Title:

The global incidence of bullous pemphigoid: a systematic review and meta-analysis

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Abstract

Bullous pemphigoid is an autoimmune blistering disorder that mainly affects older people. Although the disease is associated with considerable morbidity and mortality, the burden of disease worldwide is unclear.

The study aim is to pool the global incidence of bullous pemphigoid and determine whether this varies according to geographic area, age group, setting, and study quality.

Ovid Embase, MEDLINE, and grey literature were systematically searched on 7th April 2020. Two reviewers independently screened, extracted data, and appraised each study's quality using the JBI critical appraisal tool. Two domains, indicative of selection and survey bias, were used to identify high quality studies. The cumulative incidence was standardised to one year and pooled in a random-effects meta-analysis. Subgroup and sensitivity analyses were conducted.

Twenty-six studies were identified, of which 22 provided cumulative incidence and four provided incidence rates. The cumulative incidence of bullous pemphigoid was 8.2 (95%CI 4.8 to 13.7) per million people whereas the incidence rate was 34.2 (95%CI 19.2 to 60.7) per million person-years. Of the continents that contributed more than one study, the cumulative incidence was 10.3 (95%CI 5.8 to 18.2) and 5.6 (95%CI 3.5 to 9.0) per million people in Europe and Asia, respectively. The incidence was highestin studies including adults only (N=2), in population-based studies (N=9), and in more recent years. The cumulative incidence was higher (13.3 per million people, 95%CI 6.0 to 29.5) when restricting the analysis to higher quality studies (N=11). High heterogeneity (I^2 > 82%) was observed across all pooled estimates.

The incidence of bullous pemphigoid varies globally, is generally low but appears to be increasing with time. The burden of disease is likely to be underestimated.

Main text

Introduction

Bullous pemphigoid is a highly debilitating auto-immune blistering skin disorder that most commonly affects older people, particularly older men.(1) The aetiology of bullous pemphigoid remains poorly understood, although old age is recognised as the principal determinant for the development of bullous pemphigoid. More recently, increasing evidence is accumulating for the role of certain drugs (e.g., dipeptidyl peptidate-4 inhibitors) and neurological conditions (e.g. Parkinson's disease).(2-5)

Bullous pemphigoid is generally diagnosed in a specialist setting based on the clinical picture and laboratory investigations such as histopathological and immunofluorescence studies.(6) The classical clinical picture involves the formation of numerous and widespread tense bullae that leave moist erosions and crusts when ruptured. Another cardinal feature of bullous pemphigoid is intense itching, which adversely affects quality of life.(7) Beyond reductions in quality of life, those with bullous pemphigoid report more loneliness and social isolation and are more likely to be diagnosed with mood disorders and organic psychiatric disorders than those unaffected.(7-9) Finally, a diagnosis of bullous pemphigoid is associated with up to three-fold increased risk of death in the first two years following the diagnosis.(1)

Understanding the global burden of bullous pemphigoid is an important step in improving our understanding of the aetiology of the disease and characterising the healthcare burden. Although it is recognised that the incidence varies globally,(10) no published work has yet pooled the global incidence and systematically examined the variation in incidence observed.

The present work aimed to determine the incidence of bullous pemphigoid globally, and to determine whether this varied according to geographical region, population age, setting, study period, and study quality.

Patients and methods

Study design

The work comprised a systematic review and meta-analysis, reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).(11) The systematic review was registered on PROSPERO (registration number: CRD42020178593, link: https://www.crd.york.ac.uk/prospero) in May 2020.

Eligibility criteria

Cohort studies that estimated the incidence of bullous pemphigoid, either providing the incidence rate (per person-years) or sufficient data to calculate the cumulative incidence were included. Only population-based studies or those that estimated the incidence in the general population were included. No geographical or language restrictions were applied.

Systematic literature search

A search strategy was developed by an information specialist experienced in dermatological systematic reviews (DG). The search consisted of subject headings and keywords for bullous pemphigoid or autoimmune blistering diseases and epidemiology. The full search strategy is presented in supplementary information S1. The search was carried out on 7th April, 2020 in Ovid MEDLINE and Ovid Embase. The search was supplemented by grey literature searching via OpenGrey and EThOS, and manual review of the reference lists of included studies.

Title and abstract screening (conducted concurrently) and full text screening were conducted independently and in duplicate by two reviewers (NB, SG, or MP). Any disagreement between reviewers was resolved through discussion.

Data extraction and study quality assessment

Data extraction and study quality assessment was conducted independently and in duplicate by two reviewers (NB, SG or MP). A data extraction form, developed for the project, was used to extract the following: author, publication year, study design and setting, study duration (years), study period, country, sex distribution, population at risk, number of cases, and incidence rate. The study period was divided into decades (pre-1980s, 1980-1989, 1990-1999, 2000-2009, 2010-onwards) and we determined which decade(s) each study contributed incidence estimates to. We recorded whether the study assessed the cumulative incidence or the incidence rate of bullous pemphigoid. The cumulative incidence is the probability of developing a disease (bullous pemphigoid) over a certain period of time (e.g., one year). It represents a risk. Meanwhile, the incidence rate uses each individual's time at risk (their duration of follow-up) to determine the rate of developing a disease (bullous pemphigoid) per person-years. As follow-up is measured on an individual level, each person can be followed up for different lengths of time. The duration of follow-up of the study population is summed to determine the person-time at risk. Dividing the number of new cases by the person-years thereby generates a rate.

Study quality was assessed using the validated Joanna Briggs Institute (JBI) critical appraisal tool for prevalence studies.(12) Although not developed specifically for incidence studies, the tool assesses many methodological aspects that are also pertinent to the quality of incidence including the sampling procedure, validity of the diagnosis, and appropriateness of the analysis methods. Prior to study quality assessment, the reviewers agreed a standardised method for assessing the quality of the incidence studies to ensure consistency. The criteria utilised have been presented in the Supplementary Information. Quality scoring was presented descriptively and scores were not summated across the domains as this is not recommended by JBI. The study quality was instead presented for each study and summarised across the whole body of evidence. The criteria "Were study participants sampled in an appropriate way?" and "Was the data analysis conducted with sufficient coverage of the identified sample?" were considered measures for selection bias and incomplete outcome ascertainment. These two domains were deemed as the best indicators for study quality as methodological shortcomings in these domains were likely to impact the incidence estimate more than shortcomings in other domains. Studies that scored as appropriate across the two domains were considered "high quality" for the sensitivity analysis.

Statistical analysis

Separate meta-analyses were conducted for cumulative incidence (primary analysis) and incidence rate (secondary analysis) of bullous pemphigoid. In order to standardise the cumulative incidence across studies, we divided the number of new cases by the total observation period (years) to determine the number of new cases in a one-year period. The cumulative incidence per 1,000,000 people was then determined based on the number of new cases in one year and the population at risk. For studies presenting incidence rates, we estimated incidence rates (per 1,000,000 person-years) by dividing the number of new cases by the total person-years of follow-up and standard errors using the formula $1/\sqrt{number\ of\ incident\ cases}$.

Study estimates were pooled in a random-effects meta-analysis using DerSimonian and Laird method. Under the assumption that the true incidence of bullous pemphigoid varies according to country, healthcare system, and ascertainment method, a random effect model was implemented to

account for such differences. Assessment of heterogeneity was based on I^2, which was interpreted as low if <25%, moderate if 50-75%, and high if >75%.

Due to the low number of studies presenting incidence rates, subgroup analyses based on geographical region, study period, population age, and study setting were only conducted for the cumulative incidence. Finally, a sensitivity analysis including only higher quality studies was conducted.

Results

The literature search yielded 1,395 distinct records. After title and abstract screening, 49 full texts and 10 additional studies identified from reference checking were reviewed. Of the 59 full texts screened, 27 were deemed eligible for inclusion in the meta-analysis. The reasons for exclusion at the full-text phase are outlined in Figure 1. Twenty-five of the included studies were published in English, whilst two were in French.(13, 14)

The majority of studies included were conducted in Europe (17 studies), whilst seven were conducted in Asia, one in Africa, and two in North America (Table 1). Four of the studies determined the incidence only in the adult population, whilst the remaining 23 studies included people of all ages. The studies were generally retrospective cohort studies (n=18) that identified incident cases of bullous pemphigoid from hospital or outpatient records. Most often, the population at risk was estimated from census data of the country or region under the assumption that this overlapped with the catchment area of the hospital or outpatient records. The four studies that determined the incidence rate of bullous pemphigoid used electronic healthcare records to do so. The observation periods ranged from 1.5 years(15) to 50 years(16). The studies with longer observation periods tended to rely on retrospective review of electronic health data and provided the incidence rate of bullous pemphigoid rather than the cumulative incidence.

Quality of studies

Study quality varied considerably across the included studies. Generally, the sample frame was appropriate to address the target population. Most often the target population was the general population of the country/region, and the population at risk was the same population, identified through census data. Only five studies raised possible concerns regarding this domain, predominantly because insufficient detail was given regarding the methods. Similarly, sixteen studies reported appropriate methods for recruiting the study population. Most often this was because everyone in the target population was identified through a census and included in as the population at risk. For a subset, the methods were uncertain and may have introduced selection bias. Only ten studies were felt to have a sufficiently large sample (≥100 incident cases during observation period). In contrast, the reporting of subject and setting characteristics, the validity of the methods to identify bullous pemphigoid, and the utilisation of a reliable and standard approach was appropriate across the majority of the included studies. The statistical analysis undertaken was a source of concern regarding the validity of the study findings as the methods utilised did not generate any measures of uncertainty (e.g., confidence intervals). In addition, many studies incorrectly reported the incidence as an incidence rate without a measure of individual person-time at risk. However, the studies generally presented sufficient data on the numerator, denominator, and observation period for the cumulative incidence to be calculated by the reviewers.

Cumulative incidence of bullous pemphigoid

The pooled cumulative incidence was determined from twenty-three studies that recorded a total of 8,343 incident cases of bullous pemphigoid. The pooled cumulative incidence over a one-year period was 8.2 (95%CI 4.8 to 13.7) per 1,000,000 people (Figure 2). Heterogeneity was high (I^2 98.5%).

Variation in the cumulative incidence was observed by the subgroups. It was higher in the two studies including adults-only (30.3 per 1,000,000 people, 95%CI 6.4 to 144.1) than in the studies including all ages (7.5 per 1,000,000 people, 95%CI 5.4 to 10.6) (Figure 3). Studies were conducted across four continents, although North America and Africa only had one study each. Of the two continents with more than one study, the cumulative incidence was 5.6 per 1,000,000 people (95%CI 3.5 to 9.0; 7 studies) in Asia and 10.3 per 1,000,000 people (95%CI 5.8 to 18.2; 14 studies) in Europe (Figure 4). The cumulative incidence was lower in the 13 hospital-based studies (6.0 per 1,000,000 people, 95%CI 3.7 to 9.8) compared to the 9 population-based studies (15.0 per 1,000,000 people, 95%CI 6.2 to 36.4; Figure 5). Finally, there was a general trend for increasing incidence in more recent study periods (Figure 6). There was substantial heterogeneity within the subgroups.

Limiting the analysis to the 11 studies that were deemed higher quality, the cumulative incidence of bullous pemphigoid increased to 13.1 per 1,000,000 people (95%CI 6.0 to 29.5) (Figure 7). Heterogeneity remained high (I^2 99.2%) even within the high-quality studies.

Incidence rate of bullous pemphigoid

Four population-based studies presented the incidence rate of bullous pemphigoid in the UK (3 studies) and USA (1 study). The pooled incidence rate of bullous pemphigoid was 34.2 per 1,000,000 person-years (95%CI 19.2 to 60.7) (Figure 8).

Discussion

Main findings

This is the first study to report the pooled global incidence of bullous pemphigoid. The pooled annual cumulative incidence of bullous pemphigoid was 8.2 per 1,000,000 people (95%CI 4.8 to 13.7) globally. Only Europe and Asia had more than one study conducted, and of these the incidence was higher in Europe. The incidence was also highest adult populations, population-based studies, and in more recent study periods. Limiting the analysis to high-quality studies increased the cumulative incidence to 13.1 per 1,000,000 people (95%CI 6.0 to 29.5), indicating that the pooled value may be underestimated by bias introduced through poor study design. The pooled incidence rate of bullous pemphigoid was 34.2 per 1,000,000 person-years (95%CI 19.2 to 60.7).

Strengths and limitations

The strengths of this review include a thorough search strategy developed by an experienced information specialist, a review of grey literature and reference tracking to ensure complete identification of available evidence. In addition, study screening, data extraction, and quality assessment were conducted independently by two reviewers. Finally, no language restrictions were applied to the search to ensure greater coverage of studies globally.

The review is limited by the inability to provide a pooled incidence estimate from all available evidence. Although we initially aimed to determine the incidence rate, we found that the majority of studies presented data that only allowed the calculation of the cumulative incidence. Although described as “rates” within the publications, the studies did not follow-up study participants individually to determine time at risk, which is necessary for the determination of incidence rates. Subgroup and sensitivity analyses could therefore only be conducted for the cumulative incidence. Additionally, high heterogeneity was found across all pooled estimates, and could not be fully explained by subgroup and sensitivity analyses. The subgroup analyses conducted may be subject to ecological fallacy. For example, the finding that the incidence is higher in studies limited adults cannot be wholly attributed to an increased incidence in adults, as the difference observed could be due to additional differences in these studies. Also further exploration of the source of

heterogeneity, including examination of the incidence, including separation of data for males and females, were not possible due to the lack of data. Finally, the incidence could not be assessed across all geographical areas globally as published epidemiological studies with this aim were not available.

Comparison

This is the first meta-analysis to provide the pooled cumulative incidence and incidence rate of bullous pemphigoid globally. The variation in the incidence of bullous pemphigoid is widely known and discussed,(10) yet we are the first to quantify this phenomenon. We have identified a pre-print meta-analysis that presented a global incidence rate of 11.38 per 1,000,000 person-years (95%CI 7.73 to 15.62).(17) However, this study pooled all incidence estimates as if they were rates. As we have established, the majority of underlying studies did not determine individual time at risk and thereby could not contribute to the determination of incidence rates. As this meta-analysis did not prospectively register its protocol, we cannot determine whether the decision to pool cumulative incidence and incidence rates was justified prospectively. Methodological differences aside, the meta-analysis corroborated our findings of high heterogeneity and a higher incidence in North America and Europe than in Asia or Africa.

Meaning of the study: possible mechanisms and implications

Although all studies indicate that the incidence of bullous pemphigoid was very low, substantial heterogeneity was observed. Subgrouping by factors such as the geographical region and age of the population provided minor decreases in the heterogeneity, although levels remained high across all subgroups. This may indicate that the incidence of bullous pemphigoid varies considerably across different populations. However, the heterogeneity likely also reflects the differences between studies with regards to how the cases of bullous pemphigoid were identified, complete capture of cases, and methods for determining the population at risk (census data versus electronic health records).

The incidence was high in Europe, potentially due to long life expectancy. The incidence of bullous pemphigoid is much higher in older people, and the larger proportion of old adults in these populations secondary to higher life expectancies may result in higher overall incidence.(18) This likely also explains why we observed a higher incidence in the studies that focused only on adults as bullous pemphigoid generally does not affect children. Geographic variations may also be due to differences in the differential prevalence of risk factors for bullous pemphigoid in the underlying population. For example, the prevalence of Parkinson's disease in older age is significantly lower in Asia than in Europe and North America.(19) We also observed a higher incidence of bullous pemphigoid in population-based studies, potentially because the hospital-based studies did not capture milder cases that were not treated in hospital or because cases may have been admitted to other hospitals or clinics in the region. In addition, we found a general trend of increasing incidence in more recent study periods. This may represent a true increase in the incidence of the disease, but likely also reflects improved diagnostic methods and greater awareness of the disease that ensures that more cases are captured.

Finally, we found that the incidence was higher when excluding studies that had scored poorly across the quality domains covering selection bias and incomplete outcome ascertainment. Half the studies included in the overall estimate were unlikely to have successfully captured all new cases of bullous pemphigoid. It is therefore likely that the overall pooled incidence is an underestimate of the true incidence of bullous pemphigoid and we can expect that the global burden of disease is higher than presented.

Future research

More high-quality research is required to better understand the incidence of bullous pemphigoid. Determining the incidence rate of a rare disease such as bullous pemphigoid poses methodological difficulties. Access to electronic health records allows the ascertainment of person-time at risk, however, it is reliant on the pre-existing utilisation of such records and access to these data for research purposes. Better disease registration of rare diseases, such as bullous pemphigoid, within these sources would facilitate research in the future. However, widespread access to electronic health records is not available for research purposes in many regions globally, and as such it is necessary to determine the cumulative incidence instead. Great attention needs to be paid to the design of such studies to ensure complete capture of cases within the population at risk.

Conclusions

The incidence of bullous pemphigoid varies globally, is generally low, but appears to be increasing with time. However, the burden of disease is likely underestimated due to biases introduced from the study design of the underlying studies. Great attention needs to be paid to the design of future studies to ensure complete capture of cases within the population at risk. Finally, increased awareness of the differences between cumulative incidence and incidence rates are required to drive the conduct of high-quality epidemiological studies in bullous pemphigoid.

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Table 1. Characteristics of the 26 cohort studies included in the meta-analyses of the incidence of bullous pemphigoid globally

Study	Study design	Country	Duration	Age group	Setting	Investigations	Incidence measure	N incident cases	Denominator (N, unless specified)	JBI quality assessment**							
										1	2	3	4	5	6	7	8
Adam 1992 (20)	Unclear*	Malaysia	15 years	All ages	Hospital	DIF	Cumulative	51	2,858,320	U	U	N	Y	Y	Y	Y	N
Bernard 1995 (21)	Prospective	France	2,9 years, 1988-1992	All ages	Population	DIF, IIF	Cumulative	69	3,550,000	U	Y	N	Y	Y	Y	Y	N
Zillikens 1995 (22)	Unclear*	Germany	5.4 years, 1989-1994	All ages	Hospital	DIF, IIF	Cumulative	61	1,700,000	Y	Y	N	Y	N	Y	Y	N
Jung 1999 (23)	Retrospective	Germany	9 years, 1989-1997	All ages	Hospital	Histology, DIF, IIF	Cumulative	94	1,700,000	Y	U	N	Y	Y	Y	Y	Y
Wong 2002 (24)	Retrospective	Singapore	2 years, 1998-1999	All ages	Hospital	DIF, IIF	Cumulative	59	3,860,000	Y	Y	N	Y	N	Y	Y	N
Gudi 2004 (25)	Retrospective	Scotland	11 years, 1991-2001	All ages	Population	Histology, DIF, IIF	Cumulative	83	538,705	Y	Y	N	Y	Y	Y	Y	N
Nanda 2004 (26)	Retrospective	Kuwait	11.5 years, 1991-2002	All ages	Hospital	Histology, DIF, IIF, (ELISA)	Cumulative	27	1,140,000	U	U	N	Y	U	Y	Y	N
Nanda 2006 (27)	Retrospective	Kuwait	14 years, 1991-2005	All ages	Hospital	Histology, DIF, IIF	Cumulative	43	1,200,000	U	U	N	Y	U	Y	Y	N
Chan 2006 (28)	Retrospective	Hong-Kong	7 years, 1998-2004	All ages	Hospital	Histology, DIF, IIF	Cumulative	75	689,000	N	U	N	Y	N	Y	Y	N
Serwin 2007 (29)	Prospective & retrospective	Poland	5.5 years, 2000-2006	All ages	Hospital	Histology, DIF, IIF	Cumulative	27	1,202,425	Y	Y	N	Y	Y	Y	Y	N
Bernard 2007 (14)	Prospective	France	6 years, 2000-2005	All ages	Population	DIF	Cumulative	160	1,532,567	Y	Y	Y	N	Y	Y	Y	N
Cordel 2009 (13)	Retrospective	Guadeloupe	2.75 years, 2006-2009	All ages	Population	Histology, DIF	Cumulative	26	405,500	Y	Y	N	N	Y	Y	Y	Y
Bertram 2009 (15)	Prospective	Germany	1.5 years, 2001-2002	Adult (20+)	Hospital	DIF, IIF, ELISA	Cumulative	27	1,340,912	Y	Y	N	Y	Y	Y	Y	N
Langan 2008 (30)	Retrospective	UK	11 years, 1996-2006	Adult (20+)	Population	Code-based	Rate	869	20,292,201 py	Y	Y	Y	Y	Y	U	U	Y
Marazza 2009 (31)	Prospective	Switzerland	2 years, 2001-2002	All ages	Population	Histology, DIF, IIF, ELISA	Cumulative	140	5,808,100	Y	Y	Y	Y	Y	Y	Y	Y
Baican 2010 (32)	Prospective	Romania	6.75 years, 2001-2007	All ages	Unclear	Histology, IIF, ELISA	Cumulative	40	2,738,461	Y	U	N	Y	U	Y	Y	Y

Joly 2012 (33)	Retrospective	France	6 years, 2000-2005	All ages	Population	Histology, DIF	Cumulative	502	3,857,972	Y	Y	Y	Y	Y	Y	Y	Y
Brick 2014 (16)	Retrospective	USA	50 years, 1960-2009	All ages	Population	Histology, DIF, IIF, ELISA	Rate	87	3,625,000 py	Y	Y	N	Y	Y	Y	N	Y
Försti 2014 (34)	Retrospective	Finland	25 years, 1985-2009	All ages	Population	Code-based plus histology, DIF, IIF, ELISA	Rate	159	9,350,000 py	Y	Y	Y	Y	Y	Y	Y	Y
Serwin 2014 (35)	Retrospective	Poland	14 years, 1999-2012	All ages	Hospital	Histology, DIF, IIF	Cumulative	122	1,222,700	Y	Y	Y	Y	U	Y	Y	Y
Milinković 2016 (36)	Retrospective	Serbia	20 years, 1991-2010	All ages	Hospital	Histology, DIF, IIF	Cumulative	471	5,500,000	Y	Y	Y	N	U	Y	Y	N
Loget 2017 (41)	Prospective	France	6 years, 2010-2015	All ages	Hospital	DIF, IIF	Cumulative	538	3,900,000	Y	U	Y	Y	N	Y	Y	Y
Thorslund 2017 (37)	Retrospective	Sweden	8 years, 2005-2012	Adult (20+)	Population	Code-based + histology, immunology	Cumulative	3,761	7,122,447	Y	Y	Y	Y	Y	Y	Y	Y
Kridin 2018 (38)	Retrospective	Israel	16 years, 2000-2015	All ages	Population	Histology, DIF, IIF, ELISA	Cumulative	287	1,570,000	Y	Y	Y	Y	Y	Y	Y	Y
Lim 2019 (39)	Retrospective	Korea	5 years, 2011-2015	All ages	Population	Code-based	Cumulative	1,308	51,463,569	Y	Y	U	N	Y	U	U	N
Madu 2019 (40)	Retrospective	Botswana	7.3 years, 2008-2015	All ages	Hospital	Histology	Cumulative	35	1,300,652	Y	Y	N	U	N	U	Y	N
Persson 2020 (1)	Retrospective	England	20 years, 1998-2017	Adult (18+)	Population	Code-based	Rate	2,658	34,825,210 py	Y	U	Y	Y	Y	Y	U	Y

* Publication did not state whether study was prospective or retrospective
** JBI quality assessment score (Y, yes; U, unclear; N, no) for the following domains
1. Was the sample frame appropriate to address the target population?
2. Were the study participants sampled in an appropriate way?
3. Was the same size adequate?
4. Were the study subjects and setting described in detail?
5. Was the data analysis conducted with sufficient coverage of the identified sample?
6. Were valid methods used for the identification of the condition?
7. Was the condition measured in a standard, reliable way for all participants?
8. Was there appropriate statistical analysis?

DIF, direct immunofluorescence; ELISA, enzyme linked immunosorbent assay; IIF, indirect immunofluorescence; py, person-years