480	-0.482	0.227	0.000	99.833	78
		Private health insurance	-0.165	0.220	-0.747	0.455	-0.596	0.267	0.000	99.833	78
		Public	-0.196	0.185	-1.055	0.291	-0.559	0.168	0.000	99.833	78
	Universal vaccination strategy	intercept	0.541	0.027	20.315	0.000	0.489	0.594	25.387	99.831	78
		Yes	-0.023	0.034	-0.682	0.495	-0.090	0.044	25.387	99.831	78
Cardiovascular	Temperature	intercept	0.070	0.031	2.291	0.022	0.010	0.131	2.479	94.931	11
		temp	0.001	0.002	0.541	0.588	-0.003	0.005	2.479	94.931	11
	GDP	intercept	0.077	0.049	1.565	0.118	-0.019	0.173	0.000	95.655	11
		GDP	0.000	0.000	0.149	0.881	0.000	0.000	0.000	95.655	11
	Healthcare system	intercept	0.071	0.040	1.776	0.076	-0.007	0.148	14.371	91.797	11
		Mixed public-private	0.016	0.045	0.357	0.721	-0.072	0.104	14.371	91.797	11
	Universal vaccination strategy	intercept	0.071	0.032	2.211	0.027	0.008	0.135	0.000	94.248	11
		Yes	0.019	0.041	0.472	0.637	-0.061	0.100	0.000	94.248	11
ENT	Temperature	intercept	0.302	0.031	9.855	0.000	0.242	0.362	0.000	99.012	31
		temp	-0.006	0.003	-2.180	0.029	-0.012	-0.001	0.000	99.012	31

Category	Test	Term	Coefficient	SE	Statistic	P value	95% CI low	95% CI high	R ² (% heterogeneity accounted for)	I ² (% residual heterogeneity)	No. of studies
	GDP	intercept	0.242	0.032	7.496	0.000	0.178	0.305	0.000	99.023	31
		GDP	0.000	0.000	-0.028	0.977	0.000	0.000	0.000	99.023	31
	Healthcare system	intercept	0.206	0.035	5.952	0.000	0.138	0.274	0.000	98.945	31
		Mixed social health insurance	0.268	0.076	3.529	0.000	0.119	0.418	0.000	98.945	31
		Mixed public-private	0.039	0.040	0.980	0.327	-0.039	0.117	0.000	98.945	31
		Private health insurance	-0.099	0.100	-0.995	0.320	-0.295	0.096	0.000	98.945	31
	Universal vaccination strategy	intercept	0.314	0.018	17.591	0.000	0.279	0.349	21.897	98.703	31
		Yes	-0.121	0.023	-5.389	0.000	-0.166	-0.077	21.897	98.703	31
Gastrointestinal	Temperature	intercept	0.283	0.061	4.673	0.000	0.164	0.402	0.000	99.496	35
		temp	-0.001	0.004	-0.317	0.751	-0.010	0.007	0.000	99.496	35
	GDP	intercept	0.262	0.074	3.527	0.000	0.117	0.408	0.000	99.491	35
		GDP	0.000	0.000	0.056	0.955	0.000	0.000	0.000	99.491	35
	Healthcare system	intercept	0.198	0.058	3.390	0.001	0.083	0.312	28.903	98.800	35
		Mixed social health insurance	0.215	0.101	2.126	0.034	0.017	0.413	28.903	98.800	35
		Mixed public-private	0.068	0.065	1.050	0.294	-0.059	0.195	28.903	98.800	35
	Universal vaccination strategy	intercept	0.324	0.040	8.127	0.000	0.246	0.402	21.305	99.298	35
		Yes	-0.097	0.052	-1.874	0.061	-0.198	0.004	21.305	99.298	35
Genitourinary	Temperature	intercept	0.067	0.023	2.914	0.004	0.022	0.112	50.251	87.167	18
		temp	0.004	0.001	2.628	0.009	0.001	0.007	50.251	87.167	18
	GDP	intercept	0.155	0.027	5.680	0.000	0.102	0.209	33.288	90.790	18
		GDP	0.000	0.000	-1.572	0.116	0.000	0.000	33.288	90.790	18
	Healthcare system	intercept	0.110	0.040	2.733	0.006	0.031	0.188	0.000	93.383	18
		Mixed public-private	0.015	0.046	0.330	0.742	-0.075	0.105	0.000	93.383	18

Category	Test	Term	Coefficient	SE	Statistic	P value	95% CI low	95% CI high	R ² (% heterogeneity accounted for)	I ² (% residual heterogeneity)	No. of studies
	Universal vaccination strategy	Private health insurance	-0.019	0.069	-0.277	0.782	-0.154	0.116	0.000	93.383	18
		intercept	0.098	0.034	2.906	0.004	0.032	0.164	0.000	94.019	18
		Yes	0.027	0.040	0.686	0.492	-0.051	0.105	0.000	94.019	18
Haematological	Temperature	intercept	0.143	0.038	3.726	0.000	0.068	0.218	0.000	98.322	42
		temp	0.007	0.003	2.657	0.008	0.002	0.012	0.000	98.322	42
	GDP	intercept	0.219	0.034	6.530	0.000	0.153	0.285	8.717	98.044	42
		GDP	0.000	0.000	0.418	0.676	0.000	0.000	8.717	98.044	42
	Healthcare system	intercept	0.237	0.051	4.602	0.000	0.136	0.337	0.000	98.048	42
		Mixed social health insurance	-0.087	0.113	-0.770	0.441	-0.308	0.134	0.000	98.048	42
		Mixed public-private	0.001	0.057	0.011	0.991	-0.111	0.113	0.000	98.048	42
		Private health insurance	0.044	0.148	0.297	0.766	-0.247	0.335	0.000	98.048	42
	Universal vaccination strategy	intercept	0.168	0.028	5.939	0.000	0.113	0.223	0.000	98.090	42
		Yes	0.115	0.038	3.030	0.002	0.041	0.189	0.000	98.090	42
Infection	Temperature	intercept	0.321	0.043	7.405	0.000	0.236	0.406	0.000	99.719	49
		temp	0.000	0.003	0.111	0.911	-0.006	0.006	0.000	99.719	49
	GDP	intercept	0.285	0.051	5.598	0.000	0.185	0.385	0.000	99.711	49
		GDP	0.000	0.000	0.882	0.378	0.000	0.000	0.000	99.711	49
	Healthcare system	intercept	0.198	0.189	1.047	0.295	-0.173	0.570	0.000	99.456	49
		Mixed social health insurance	0.592	0.219	2.699	0.007	0.162	1.022	0.000	99.456	49
		Mixed public-private	0.124	0.192	0.645	0.519	-0.252	0.500	0.000	99.456	49
		Private health insurance	-0.004	0.269	-0.015	0.988	-0.531	0.523	0.000	99.456	49
		Public	-0.079	0.208	-0.378	0.706	-0.486	0.329	0.000	99.456	49
		intercept	0.425	0.029	14.490	0.000	0.367	0.482	33.442	99.545	49

Category	Test	Term	Coefficient	SE	Statistic	P value	95% CI low	95% CI high	R ² (% heterogeneity accounted for)	I ² (% residual heterogeneity)	No. of studies
	Universal vaccination strategy	Yes	-0.170	0.038	-4.438	0.000	-0.244	-0.095	33.442	99.545	49
Liver	Temperature	intercept	0.156	0.041	3.755	0.000	0.074	0.237	0.000	98.227	24
		temp	0.001	0.003	0.260	0.794	-0.004	0.006	0.000	98.227	24
	GDP	intercept	0.221	0.050	4.440	0.000	0.124	0.319	4.245	97.941	24
		GDP	0.000	0.000	-1.301	0.193	0.000	0.000	4.245	97.941	24
	Healthcare system	intercept	0.079	0.089	0.891	0.373	-0.095	0.254	43.750	94.648	24
		Mixed social health insurance	0.012	0.128	0.094	0.925	-0.238	0.262	43.750	94.648	24
		Mixed public-private	0.105	0.092	1.138	0.255	-0.076	0.285	43.750	94.648	24
		Private health insurance	0.019	0.128	0.152	0.880	-0.232	0.271	43.750	94.648	24
		Public	0.055	0.101	0.551	0.582	-0.142	0.252	43.750	94.648	24
	Universal vaccination strategy	intercept	0.196	0.025	7.919	0.000	0.147	0.244	50.465	95.058	24
		Yes	-0.064	0.035	-1.823	0.068	-0.133	0.005	50.465	95.058	24
Musculoskeletal	Temperature	intercept	0.160	0.017	9.148	0.000	0.125	0.194	0.000	97.372	34
		temp	-0.002	0.001	-1.880	0.060	-0.005	0.000	0.000	97.372	34
	GDP	intercept	0.070	0.024	2.923	0.003	0.023	0.117	0.000	97.411	34
		GDP	0.000002	0.000	2.940	0.003	0.000	0.000	0.000	97.411	34
	Healthcare system	intercept	0.065	0.016	4.100	0.000	0.034	0.097	45.837	95.286	34
		Mixed social health insurance	0.232	0.041	5.615	0.000	0.151	0.312	45.837	95.286	34
		Mixed public-private	0.071	0.019	3.799	0.000	0.035	0.108	45.837	95.286	34
		Private health insurance	0.095	0.052	1.835	0.067	-0.006	0.197	45.837	95.286	34
	Universal vaccination strategy	intercept	0.147	0.014	10.716	0.000	0.120	0.174	30.251	96.135	34
		Yes	-0.031	0.018	-1.715	0.086	-0.066	0.004	30.251	96.135	34

Category	Test	Term	Coefficient	SE	Statistic	P value	95% CI low	95% CI high	R ² (% heterogeneity accounted for)	I ² (% residual heterogeneity)	No. of studies
Neurological	Temperature	intercept	0.279	0.027	10.237	0.000	0.225	0.332	0.000	99.516	69
		temp	−0.001	0.002	−0.503	0.615	−0.005	0.003	0.000	99.516	69
	GDP	intercept	0.267	0.029	9.176	0.000	0.210	0.324	0.000	99.500	69
		GDP	0.000	0.000	−0.014	0.989	0.000	0.000	0.000	99.500	69
	Healthcare system	intercept	0.233	0.095	2.444	0.015	0.046	0.420	9.450	99.284	69
		Mixed social health insurance	0.135	0.111	1.215	0.224	−0.083	0.352	9.450	99.284	69
		Mixed public–private	0.044	0.096	0.452	0.651	−0.145	0.232	9.450	99.284	69
		Private health insurance	0.139	0.137	1.013	0.311	−0.130	0.407	9.450	99.284	69
		Public	−0.038	0.099	−0.386	0.699	−0.232	0.156	9.450	99.284	69
	Universal vaccination strategy	intercept	0.277	0.018	15.491	0.000	0.242	0.313	18.792	99.382	69
		Yes	−0.020	0.023	−0.893	0.372	−0.065	0.024	18.792	99.382	69
Ocular	Temperature	intercept	0.160	0.032	5.026	0.000	0.097	0.222	0.000	93.444	23
		temp	0.000	0.003	−0.135	0.892	−0.006	0.005	0.000	93.444	23
	GDP	intercept	0.162	0.027	6.029	0.000	0.109	0.214	0.000	93.652	23
		GDP	0.000	0.000	−0.302	0.762	0.000	0.000	0.000	93.652	23
	Healthcare system	intercept	0.149	0.019	7.725	0.000	0.111	0.187	0.000	93.604	23
		Mixed social health insurance	0.072	0.048	1.494	0.135	−0.022	0.166	0.000	93.604	23
		Mixed public–private	−0.011	0.026	−0.438	0.661	−0.063	0.040	0.000	93.604	23
		Private health insurance	0.045	0.046	0.992	0.321	−0.044	0.135	0.000	93.604	23
	Universal vaccination strategy	intercept	0.144	0.020	7.311	0.000	0.105	0.182	0.000	93.680	23
		Yes	0.017	0.025	0.663	0.507	−0.033	0.066	0.000	93.680	23
Other	Temperature	intercept	0.209	0.024	8.690	0.000	0.162	0.256	0.000	99.067	37
		temp	0.002	0.002	1.053	0.292	−0.002	0.005	0.000	99.067	37

Category	Test	Term	Coefficient	SE	Statistic	P value	95% CI low	95% CI high	R ² (% heterogeneity accounted for)	I ² (% residual heterogeneity)	No. of studies
	GDP	intercept	0.213	0.030	7.012	0.000	0.154	0.273	1.260	99.017	37
		GDP	0.000	0.000	0.601	0.548	0.000	0.000	1.260	99.017	37
	Healthcare system	intercept	0.325	0.085	3.827	0.000	0.159	0.492	0.000	98.889	37
		Mixed social health insurance	0.204	0.107	1.909	0.056	-0.005	0.413	0.000	98.889	37
		Mixed public–private	-0.128	0.087	-1.470	0.142	-0.298	0.043	0.000	98.889	37
		Private health insurance	0.058	0.122	0.472	0.637	-0.182	0.298	0.000	98.889	37
		Public	-0.073	0.090	-0.802	0.422	-0.250	0.105	0.000	98.889	37
	Universal vaccination strategy	intercept	0.253	0.019	13.021	0.000	0.215	0.291	6.832	98.971	37
		Yes	-0.035	0.024	-1.470	0.142	-0.083	0.012	6.832	98.971	37
Respiratory	Temperature	intercept	0.277	0.026	10.772	0.000	0.227	0.328	0.000	99.289	70
		temp	0.001	0.002	0.711	0.477	-0.002	0.005	0.000	99.289	70
	GDP	intercept	0.366	0.024	15.028	0.000	0.319	0.414	13.854	99.153	70
		GDP	0.000000	0.000	-3.424	0.001	0.000	0.000	13.854	99.153	70
	Healthcare system	intercept	0.304	0.122	2.493	0.013	0.065	0.543	0.000	99.209	70
		Mixed social health insurance	0.006	0.151	0.039	0.969	-0.290	0.302	0.000	99.209	70
		Mixed public–private	-0.013	0.123	-0.104	0.917	-0.254	0.228	0.000	99.209	70
		Private health insurance	-0.112	0.150	-0.746	0.456	-0.407	0.182	0.000	99.209	70
		Public	0.015	0.126	0.123	0.902	-0.232	0.263	0.000	99.209	70
	Universal vaccination strategy	intercept	0.308	0.019	16.133	0.000	0.271	0.346	14.745	99.131	70
		Yes	-0.025	0.024	-1.034	0.301	-0.071	0.022	14.745	99.131	70
Skin	Temperature	intercept	0.457	0.063	7.294	0.000	0.334	0.580	0.000	99.859	63
		temp	0.001	0.004	0.179	0.858	-0.008	0.009	0.000	99.859	63
	GDP	intercept	0.547	0.065	8.465	0.000	0.420	0.673	0.000	99.858	63

Category	Test	Term	Coefficient	SE	Statistic	P value	95% CI low	95% CI high	R ² (% heterogeneity accounted for)	I ² (% residual heterogeneity)	No. of studies
	Healthcare system	GDP	0.000	0.000	-1.411	0.158	0.000	0.000	0.000	99.858	63
		intercept	0.654	0.197	3.316	0.001	0.267	1.040	34.506	99.761	63
		Mixed social health insurance	-0.006	0.228	-0.026	0.980	-0.453	0.441	34.506	99.761	63
		Mixed public-private	-0.165	0.199	-0.829	0.407	-0.556	0.225	34.506	99.761	63
		Private health insurance	-0.165	0.242	-0.680	0.496	-0.639	0.310	34.506	99.761	63
		Public	-0.350	0.206	-1.701	0.089	-0.754	0.053	34.506	99.761	63
	Universal vaccination strategy	intercept	0.495	0.042	11.722	0.000	0.412	0.578	28.621	99.799	63
		Yes	-0.046	0.054	-0.864	0.388	-0.152	0.059	28.621	99.799	63
Severe varicella	Temperature	intercept	0.342	0.162	2.114	0.035	0.025	0.659	20.322	98.816	12
		temp	0.012	0.011	1.081	0.280	-0.010	0.034	20.322	98.816	12
	GDP	intercept	0.387	0.204	1.895	0.058	-0.013	0.788	0.000	99.138	12
		GDP	0.000	0.000	0.581	0.561	0.000	0.000	0.000	99.138	12
	Healthcare system	intercept	1.045	0.288	3.627	0.000	0.480	1.610	5.415	99.209	12
		Mixed social health insurance	-0.796	0.409	-1.946	0.052	-1.597	0.006	5.415	99.209	12
		Mixed public-private	-0.580	0.302	-1.921	0.055	-1.173	0.012	5.415	99.209	12
	Universal vaccination strategy	intercept	0.369	0.237	1.555	0.120	-0.096	0.835	0.000	99.133	12
		Yes	0.151	0.260	0.579	0.563	-0.359	0.661	0.000	99.133	12

CI, confidence interval; ENT, ears, nose and throat; GDP, gross domestic product; I², proportion of variance; R², coefficient of determination; SE, standard error

Note: Data on average temperature, GDP per capita, country income bracket, healthcare system, and universal varicella vaccination status were collected for the year 2021 and specific to the regions or countries under investigation.

Table S9. All complications summary stratified by age subgroups (adults vs children)

Complication Age subgroup	Related studies	Sample size	Complication rate, % (95% CI)	Heterogeneity				
	(reference number)			I ² , %	p value	Egger's statistic ^a	Egger's p value ^a	E-Value
Cardiovascular								
Adults	2	61,126	0.09 (0.00–2.27)	79.72	0.03	NA	NA	37.04
Children	8	66,437	0.48 (0.01–1.38)	95.67	p<0.01	NA	NA	25.36
ENT								
Adults	5	62,369	2.49 (0.00–8.11)	97.61	p<0.01	NA	NA	10.28
Children	27	103,140	6.37 (4.80–8.13)	98.58	p<0.01	3.47	p<0.01	7.20
Gastrointestinal								
Adults	6	62,565	2.45 (0.00–8.14)	98.33	p<0.01	NA	NA	11.58
Children	29	97,290	7.34 (4.38–10.95)	99.56	p<0.01	2.53	0.02	6.66
Genitourinary								
Adults	2	61,126	1.27 (0.00–4.47)	75.84	0.04	NA	NA	15.80
Children	14	68,368	0.76 (0.44–1.14)	70.66	p<0.01	1.34	0.20	19.87
Haematological								
Adults	6	61,920	15.13 (3.13–33.60)	99.03	p<0.01	NA	NA	4.41
Children	34	82,839	4.35 (2.78–6.21)	98.33	p<0.01	5.42	p<0.01	8.65
Infection								
Adults	5	62,149	7.96 (1.83–17.61)	98.29	p<0.01	NA	NA	6.34
Children	42	90,164	10.57 (5.86–16.44)	99.73	p<0.01	1.97	0.06	5.44
Liver								
Adults	5	61,519	2.94 (0.02–9.21)	95.40	p<0.01	NA	NA	10.51
Children	19	71,046	1.98 (0.68–3.86)	98.34	p<0.01	4.05	p<0.01	13.16
Musculoskeletal								

Adults	2	61,124	0.02 (0.00–0.80)	48.10	0.17	NA	NA	45.23
Children	30	78,089	1.85 (1.16–2.68)	94.95	p<0.01	5.95	p<0.01	13.31
Neurological								
Adults	10	63,682	1.11 (0.31–2.25)	85.19	p<0.01	0.78	0.46	14.69
Children	55	197,181	8.04 (6.24–10.03)	99.45	p<0.01	4.47	p<0.01	6.34
Ocular								
Adults	4	61,338	0.24 (0.00–2.97)	84.59	p<0.01	NA	NA	17.89
Children	20	79,002	2.43 (1.65–3.35)	94.35	p<0.01	3.47	p<0.01	11.65
Respiratory								
Adults	11	83,527	5.34 (3.10–8.11)	99.11	p<0.01	0.65	0.53	7.89
Children	54	126,525	8.10 (6.24–10.17)	99.15	p<0.01	5.59	p<0.01	6.30
Severe varicella								
Adults	NA	NA	NA	NA	NA	NA	NA	NA
Children	9	3,257	21.20 (8.06–38.37)	98.96	p<0.01	NA	NA	3.58
Skin								
Adults	10	73,527	4.98 (3.24–7.05)	97.29	p<0.01	4.13	p<0.01	8.17
Children	52	127,983	20.86 (15.37–26.94)	99.80	p<0.01	3.18	p<0.01	3.62
Other								
Adults	7	82,316	0.34 (0.04–0.85)	96.55	p<0.01	NA	NA	27.92
Children	31	111,782	5.83 (4.28–7.59)	98.87	p<0.01	3.17	p<0.01	7.54

CI, confidence interval; ENT, ears, nose and throat; I², proportion of variance

^a Egger's statistic not possible with fewer than 10 studies.

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