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ORIGINAL RESEARCH

Global Prevalence of Varicella-Associated Complications: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Varicella (chickenpox) is an infectious disease caused by the varicella zoster virus affecting children, adolescents, and adults. Varicella symptoms are usually self-limiting; however, different complications with widespread and systemic manifestations can occur. This systematic literature review aims to explore and quantify varicella-associated complication rates.

Methods: Two databases (Embase and MEDLINE), congress abstracts, and reference lists of systematic reviews were screened to identify evidence on varicella complications. Complications were identified and grouped into 14 clinically relevant categories. Proportional meta-analyses were conducted using a random-effects model and tests for heterogeneity and publication bias were performed. Subgroup, sensitivity, and meta-regression analyses were also conducted. A total of 78 studies, spanning 30 countries, were included in the meta-analysis.

Results: Pooled prevalence was highest in severe varicella (22.42%; 95% confidence interval [CI] 10.13–37.77), skin-related complications (20.12%; 95% CI 15.48–25.20), and infection-related complications (10.03%; 95% CI 7.47–12.90). Cardiovascular (0.55%; 95% CI 0.08–1.33), genitourinary (1.17%; 95% CI 0.55–1.99), and musculoskeletal (1.54%; 95% CI 1.06–2.11) complications had the lowest pooled prevalence. The remaining complication categories ranged between 1% and 10%. Subgroup analysis showed that complications were more prevalent in children versus adults and in hospitalized patients versus outpatients. Meta-regression analysis found that no ecological level covariates were accurate predictors for the overall prevalence of varicella-associated complications. There was substantial heterogeneity and publication bias across all meta-analyses.

Conclusion: Results suggest that different types of varicella-associated complications could be

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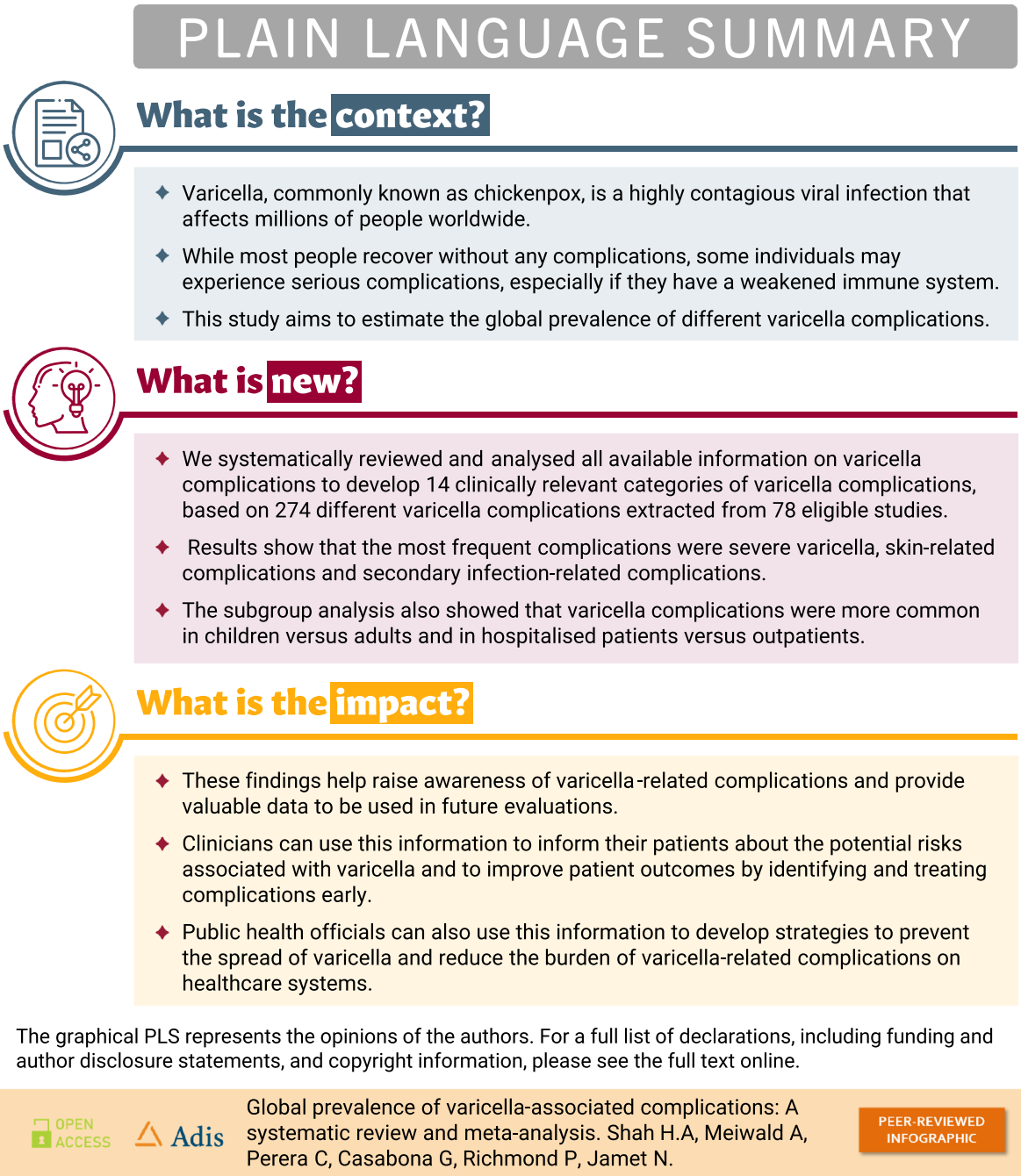
frequent, impacting quality of life, and healthcare resource utilisation and budgets. These findings are crucial to raise awareness of the health and economic burden of varicella disease.

PLAIN LANGUAGE SUMMARY

A graphical plain language summary is available with this article.



Keywords: Chickenpox; Complications; Meta-analysis; Paediatric diseases; Prevalence; Systematic review; Varicella

Key Summary Points

Why carry out this study?

A comprehensive global synthesis of all varicella-associated complications has not yet been conducted.

This research aimed to quantify the proportion of varicella cases experiencing a specific complication type by analysing currently available observational data.

What was learned from the study?

The most frequent complications were severe varicella, skin- and infection-related complications.

Other less frequent complications included cardiovascular; ear, nose and throat; gastrointestinal; haematological; liver; musculoskeletal; neurological; ocular; genitourinary; respiratory; and 'other' complications.

Complications were more prevalent in children and hospitalised patients.

DIGITAL FEATURES

This article is published with digital features, including a graphical plain language summary, summarising the context, novelty, and impact of this study. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24630987.

INTRODUCTION

Varicella (chickenpox) is an infectious disease caused by the varicella zoster virus (VZV) [1]. Varicella is prevalent globally and has a significant burden. The World Health Organization estimates the annual global burden of varicella to be approximately 140 million cases with 4.2 million severe complications requiring hospitalisation, and 4200 deaths [2]. Varicella is highly contagious, with an incubation period of 14–16 days after exposure, and is transmitted through airborne droplets, as well as through direct contact with skin lesions [3]. In the absence of a universal varicella vaccination (UVV) programme, most infections occur during childhood. However, some geographic variation in the age at which varicella occurs can be observed. Across Europe, varicella incidence is the highest among children less than 5 years of age and ranges from 7052 to 17,974 per 100,000 population [4]. In tropical regions, adults are observed to acquire the infection more frequently [2].

Varicella can often lead to complications whose manifestations can be widespread and systemic [5], especially when occurring in adults and immunocompromised patients, who are at risk of severe disease [1]. Results from two studies in England and Italy suggest that common complications in adults include bacterial skin infections (11.25%), pneumonia (4.82%), febrile convulsions (3.39%), and encephalitis (2.44%). Incidence of complications as well as the severity increase with age [6]. Among children, increased neurological and respiratory difficulties have been reported in complicated chickenpox cases, leading to high hospitalisation rates [7]. However, whether such trends exist irrespective of jurisdiction is unknown.

Additional diagnostic procedures and hospitalisations due to complications can contribute to an increase in the overall costs incurred by patients and the health system, as well as an increase in healthcare resource utilisation [8–10]. In Europe, the economic cost associated with varicella in the absence of UVV amounted to an estimated €660 million in 2018 [11]. The total annual costs of varicella in Canada (medical and societal costs) were reported to be $122 million Canadian Dollars (CAD) or CAD 353 per case [12] and the median cost of varicella hospitalisation in Mexico was estimated at $4434 United States dollars (USD) per varicella confirmed case (ranging from $1847 to $19,586) [9].

Many complications have been reported in the literature; however, a comprehensive global synthesis of all complications has not yet been conducted. Therefore, we aimed to quantify the global prevalence of varicella-associated complications using a systematic literature review (SLR) and meta-analysis approach following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting standards for medical and epidemiological evidence syntheses [13].

METHODS

The primary research question investigated by this review was: What proportion of varicella cases experience a specific complication type within the currently available observational data? Additionally, this review aims to investigate secondary research questions: What proportion of varicella cases that lie within a subgroup experience a specific complication? Within a complication category, what are the differences across the subgroups?

The protocol for the SLR was designed following best practices and international standards, including the Cochrane collaboration [14], PRISMA guidelines [13], National Institute for Health and Care Excellence health technology assessment methods guide [15], and best practices for conducting SLRs in healthcare [16].

Data Sources and Search Strategy

A search strategy was developed for the Embase and MEDLINE databases. The search algorithm utilised a combination of subject heading/index and free-text terms for varicella, combined with terms designed to capture the relevant study design and topic areas of interest, while staying within the proposed temporal limits, where applicable. These algorithms were adapted to the idiosyncrasies of each database but maintained the same search terms. The detailed search strategy is available in Tables S1 and S2. All retrieved documents underwent two levels of screening, namely abstract (level 1) and full-text (level 2) screening. Screenings were performed by two reviewers independently and disagreements around selected studies were resolved by a third reviewer.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Therefore an ethics committee approval was not required. The authors confirm that this study was performed in accordance with the ethical standards of the Declaration of Helsinki 1964 and its amendments.

Eligibility Criteria

The screening process was guided by the inclusion and exclusion criteria based on the Population, Intervention, Comparison, Outcome and Study (PICOS) framework (Table 1). The data from the included studies were extracted into a pre-defined data extraction form in Microsoft Excel.

Quality Assessment and Data Extraction

For the SLR, data extraction was performed by one investigator, and the entries were reviewed and validated by a senior scientist. For the meta-analysis, the SLR studies were re-reviewed to extract data on the number of patients who experienced a complication of varicella in specific subgroups, e.g. age category (adults or children), hospitalisation status (hospitalised or outpatient), vaccination status (vaccinated or unvaccinated), and immune status (immunocompromised or immunocompetent). Age group stratifications were extracted when available (e.g. 0–5 years). Studies published in multiple articles (including interim and/or final/complete results) were extracted as one study. Furthermore, data were included on average temperature in 2021 in the study country (given varicella can be a seasonal disease), gross domestic product (GDP) per capita (2021 United States dollars [$]), country income bracket (high income, higher-middle income, lower-middle income), healthcare system (i.e. public, mixed social health insurance, mixed public–private, or private health insurance), and whether a country has UVV. The

Table 1 Study eligibility criteria defined by the PICOS criteria

Items	Inclusion criteria	Exclusion criteria
Population	Immunocompetent and immunocompromised children, adolescents, and adults infected with varicella (chickenpox)	Pregnant women
	Primary varicella	
	Breakthrough varicella cases	
Intervention	Any, none required	No exclusion based on 'intervention'
Comparators	Any, none required	No exclusion based on 'comparator'
Outcomes of interest	Complications of varicella infection	Studies that do not report on complications associated with varicella infection
	Description of patients with complications	
	Risk of complication	
Study design	Observational studies, including retrospective or prospective designs	All other types of studies (including abstracts, posters, book chapters)

PICOS Population, Intervention, Comparison, Outcome, Study design

methodological quality of the included studies was assessed using the Downs and Black checklist for non-interventional studies [17].

Complication Categorisation

All extracted complications were grouped into 14 clinically relevant categories (Tables 2, S3). The groups were based on the International Classification of Diseases 10th Revision (ICD-10) codes and informed by published literature [6, 7]. The complication groups were further expanded and validated by a clinical expert whose recommendations were considered to update the complication groups and remove several unique complications deemed to be non-specific.

Statistical Analysis

A proportional meta-analysis was performed to calculate a pooled overall proportion of varicella complications based on several individual proportions [18, 19]. This method of data synthesis allowed for the generation of a single summary estimate and its variance for each complication category. In addition, individual studies are usually not powered to detect differences in complications across different patient subgroups and as such a meta-analysis, by pooling sources, is able to have adequate statistical power to detect these differences.

As a result of the significant heterogeneity of the included studies, a random-effects model was used, which assumed that the true underlying effect between the studies could vary. A fixed-effect model was not used because of the assumption that one true estimate could not be applied across different studies reporting proportional data [20]. As patients could experience multiple complications, a single data point based on the largest denominator and the largest numerator from each study was included for each analysis, to prevent an overestimation of the complication rate.

Subgroup and Sensitivity Analysis

Subgroup and sensitivity analyses were conducted to further assess variation in heterogeneity. Subgroups were included based on age category (adults or children), hospitalisation status (hospitalised or outpatient), vaccination status (vaccinated or unvaccinated), and immune status (immunocompromised or immunocompetent) (Table S4). Additionally, a sensitivity analysis was performed to assess the

Table 2 All complications summary table

Complication	Related studies (Reference number)	Sample size	Complication rate, % (95% CI)	Heterogeneity			
				I^2, %	*p* value	Egger's statistic	Egger's *p* value
Cardiovascular	11	68,474	0.55 (0.08–1.33)	95.27	< 0.01	3.23	0.01
ENT	31	844,966	5.50 (4.45–6.65)	98.99	< 0.01	5.05	< 0.01
Gastrointestinal	35	100,423	6.73 (4.17–9.84)	99.49	< 0.01	2.50	0.02
Genitourinary	18	70,622	1.17 (0.55–1.99)	93.78	< 0.01	0.93	0.37
Haematological	42	88,317	4.97 (3.47–6.70)	98.28	< 0.01	5.42	< 0.01
Infection	49	832,335	10.03 (7.47–12.90)	99.71	< 0.01	2.84	< 0.01
Liver	24	73,826	2.51 (1.19–4.27)	98.18	< 0.01	4.94	< 0.01
Musculoskeletal	34	219,416	1.54 (1.06–2.11)	97.33	< 0.01	6.52	< 0.01
Neurological	69	946,841	6.74 (5.56–8.02)	99.51	< 0.01	7.04	< 0.01
Ocular	23	81,903	2.09 (1.44–2.84)	93.66	< 0.01	3.22	< 0.01
Other	37	857,466	5.04 (4.05–6.12)	99.05	< 0.01	3.08	< 0.01
Respiratory	70	877,770	8.17 (6.88–9.55)	99.28	< 0.01	6.40	< 0.01
Severe varicella	12	4665	22.42 (10.13–37.77)	99.15	< 0.01	− 0.93	0.37
Skin	63	274,142	20.12 (15.48–25.20)	99.86	< 0.01	5.05	< 0.01

CI confidence interval, *ENT* ear, nose and throat, I^2 proportion of variance

impact of excluding studies that used a different study design from most of the other studies (exclusion of case series and chart reviews) and any study considered to be biased (defined as a rating of 'poor') on the meta-analytic complication rates.

Heterogeneity and Publication Bias

In this meta-analysis of observational studies, it was important to investigate heterogeneity due to the diversity of study designs and potential risk of bias [21]. Heterogeneity was evaluated through statistical tests such as *Q* and I^2 statistics, and classified as unimportant (0–40%), moderate (30–50%), substantial (50–90%), or considerable (75–100%) [22, 23]. A meta-regression analysis was also conducted to investigate potential sources of heterogeneity by testing various factors, including average temperature in study country, GDP per capita (United States dollar [USD], healthcare system types, and vaccination recommendations. Differences between subgroups were investigated using the χ^2 test [24].

To ensure that the results were not affected by publication bias, the authors assessed small study effects using Egger's test and visual inspection of funnel plots [25, 26].

Software

This meta-analysis utilised Microsoft Excel for screening and data extraction. The R Project (R version 4.2.1) was chosen due to the availability of validated meta-analysis packages and it being free software [27]. The R packages used included 'dplyr' and 'tidyr' for data cleaning; 'meta' for the meta-analysis; 'ggplot2', 'ggridges', and 'forcats' for data visualisations; and 'broom' for formatting regression outputs.

RESULTS

Narrative Synthesis

A total of 2030 records were identified via Embase and MEDLINE. After screening for title and abstract relevance, 1754 records were excluded. After the full-text review, a further 146 publications were removed, leaving 130 studies for inclusion in the SLR [6–9, 28–153]. Of these, 52 studies were excluded from the meta-analysis, leaving 78 studies eligible for meta-analysis (Fig. 1) [6–9, 28, 30–32, 34, 35, 37, 38, 41, 43, 46, 47, 51, 53, 57–68, 71–74, 76–78, 81, 85, 87, 91–94, 99–102, 104, 105, 107, 109, 112–114, 116–118, 120, 121, 124, 125, 128–132, 134, 136, 138–140, 142, 143, 145–147, 150]. From the selected studies, 632 unique complications were extracted, of which 303 were included after clinical review. Among these, 274 unique complications were categorised into 14 groups, namely cardiovascular (n = 11); ear, nose and throat (ENT) (n = 31); gastrointestinal (n = 35); genitourinary (n = 18); haematological (n = 42); infection-related (n = 49); liver (n = 24); musculoskeletal (n = 35); neurological (n = 69); ocular (n = 23); respiratory (n = 70); severe varicella (n = 13); skin-related (n = 63); and other complications (n = 37) (Table S4).

The included studies were conducted in 30 countries. Please see Table S5 for a description of the study characteristics based on study setting, study design, and risk of bias.

Overall, respiratory and neurological complications were the two most frequently reported complications, being reported in 70 and 69 studies, respectively. The least frequently reported complications were severe varicella and cardiovascular complications, being reported in 12 and 11 studies, respectively. A ridgeline plot describing most studies reported less than 10% of patients experiencing any complication (Fig. 2). A plain language summary describes the context, outcomes, and impact of this study for a simpler understanding.

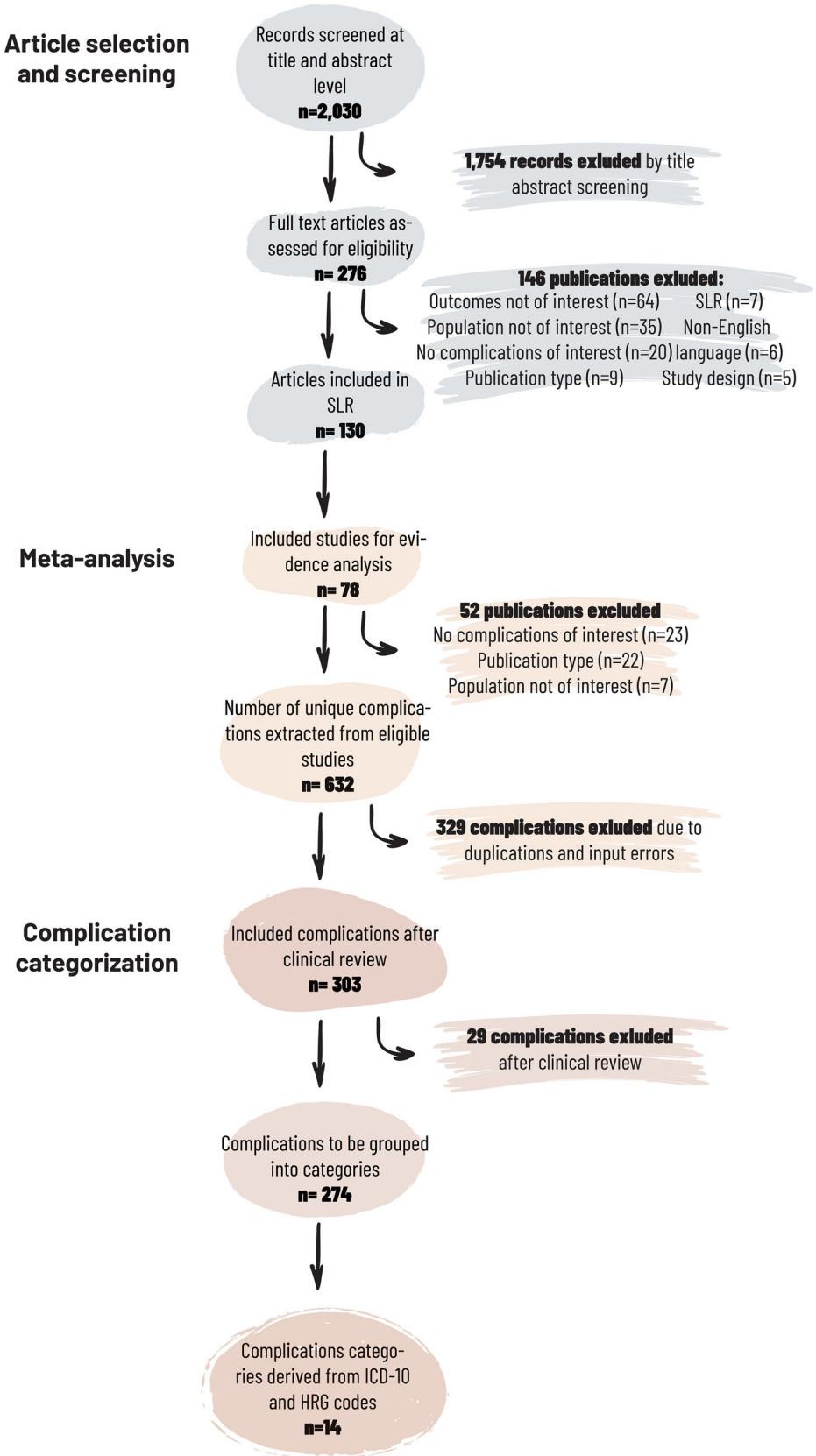
Meta-Analysis

The highest pooled prevalence was seen for the complication categories severe varicella (22.42%; 95% CI 10.13–37.77, I^2 = 99.15%), skin-related complications (20.12%; 95% CI 15.48–25.20, I^2 = 99.86%), and infection-related complications (10.03%; 95% CI 7.47–12.90, I^2 = 99.71%). The lowest pooled prevalence was seen for the complication categories cardiovascular (0.55%; 95% CI 0.08–1.33, I^2 = 95.27%), genitourinary (1.17%; 95% CI 0.55–1.99, I^2 = 93.78), and musculoskeletal (1.54%; 95% CI 1.06–2.11, I^2 = 97.33%). Additional complication categories had a pooled prevalence that ranged between 1% and 10% including ENT (5.50%; 95% CI 4.45–6.65), gastrointestinal (6.73%; 95% CI 4.17–9.84), haematological (4.97%; 95% CI 3.47–6.70), liver (2.51%; 95% CI 1.19–4.27), neurological (6.74%; 95% CI 5.56–8.02), ocular (2.09%; 95% CI 1.44–2.84), respiratory (8.17%; 95% CI 6.88–9.55), and other (5.04%; 95% CI 4.05–6.12) (Table 2, Fig. S1). Considerable heterogeneity was seen across all pooled prevalence for each complication category (I^2 range 93.66–99.86%). Publication bias was present for all complication categories ($p < 0.01$), other than severe varicella and genitourinary, where there was no evidence of publication bias based on the Egger's test (Egger's test $t = -0.93$, $p = 0.37$; $t = 0.93$, $p = 0.37$, respectively) (Table 2, Fig. 3).

Subgroup Analysis

Adults and Children

Adults were found to have a high prevalence of haematological complications (15.1%; 95% CI 3.1–33.6, I^2 = 99%; $p < 0.01$), whereas children were found to have a high prevalence of severe varicella (21.2%; 95% CI 8.1–38.4, I^2 = 99%; $p < 0.01$) and skin-related complications (20.9%; 95% CI 15.4–26.9, I^2 = 99%; $p < 0.01$) (Fig. 4). When performing a comparative meta-analysis, a significant difference was observed in the proportion of adults and children developing musculoskeletal complications (1.5%; 95% CI 1.0–2.0, I^2 = 96%; $p < 0.01$),


Article selection and screening
Records screened at title and abstract level
n=2,030
1,754 records exluded by title abstract screening
Full text articles assessed for eligibility
n= 276
146 publications exluded:
Outcomes not of interest (n=64)
SLR (n=7)
Population not of interest (n=35)
Non-English
No complications of interest (n=20)
language (n=6)
Publication type (n=9)
Study design (n=5)
Articles included in SLR
n= 130
Meta-analysis
Included studies for evidence analysis
n= 78
52 publications excluded
No complications of interest (n=23)
Publication type (n=22)
Population not of interest (n=7)
Number of unique complications extracted from eligible studies
n= 632
329 complications exluded due to duplications and input errors
Complication categorization
Included complications after clinical review
n= 303
29 complications exluded after clinical review
Complications to be grouped into categories
n= 274
Complications categories derived from ICD-10 and HRG codes
n=14

◀**Fig. 1** PRISMA for SLR and meta-analysis. *ICD-10* International Classification of Diseases 10th Revision, *HRG* healthcare resource group, *n* number of studies, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *SLR* systematic literature review

neurological complications (6.8%; 95% CI 5.4–8.3, $I^2 = 99\%$; $p < 0.01$), and skin-related complications (18.0%; 95% CI 13.9–22.5, $I^2 = 100\%$; $p < 0.01$). A significant difference in the prevalence of other skin-related complications was also found between adults and children (4.3%; 95% CI 3.3–5.4, $I^2 = 99\%$; $p < 0.01$). Heterogeneity and publication bias were substantially high for all three complications (musculoskeletal, neurological, and skin-related complications). Within the subgroup analysis, heterogeneity was lower for cardiovascular, musculoskeletal, neurological, and ocular complications when stratified by adults and for genitourinary complications when stratified by children.

Outpatient and Hospitalised

The complications found to be prevalent in an outpatient setting were infection-related (17.6%; 95% CI 3.7–38.7, $I^2 = 99\%$; $p < 0.01$), ENT (10.1%; 95% CI 4.0–18.5, $I^2 = 99\%$; $p < 0.01$), musculoskeletal (4.7%; 95% CI 0.4–13.0, $I^2 = 99\%$; $p < 0.01$), and ocular (4.6%; 95% CI 1.7–8.6, $I^2 = 96\%$; $p < 0.01$). On the other hand, complications prevalent in a hospitalised setting were severe varicella (22.4%; 95% CI 10.1–37.8, $I^2 = 99\%$; $p < 0.01$), skin-related (21.9%; 95% CI 17.2–26.9, $I^2 = 99\%$; $p < 0.01$), and respiratory (11.1%; 95% CI 7.5–15.3, $I^2 = 99\%$; $p < 0.01$) (Fig. 4). When performing a comparative meta-analysis, a significant difference was seen for the proportion of hospitalised patients and outpatients developing gastrointestinal complications (6.6%; 95% CI 4.3–9.4, $I^2 = 99\%$; $p = 0.01$), haematological complications (5.2%; 95% CI 3.5–7.1, $I^2 = 98\%$; $p < 0.01$), ocular complications (2.2%; 95% CI 1.5–3.0, $I^2 = 93\%$; $p = 0.04$), and respiratory complications (10.0%; 95% CI 7.0–13.5, $I^2 = 100\%$; $p < 0.01$). No significant difference in the prevalence of complications was found between the outpatient and hospitalised subgroups for other complications. Heterogeneity and publication bias remained high for the comparative analysis. However, heterogeneity did decrease when stratifying haematological

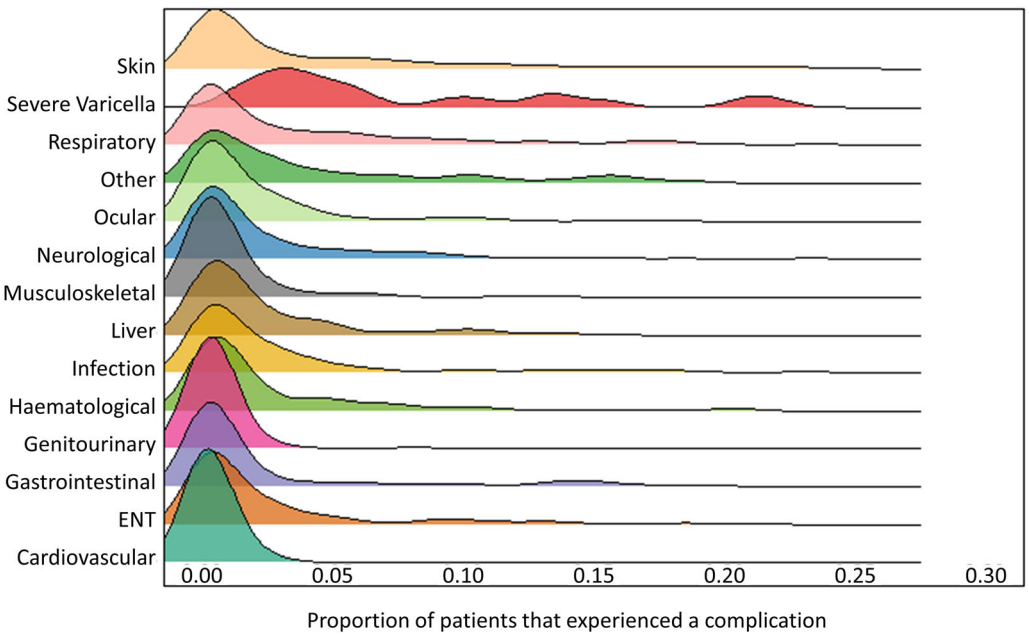


Fig. 2 Varicella complication proportion density by complication category. *ENT* ear, nose and throat

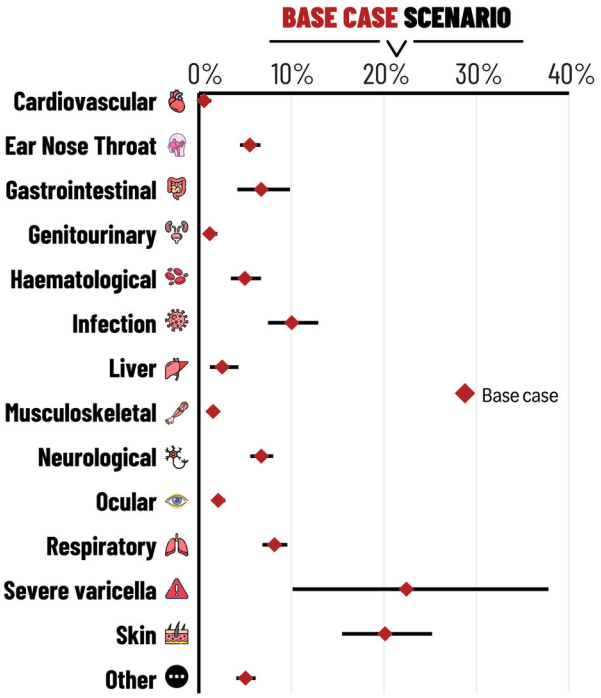


Fig. 3 Proportion of patients experiencing a complication: base case. The complications are not mutually exclusive, as one patient can be present in multiple subgroups

complications in an outpatient setting and ocular complications in a hospitalised setting.

Immunocompetent and Immunocompromised

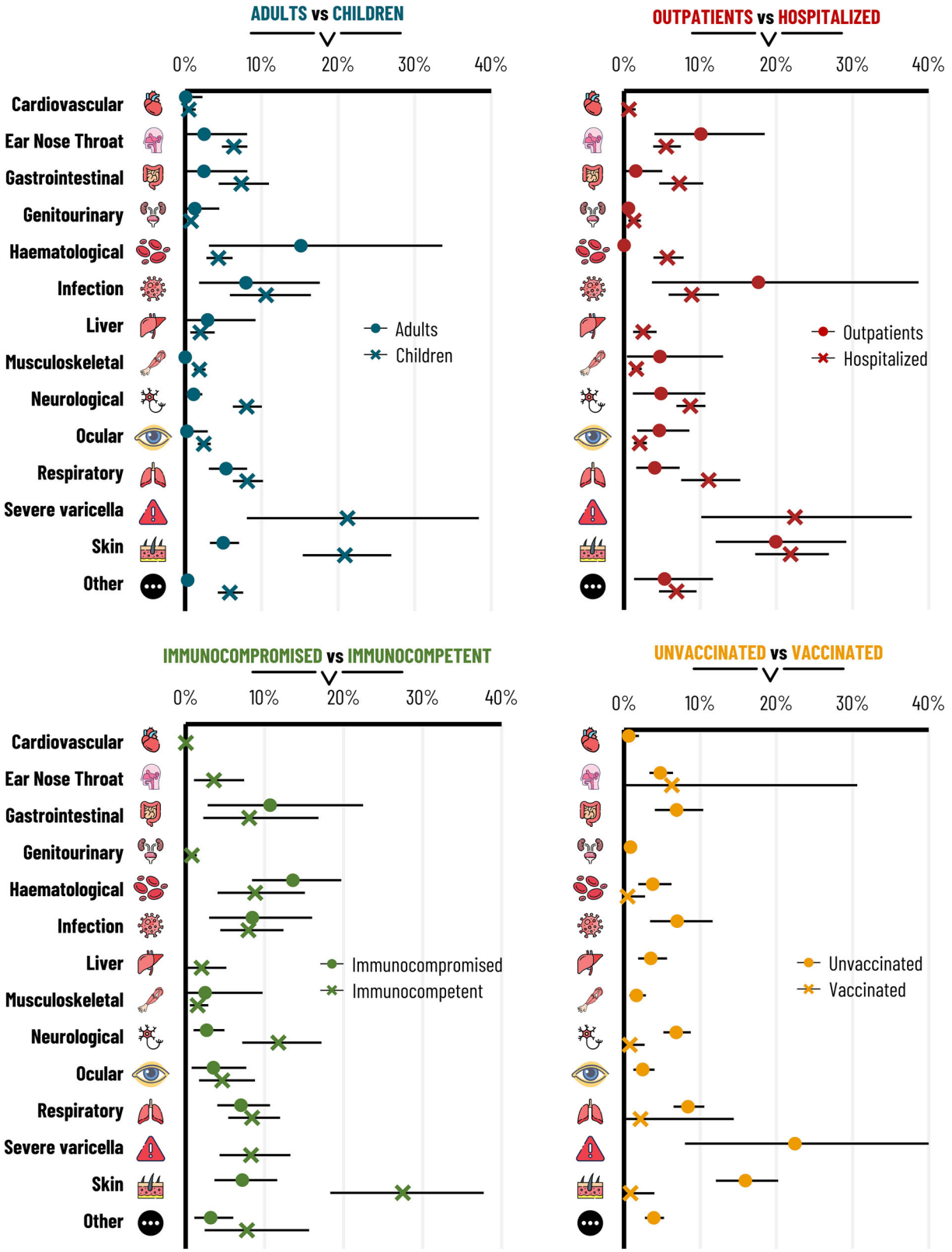
Among the immunocompetent subgroup, a higher prevalence of skin-related (27.5%; 95% CI 18.3–37.7, $I^2 = 99\%$; $p < 0.01$), neurological (11.7%; 95% CI 7.2–17.2, $I^2 = 99\%$; $p < 0.01$), and haematological (8.8%; 95% CI 4.0–15.1, $I^2 = 99\%$; $p < 0.01$) complications was observed. In the immunocompromised subgroup, the prevalence was higher for haematological (13.6%; 95% CI 8.4–19.7, $I^2 = 78\%$; $p < 0.01$), gastrointestinal (10.7%; 95% CI 2.8–22.5, $I^2 = 75\%$; $p = 0.04$), and infection-related (8.4%; 95% CI 3.0–16.0, $I^2 = 88\%$; $p < 0.01$) complications (Fig. 4). Results of the comparative meta-analysis showed that there was a significant difference between immunocompetent and immunocompromised subgroups for skin-related (21.2%; 95% CI 14.6–28.6, $I^2 = 99\%$; $p < 0.01$) and neurological (8.8%; 95% CI 5.6–12.5, $I^2 = 98\%$; $p < 0.01$) complications. No significant difference in the prevalence of complications was found between the immunocompetent and immunocompromised subgroups for other complications. Heterogeneity and publication bias remain high for both complications (skin-related and neurological complications). There was a consistent decrease in heterogeneity for the immunocompromised subgroup for gastrointestinal ($I^2 = 75\%$), haematological ($I^2 = 78\%$), infection-related ($I^2 = 88\%$), musculoskeletal ($I^2 = 56\%$), neurological ($I^2 = 71\%$), ocular ($I^2 = 0.0\%$), respiratory ($I^2 = 72\%$), skin-related ($I^2 = 76\%$), and other ($I^2 = 0.0\%$) complications.

Unvaccinated and Vaccinated

Among the unvaccinated subgroup, the prevalence was highest for severe varicella (22.4%; 95% CI 8.0–41.4, $I^2 = 99\%$; $p < 0.01$), skin-related (15.9%; 95% CI 12.1–20.2, $I^2 = 99\%$; $p < 0.01$), and respiratory (8.4%; 95% CI 6.5–10.5, $I^2 = 99\%$; $p < 0.01$) complications. In the vaccinated subgroup, the most prevalent complications were ENT (6.3%; 95% CI 0.0–30.6, $I^2 = 99\%$; $p < 0.01$), respiratory (2.1%; 95% CI 0.0–14.4, $I^2 = 98\%$; $p < 0.01$), and skin-related (0.8%; 95% CI 0.0–4.0, $I^2 = 94\%$; $p < 0.01$) complications (Fig. 4). From the comparative meta-analysis, it was observed that there was a significant difference in the proportion of unvaccinated and vaccinated subgroups for haematological (3.4%, 95% CI 1.7–5.5, $I^2 = 98\%$; $p = 0.02$), neurological (6.1%, 95% CI 4.6–7.8, $I^2 = 99\%$; $p < 0.01$), and skin-related (14.4%, 95% CI 10.9–18.2, $I^2 = 100\%$; $p < 0.01$) complications. No significant difference in the prevalence of complications was found between the unvaccinated and vaccinated subgroups for other complications. Heterogeneity and publication bias among all complications remained high. Generally, heterogeneity remained high for all complications with decreases only seen in the cardiovascular and genitourinary complications in the unvaccinated subgroup.

Sensitivity Analysis

Overall, when low quality studies were excluded the proportion of patients experiencing a


ADULTS vs CHILDREN
0%
10%
20%
30%
40%
Cardiovascular
Ear Nose Throat
Gastrointestinal
Genitourinary
Haematological
Infection
Liver
Musculoskeletal
Neurological
Ocular
Respiratory
Severe varicella
Skin
Other
Adults
Children
OUTPATIENTS vs HOSPITALIZED
Outpatients
Hospitalized
IMMUNOCOMPROMISED vs IMMUNOCOMPETENT
Immunocompromised
Immunocompetent
UNVACCINATED vs VACCINATED
Unvaccinated
Vaccinated

◀**Fig. 4** Proportion of patients experiencing a complication stratified by subgroup: base case. Point estimates are not provided for certain complications within specific subgroups because of missing data

complication in nine of the complication groups increased (cardiovascular, ENT, gastrointestinal, infection, liver, musculoskeletal, neurological, severe varicella, and other) and five groups slightly decreased (genitourinary, haematological, ocular, respiratory, and skin). The largest increase was by 2.3% for severe varicella complication (22.4–24.7%). The largest decrease in complication rate was 1.4% for skin-related complications (20.1–18.7%) (Fig. 5, Table S6).

When low evidence study designs were excluded, the proportion of patients experiencing a complication in three of the complication groups remained similar (ENT, genitourinary, and musculoskeletal), three complication groups increased (gastrointestinal, haematological, and infection), and six complication groups decreased (neurological, ocular, respiratory, severe varicella, skin-related, and other). The largest increase in complication rate was by 0.4%, observed for infection-related complication (10.0–10.4%). The largest decrease was 4.0%, observed for severe varicella (22.4–18.4%) (Fig. 5, Table S7).

Meta-Regression Analysis of Complication Groups

Temperature was significantly positively correlated with genitourinary and haematological complications. Here, the global prevalence of genitourinary and haematological complications increased by 0.007 for every degree increase in temperature. Musculoskeletal complications reduced by a coefficient of 0.002 and respiratory complications increased by 0.001 for every degree increase in temperature. All other complication categories were not correlated with temperature (Table S8).

GDP per capita was positively correlated with musculoskeletal complications ($p = 0.01$; $R^2 = 0\%$) with the coefficient associated with GDP of 0.000002. In other words, the complication rate increased by 0.000002 for every GDP per capita increase by USD for musculoskeletal complications. Respiratory complications were positively correlated with GDP per capita ($p = 0.001$; $R^2 = 13\%$). All other complications did not show any significant correlation with GDP per capita (Table S8).

A mixed social health insurance showed higher gastrointestinal complication rates than studies with a public healthcare system alone ($p < 0.05$; $R^2 = 28.9\%$). A mixed social health insurance was a significant predictor of infection-related complications based on a coefficient of 0.592 ($p < 0.01$; $R^2 = 0$). Having a mixed social health insurance system, a mixed private and public social health system, and a private health insurance system was a significant predictor of musculoskeletal complications with a positive correlation ($p < 0.001$; $R^2 = 45.8\%$). This indicated that musculoskeletal complications increased with mixed and private health systems in comparison to public health systems (Table S8).

Having a vaccination recommendation was negatively correlated with ENT ($p < 0.001$) and infection-related ($p < 0.001$) complications. Compared with no vaccination recommendation, having a recommendation reduced the rate of ENT complications by 0.121 ($R^2 = 21.9\%$) and infection-related complications by 0.17 ($R^2 = 33.4\%$). When compared with no vaccine recommendation, having a recommendation increased the haematological complication rate by 0.12 ($p = 0.004$; $R^2 = 0\%$) (Table S8).

DISCUSSION

On the basis of the systematic review and meta-analysis performed, severe varicella, skin-related and infection-related complications were the most prevalent. The least prevalent complications were for the categories cardiovascular, genitourinary, and musculoskeletal. ENT, gastrointestinal, haematological, liver, neurological, ocular, respiratory, and other complications all had consistent prevalence rates. Children

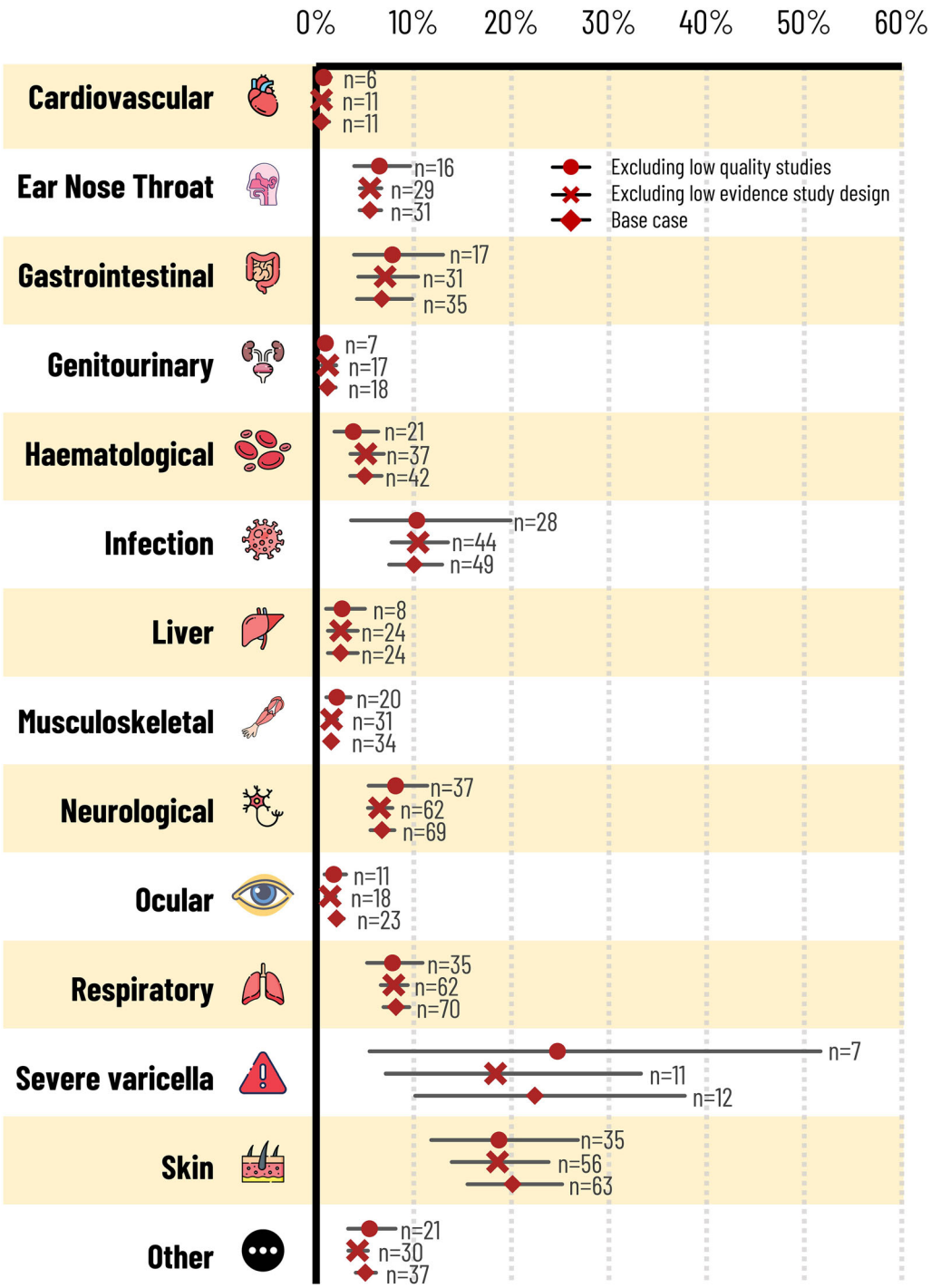


Fig. 5 Summary plot showing studies excluded on the basis of low quality or low evidence study designs. *n* number of studies

and hospitalised patients had a higher prevalence of complications when compared with adults and outpatient subgroups, respectively. Across all the complication rates assessed in this study, the subgroup and sensitivity analyses showed a strong level of consistency, helping to

strengthen the conclusions that may be drawn from these assessments.

Severe varicella had the highest pooled prevalence (22.42%) but with wide confidence intervals. This may be due to complications included within this category being non-specific (i.e. extreme varicella) or that such a broad category could cover combinations of complications across several organs [116]. In addition, all patients within this category were hospitalised, thereby leading to a higher prevalence compared with other groups. Severe varicella also had low study inclusion (n = 12), which may have contributed to diverse estimates, increasing heterogeneity and variation in crude prevalence.

Skin-related and infection-related complications were commonly observed, which is in line with the Centers for Disease Control and Prevention's findings that these are the most frequently occurring complications in children [3]. Here, skin-related complications have almost as high a prevalence (20.12%) as severe varicella with similar wide confidence intervals, whereas infection-related complications were moderately prevalent (10.03%). Results suggest that data included within these two categories can be heterogeneous because of several specific complications being attributed to the skin category (i.e. balanitis, cellulitis, haemorrhagic vesicular rash, urticaria, skin or soft tissue infection) [6, 41, 64]. In addition, there may be some subjectivity in the way complications are grouped where bacterial skin infections could be considered both a skin-related and an infection-related complication. However, results are in line with previous research; for example, Bernal et al. [6] found that bacterial skin infections were the most common complication of varicella infection in the UK. This suggests broad consistency with our methodology and complication groupings.

A lower proportion of adults when compared with children experienced cardiovascular (0.09% vs 0.48%), ENT (2.49% vs 6.37%), gastrointestinal (2.45% vs 7.34%), infection (7.96% vs 10.57%), musculoskeletal (0.02% vs 1.85%), neurological (1.11% vs 8.04%), ocular (0.24% vs 2.43%), respiratory (5.34% vs 8.10%), skin (4.98% vs 20.86%), and other (0.34% vs 5.83%) complications (Table S9). This was expected and consistent with previous literature, which reported that the frequency of non-severe varicella incidence is highest among children [4, 154]. Three complications showed significant differences between adults and children (skin-related, neurological, and musculoskeletal). This may have been due to a lower number of studies reporting an adult subgroup (n = 11) compared with children (n = 62), leading to wide confidence intervals.

We observed that a higher proportion of patients experienced a complication if they were hospitalised versus the outpatient subgroup. This could be because more studies were conducted in a hospital setting and therefore a higher sample size was reported for the hospitalised group. A higher proportion of hospitalised patients than outpatients experienced gastrointestinal (7.25% vs 1.54%), haematological (5.68% vs 0.00%), respiratory (11.09% vs 4.03%), genitourinary (1.26% vs 0.58%), neurological (8.68% vs 4.85%), skin-related (21.85% vs 19.92%), and other (6.86% vs 5.31%) complications, which was expected given these complications can be extremely severe. Conversely, a higher proportion of outpatients than hospitalised patients experienced ENT (10.08% vs 5.51%), infection-related (17.63% vs 8.89%), ocular (4.63% vs 2.05%), and musculoskeletal complications (4.70% vs 1.60%). This may be because ocular complications are often treated in the community via primary care visits or specialist clinics [155].

Since the introduction of a UVV strategy in Germany, Greece, Italy, and Spain, a decrease in incidence, hospitalisations, and complications has been observed in Europe [156], while breakthrough varicella cases are usually mild [3]. It was expected that a lower proportion of vaccinated patients would experience complications when compared with unvaccinated patients, and this was confirmed for the complication groups that showed a significant difference: haematological (0.46% vs 3.76%), neurological (0.74% vs 6.85%), and skin-related (0.83% vs 15.93%). Additionally, a very low number of studies reported a vaccinated population (highest for skin-related complications with four studies reporting a vaccinated

population), which makes it difficult to ascertain whether these are true differences.

Previous literature has indicated that varicella complications occur mostly among immunocompromised patients [113], although recent studies have demonstrated that the burden of varicella complications is significant in patients without underlying disease [112, 157]. The present study observed that immunocompetent patients when compared with immunocompromised patients had a significantly higher prevalence of neurological (11.73% vs 2.65%) and skin (27.49% vs 7.17%) complications. This has been seen in other studies [6] which reported that immunocompromised patients had lower rates of skin and neurological complications in comparison to immunocompetent patients. Fewer studies reported an immunocompromised population than an immunocompetent population for neurological (n = 7 vs n = 17) and skin-related complications (n = 7 vs n = 17), thereby leading to a selection bias. This outcome is not reported widely in the literature and thus further research should be conducted to evaluate the occurrence of varicella complications in these population subgroups. However, the data for the meta-analysis was based on the SLR. The SLR excluded studies reporting only an immunocompromised population or breakthrough varicella cases. Although immunocompromised and vaccinated patients formed a subgroup analysis, not all relevant studies will have been captured. A much higher sample size is available for the immunocompetent and unvaccinated subgroups across all complication groups.

Five of the 14 complication groups were negatively associated with GDP per capita (US $), and of the 14 groups two were significant with one positively and one negatively associated. The R^2 shows a poor predictability of GDP per capita on the complication rates, with the range being 0.0–33.3%. Temperature showed two analyses where the R^2 was greater than 10% and of the two analyses, one was significant (genitourinary). The analysis showed that temperature was poorly correlated with complication rates, which was expected for some complication groups but was against expectation for severe varicella. The subgroup analysis also showed that vaccinated patients were not significantly different to unvaccinated patients (except for haematological, neurological, and skin-related complications); therefore, it was expected that a vaccine recommendation would be unlikely to accurately predict complication rates. This was shown by there being only three significant associations (two of which were negatively associated). Of the national healthcare systems within the studies, mixed social health insurance was a significant predictor in four complication groups and approaching significance in two additional complication groups. In all six of these, mixed social health insurance was positively associated with complication rates compared with compulsory national health insurance. Results of the meta-regression should be viewed in the context of the methods utilised to define complication groupings, so as to avoid any generalisations. Specifically, the meta-regression will be highly prone to aggregation error, because of which results should not be generalised.

Seven different study designs were included with a highly mixed population. The heterogeneity was comprehensively tested through meta-regression and planned subgroup analysis, and there was limited success in decreasing heterogeneity for some subgroups to elucidate the factors associated with the variability among the estimates. These subgroup analyses were pre-planned, but multiple analyses can increase the chance of a spurious significant result. Although the I^2 statistic is commonly applied to estimate heterogeneity for proportional analysis, it was primarily developed for randomised control trials, and as such a high I^2 statistic does not necessarily mean that the results are inconsistent [18]. Prediction intervals can sometimes be useful for presenting the extent of between-study variations, but assume a normal distribution across studies and are recommended if there is no clear funnel plot asymmetry [158]. As clear asymmetry is seen in the funnel plots, the prediction intervals need to be interpreted with caution. More research on how to capture and test for heterogeneity when doing meta-analysis of observational studies for proportional outcomes would be beneficial.

This study provides valuable insights into the burden of varicella-related complications and its global prevalence. The findings of this study could be used for clinical decision-making and in future economic analyses to capture the costs and health impacts of varicella disease. Improved consistency in the reporting of complication rates by single age years and specific populations would allow for an improved understanding of the differences in reported complication rates across complication groups and age groups.

Several strengths of this study were identified. Notably, it is the first SLR to comprehensively map and explore varicella complication rates across 30 different countries. This broad geographic scope provides a more global perspective on the burden of varicella complications. The SLR compiled results from literature on varicella complications to estimate the proportion of patients experiencing a type of complication. This abundance of data allowed for the development of clinically relevant groups that highlighted the differing types of complications that can occur and how these complications are impacted by specific confounders. The proportion of cases that fell into subgroups provided valuable insights into where the heterogeneity lies.

Limitations faced by this analysis included the high level of heterogeneity across the included studies. This was expected given the variety of study designs, sample sizes, and effect sizes across the numerous different complications that were extracted and explored. Due to this limitation, the results may not be generalised and addressing the high level of heterogeneity across the included studies could be a focus for future research. Additionally, the definitions of the reported complications are different between studies. It is unclear whether studies that grouped their complications used the same process as within this study. In addition, complications are not always mutually exclusive and may fit into more than one group. Patient and disease characteristics that are known to influence varicella complications, such as seasonal variance, were not accounted for in most studies, and published data did not allow stratification of these characteristics. This meta-analysis only assessed the type of complication and the proportion of patients who had a varicella complication. The severity, duration, and fatality of the complications were not assessed, so the outcomes of this analysis may have to be used with additional information to assess the burden of disease. The meta-regression analysis accounts for potential confounders at the ecological level such as temperature or type of health system. However, many other potential confounders could also be explored and further research could highlight key confounders that may impact the prevalence of varicella-associated complications. Lastly, reporting of complication data was extremely heterogeneous. Improved consistency in the reporting of complication rates by single age years and specific populations would allow for an improved understanding of the differences in reported complication rates across complication groups and age groups.

CONCLUSION

Varicella-associated complications can be frequent, thereby impacting quality of life, and healthcare resource utilisation and budgets. This study accumulates and synthesises research conducted on varicella-related complications and provides valuable insights into the burden of varicella-related complications and its global prevalence. The findings of this study could be used in clinical decision-making and future economic analyses to capture the costs and health impacts of varicella disease.

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had full access to the data and gave final approval before submission. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The work described was carried out in accordance with the recommendations of the International Committee of Medical Journal Editors for conduct, reporting, editing, and publication of scholarly work in medical journals. Hiral Anil Shah and Nicolas Jamet were involved in the conception and/or the design of the study, and participated in the acquisition of the study data. Anne Meiwald, Chamath Perera, Giacomo Casabona, Hiral Anil Shah, Nicolas Jamet and Peter Richmond were involved in the analysis/interpretation of the data, and reviewed and approved the final manuscript.

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Declarations

Conflict of Interest. Giacomo Casabona, Hiral Anil Shah and Nicolas Jamet are employed by GSK. Giacomo Casabona and Hiral Anil Shah holds shares in GSK. Anne Meiwald and Chamath Perera are employed by Adelphi Values PROVE and received funding from GSK to complete the work disclosed in this manuscript. Adelphi Values PROVE has received other consultancy fees from other pharmaceutical companies for unrelated work. PR declared research grants and participation on advisory boards from GSK and Merck, consulting fees, and payment for lectures to his institution and support for attending meetings from GSK, outside of the submitted work. The authors declare no other financial and non-financial relationships and activities.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Due to this reason an ethics committee approval was not required. The authors confirm that this study was performed in accordance with the ethical standards of the Declaration of Helsinki 1964 and its amendments.

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