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ORIGINAL ARTICLE

# Epidemiology of inherited epidermolysis bullosa in Germany

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## Abstract

**Background:** Epidermolysis bullosa (EB) is a rare genetic disorder manifesting with skin and mucosal membrane blistering in different degrees of severity.

**Objective:** Epidemiological data from different countries have been published, but none are available from Germany.

**Methods:** In this population-based cross-sectional study, people living with EB in Germany were identified using the following sources: academic hospitals, diagnostic laboratories and patient organization.

**Results:** Our study indicates an overall EB incidence of 45 per million live births in Germany. With 14.23 per million live births for junctional EB, the incidence is higher than in other countries, possibly reflecting the availability of early molecular genetic diagnostics in severely affected neonates. Dystrophic EB was assessed at 15.58 cases

per million live births. The relatively low incidence found for EB simplex, 14.93 per million live births, could be explained by late or missed diagnosis, but also by 33% of cases remaining not otherwise specified. Using log-linear models, we estimated a prevalence of 54 per million for all EB types, 2.44 for junctional EB, 12.16 for dystrophic EB and 28.44 per million for EB simplex. These figures are comparable to previously reported data from other countries.

**Conclusions:** Altogether, there are at least 2000 patients with EB in the German population. These results should support national policies and pharmaceutical companies in decision-making, allow more precise planning of drug development and clinical trials, and aid patient advocacy groups in their effort to improve quality of life of people with this orphan disease.

## INTRODUCTION

Inherited epidermolysis bullosa (EB) comprises a spectrum of rare genetic disorders that manifest with mechanically induced blistering of the skin and mucosal membranes.[1,2] Pathogenic variants in 16 distinct genes result in four main classical EB types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler EB (KEB). EB types are subclassified according to their clinical severity (severe, intermediate and localized, or with extracutaneous involvement) and the underlying molecular defect in more than 30 subtypes. Besides this classical EB, other disorders with skin fragility previously counted among EB have been defined as separate entities in the most recent classification, including peeling skin disorders, erosive and hyperkeratotic disorders.[1]

Infants with EB who are born with widespread (generalized) skin blistering and/or show a severe course of the disease are diagnosed early in life. They require multidisciplinary care, often suffer from extracutaneous manifestations, and later experience high psychological and socioeconomic disease burden.[3,4] Mild skin fragility leading to localized blistering on hands and feet may start later in life, but can likewise cause limitations in every-day and professional activities, and reduction of the quality of life.[5] This latter group of EB patients likely remains underreported, either because it is not diagnosed, diagnosed later in life, or because it requires little or no medical care at all.

Mortality related to EB occurs in the most severe subtypes at different ages. It is common in early infancy in cases of severe JEB and EB with pyloric atresia.[6,7] In severe recessive DEB (RDEB), mortality related to EB is rare during childhood, but common in young adulthood.[8] Individuals with localized EB subtypes have a normal life expectancy, and mortality due to EB is unusual.

EB incidence and prevalence reported from other countries vary significantly (Table 1).[8–15] So far, precise epidemiologic data on EB in Germany were lacking, and calculation is hindered by the absence of a national healthcare registry. The number of patients with EB in Germany was roughly estimated at 2000[16] with a high rate of underreported mild cases although. Patient numbers reported by dermatological and paediatric departments were even lower than this.[17]

With the aim of obtaining more precise epidemiological numbers, we performed a population-based cross-sectional study to determine the clinical and genetic spectrum, the incidence, point prevalence and mortality of EB in Germany.

## MATERIAL AND METHODS

### Study population and collected data

In this population-based cross-sectional study, patients suffering from EB in Germany were identified using the following sources: (1) the University Medical Center Freiburg (EB center in the Department of Dermatology and Institute of Human Genetics), as the main provider of EB care and diagnostics in Germany,[17,18] named FREIBURG in the following; (2) Departments of Dermatology or Paediatrics in Berlin, Cologne, Dresden, Erlangen, Göttingen, Hamburg, Kiel, Lübeck, Munich, Münster, and Rostock and a genetic practice in Stuttgart (genetikum® Stuttgart), named LOCAL in the following; (3) the patients' organization "Interessengemeinschaft Epidermolysis bullosa (IEB) e.V. Debra Deutschland", named IEB in the following. Further dermatological departments were invited to participate but declined due to local institutional review board (IRB) constraints. Data were collected from 01.10.2020 to 15.05.2021. This project was approved by the Ethics committee of the University of Freiburg (vote nr. 585/19) and, where applicable, additionally by the local IRBs of participating centres.

Data included patient initials, month and year of birth, postal code (first two digits), type and subtype of EB, affected gene, mode of inheritance, further affected family members and ethnic background. It was recorded whether diagnosis had been confirmed by genetic testing. If patients were known to have deceased, this was recorded with date where available. If the patient had been in contact with one of the participating physicians within the past 2 years, EB-related death was deemed unlikely, and the patient marked "alive"

**TABLE 1** Overview of the epidemiology of EB in Germany and worldwide

| Country | EB (all types) | | EBS | | JEB | | DEB | |
|---|---|---|---|---|---|---|---|---|
| | Incidence (per million live births) | Prevalence (per million) | Incidence (per million live births) | Prevalence (per million) | Incidence (per million live births) | Prevalence (per million) | Incidence (per million live births) | Prevalence (per million) |
| Europe | | | | | | | | |
| Germany (this study) | **45** | **54.03** | **14.9** | **28.44** | **14.23** | **2.44** | **15.58** | **12.16** |
| England and Wales[10] | 67.8 | 34.8 | 32.5 | 17 | 8.9 | 1 | 26.1 | 10 |
| Scotland[11] | NA | 49 | 0.43 | 28.6 | 0.05 | 0.4 | 0.2 | 20.4 |
| The Netherlands[8] | 41.3 | 22.4 | 17.5 | 11.9 | 9.3 | 2.1 | 14.1 | 8.3 |
| Northern Ireland[12] | 1.4 | 32 | NA | 28 | NA | 0.7 | NA | 3 |
| Norway[14] | | 54 | 1:580,000 | 23 | 5–7 | 2 | 1:180,000 | 1.4 |
| Romania[32] | 25 | 4.42 | NA | NA | NA | NA | NA | NA |
| Slovenia[33] | NA | 20 | NA | NA | NA | NA | NA | NA |
| Spain[22] | NA | NA | NA | NA | NA | NA | NA | 15.3 |
| North America | | | | | | | | |
| USA[9,26] | 19.5 | 11.1 | 7.87 | 6 | 2.68 | 0.49 | 3.05[a]/95 | 1.39[a] |
| Asia | | | | | | | | |
| Iran[34] | NA | 6.72 | NA | NA | NA | NA | NA | NA |
| Japan[15] | NA | 4.03–5.16 | NA | 1.54 | NA | 0.34 | NA | 1.60[a] |
| Australia and Oceania | | | | | | | | |
| Australia[13] | NA | 10.3 | NA | 5.8 | NA | 0.7 | NA | 3.8 |
| New Zealand[35] | NA | 19.5 | NA | 10.4 | NA | 0.9 | NA | 8.6 |

Values reported in the present study (in bold).

Abbreviation: DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EBS, EB simplex; JEB, junctional epidermolysis bullosa; NA, not available.

[a] RDEB, recessive dystrophic EB.

in the register. We considered death in patients >2 years suffering from the early-lethal subtype JEB severe and lost to follow-up as probable. Patients living outside Germany were excluded.

## Diagnostic of EB

Epidermolysis bullosa was diagnosed clinically based on typical manifestations easily recognizable in older children and adults. An experienced paediatric dermatologist can clinically distinguish localized EBS, KEB, and severe forms of EBS, JEB and DEB, as well as some intermediate and other localized EB subtypes beyond infancy. The subclassification of the latter two categories requires expert knowledge. Some patients suspected of having EB demonstrated unspecific manifestations and late onset of skin fragility. They were often lost to follow-up, indicating that other differential diagnoses were probably established in the meantime. In neonates and infants, blistering and congenital focal absence of the skin represent key clinical features of EB, but they rarely allow classification into EB types and subtypes. Laboratory diagnostics of EB is mainly based on genetic testing, either of the candidate gene, or of an EB-gene-panel. Immunofluorescence mapping is a rapid method particularly used in neonates, because it can distinguish severe EB subtypes based on the absence of immunoreactivity of corresponding proteins.[19,20] This diagnostic method must always be complemented by genetic testing. For our evaluation, we assumed that affected family members had the familial pathogenic variants even if they were not available for testing.

In the present dataset, we distinguished the following categories: (1) patients with clinical and/or molecular genetic diagnosis that could be classified according to the current classification system[1]; (2) patients with skin fragility in whom genetic diagnostics was performed but did not identify pathogenic variants in candidate or in all EB genes; (3) patients in whom EB was "suspected", but not confirmed, neither based on clinical, nor on molecular genetic criteria because of lack of information or loss to follow-up.

## Incidence and prevalence

Using the most comprehensive list from FREIBURG as a template, we compared and matched data from LOCAL and IEB lists and applied the capture–recapture method.[21,22] We used the resulting estimated total numbers to calculate incidence and prevalence of EB and its subtypes by using demographic statistics for Germany available from the German Federal Statistical Office (www.destatis.de). Patients without a clear diagnosis ("suspected") were not considered. We used the information on patients with EB born between 2003 and 2019 to determine the incidence of the disease. We estimated EB prevalence based on three sources (FREIBURG, LOCAL and IEB) and used log-linear models to model the joint distribution of the frequencies with which patients are captured by one or multiple sources. Patients were matched based on the initials of first and last name as well as date of birth, considering the month and the year. As the frequency of the patients not captured by any list is unknown, leading to an underestimation, log-linear models allow for estimating this frequency based on the frequencies with which patients show up in the sources. In the estimation of prevalence, heterogeneity (h) is defined as different probabilities with which different patients are captured. Different approaches using random effects have been proposed to address heterogeneity. Of these, we used Darrochs[23,24] method, where the random effect follows a mixed normal distribution, as it is the most anticonservative correction, resulting in higher estimates, albeit larger error of estimation. Capture probability can also differ between capture occasions (t), that is, the three sources, and these differences were addressed in the modelling as well. Estimation of EB prevalence with log-linear models was conducted with Rcapture.[25] We fit multiple models which allow for capture heterogeneity between patients and occasions, specifically Mth models, considered different interactions between the sources, that is, investigated different models, and selected the best non-saturated model, that is, a model with non-zero standard error based on the Bayesian information criterion. As no clear vitality status was available for many patients, we included these patients in the prevalence analysis since a missing vitality status was considered more likely indicating an alive patient than his/her death.

Graphical representation was done with GraphPrism version 9 XML and basic plot functionality of R. Maps of Germany were retrieved from the GADM database (www.gadm.org) and imported in R via the rgdal package (v. 1.5-23).

# RESULTS

## Landscape of EB in Germany

This cross-sectional study of people with EB in Germany yielded 2092 entries: 1581 from the University Medical Center Freiburg, 318 from other hospitals or diagnostic centers, and 193 from the patients' organization. For 91 individuals, no date of birth was available which prevented matching; these individuals were discarded from the analyses, leaving 2001 entries. After matching and removal of duplicates, 1779 people with EB were identified.

We captured 700 cases with EBS, 305 with JEB, 578 with DEB and 9 with KEB (Figure 1a). In 108 cases, no information on clinical or molecular aspects was available, hindering precise classification (designated as "EB suspected"). The remaining had other genetic disorders with skin fragility, of which the acral peeling skin syndrome (APSS) was most common (76 cases).

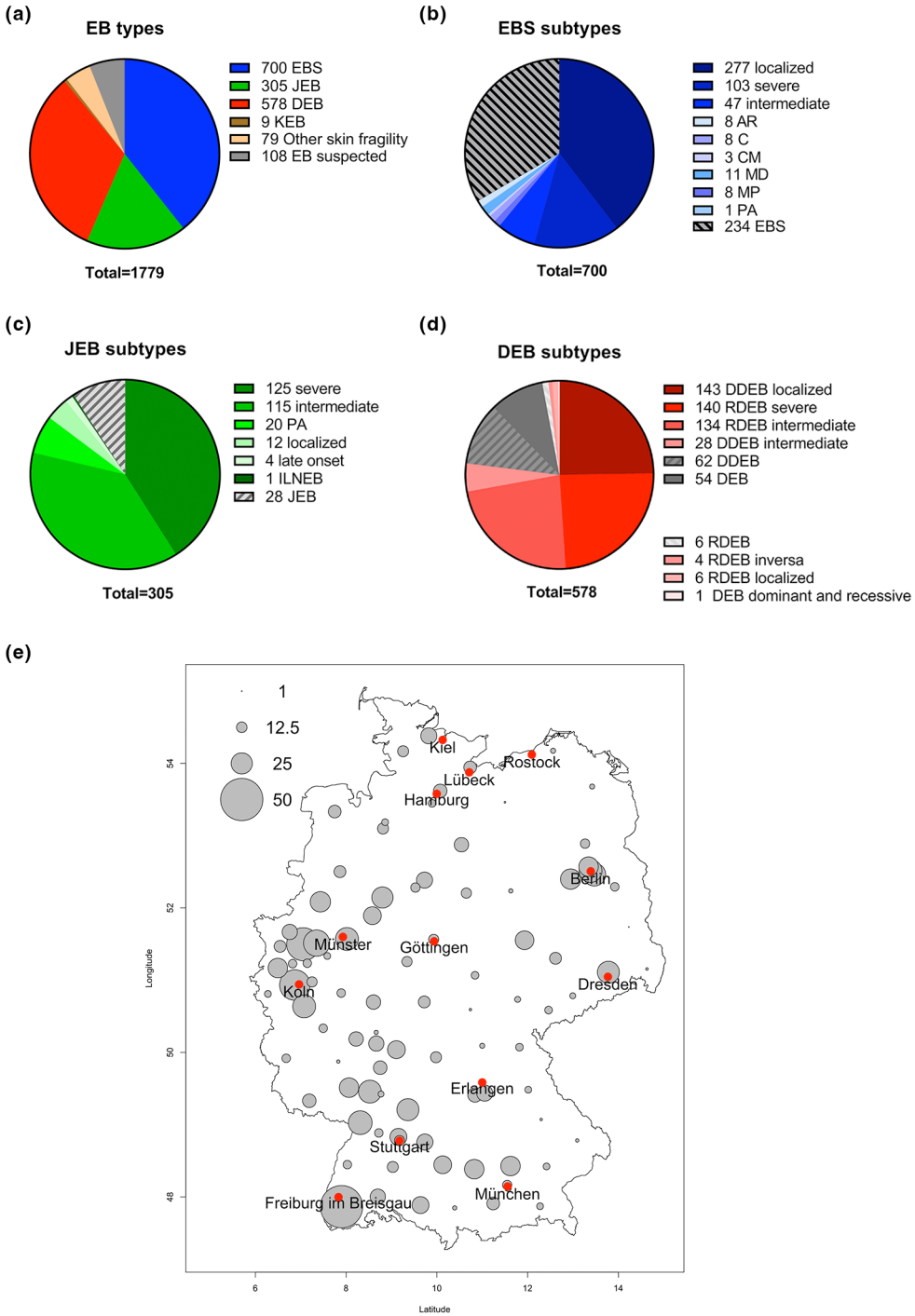


**FIGURE 1** EB in Germany. (a) Number of patients with epidermolysis bullosa (EB) and other genetic skin fragility disorders. (b) Number of patients with EBS subtypes, (c) JEB subtypes, (d) DEB subtypes. (e) Geographic distribution of people living with EB in Germany and location of dermatology departments participating in the study. The size of the circle corresponds to the number of people living with EB. AR, autosomal recessive; C, with cardiomyopathy; CM circinate erythema; DDEB, dominant dystrophic epidermolysis bullosa; DEB, dystrophic epidermolysis bullosa; EBS, EB simplex; ILNEB, interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa; JEB, junctional epidermolysis bullosa; MD, muscular dystrophy; MP, mottled pigmentation; PA, pyloric atresia; RDEB, recessive dystrophic epidermolysis bullosa. Shaded portions denote patients who could not be further subclassified.

Whenever information was available, EB types were further classified into subtypes. The most common EBS subtypes were localized (39.5%) and severe (14.7%) EBS (Figure 1b). The majority of JEB cases was subclassified as severe (40.9%) or intermediate (37.7%) (Figure 1c). Among the DEB cases, 40.3% had dominant DEB (DDEB) and 48.4% had recessive DEB (RDEB), with localized DDEB (24.7%), severe RDEB (24.2%) and intermediate RDEB (23.2%) being

the most common subtypes (Figure 1d). For each EB type, there were cases for which no precise information on phenotype, family history or disease-causing genetic variants was available and thus were not subclassified. EBS was the subtype for which the highest number of patients (33.4%) lacked a subclassification. Using regression models for count data, we did not observe a significant change in the incidence for severe cases over time.

The ethnic origin was German in 64.2% (1142 cases), followed by Middle East in 16.40% (291), and small numbers of cases originating from other geographic regions worldwide. The overall gender distribution female:male was almost equal (50.3%:49.7%), and ranged from 44.4% (KEB) to 64.8% for females ("EB suspected"). The median age in years of those with confirmed vital status was 19.0 for EBS range (1–80 years), 1.1 for JEB (range 0.4 months – 87.2 years), 19.4 for DEB (range 1.2–76.3) and 19.8 for KEB (range 13.9–35 years).

People with EB captured in our study were based all over Germany (Figure 1e). The highest numbers were observed in southern and western regions, the most populated regions of the country. The median distance from a centre with EB expertise ranged from few kilometres to about 60 km, and the median distance to Freiburg was about 400 km.

## Genetic basis of EB in Germany

Genetic testing was performed and identified the molecular basis of EB in 1178 (66.2%) cases (including affected family members). In 128 (10.9%) of the cases, no pathogenic variant was found in the candidate gene or in all EB genes. EBS and DEB can be inherited by either autosomal dominant or recessive traits, and EBS and JEB are genetically heterogeneous. Autosomal dominant inheritance was present in 421 (66%), autosomal recessive in 31 (5%) cases with EBS, while the remainder were either single cases or the family history was not known. The distribution of pathogenic variants of the patients throughout EBS genes was: 44.7% *KRT5*, 44.2% *KRT14*, 8.5% *PLEC*, 1.9% *KLHL24*, 0.5% *EXPH5*, and 0.2% *DST* (Figure 2a). The most commonly affected gene in JEB was *LAMB3* in 37.9%, followed by *COL17A1* in 29.7%, *LAMA3* in 16.0%, *ITGB4* in 8.2% and *LAMC2* in 6.9% of cases, while *ITGA6* and *ITGA3* mutations were found in two and one single cases, respectively (Figure 2b). In DEB and KEB, all pathogenic variants were in the corresponding genes, *COL7A1* and *FERMT1*, respectively. In DEB, the inheritance pattern was autosomal dominant in 222, recessive in 275, dominant and recessive in one case, and not available in 53 cases.

## Estimation of incidence, prevalence and mortality of EB in the German cohort

The overall mean incidence of EB was calculated at 45.09 per 1,000,000, or 1 in 22,178 live births per year. The mean incidence for EBS is 14.93 (1:66,979), for JEB 14.23 (1:70,274), for DEB 15.58 (1:64,184) and for KEB 0.35 (1:2,857,143) in 1,000,000 live births (Figure 3a).

We estimated the prevalence for all EB subtypes combined at 54.02 per million (4497.1 95% CI 2935.8–7526.9), for DEB at 12.16 per million (1012.1 95% CI 721.9–1688), for JEB at 2.44 per million (202.7 95% CI 159.7–328.9) and for EBS at 28.44 per million (2367.6 95% CI 1286–5141.9). The reported numbers are estimated based on Darroch's[23,24] method to reflect the high capture heterogeneity, in order to avoid underreporting of the EB rates.

Information on vital status was available from 741 patients with EB, although the relationship of death to EB, or the precise date were not always clear. As expected, patients with JEB had the highest mortality rate of 68.7% (145 cases of those for which the information was available) and the youngest age at death. Second highest mortality of 15.9% was found in the DEB group (41 cases of those for which the information was available; Figure 3b). For severe JEB, the median age of death was 3.96 months, range 0.4 months–2.5 years and for severe DEB median age of death was 23.8 years, range 2.6–51.9 years (Figure 3c).

# DISCUSSION

The evaluation of the landscape of EB in Germany is complex and challenging due to the broad clinical spectrum of EB itself,

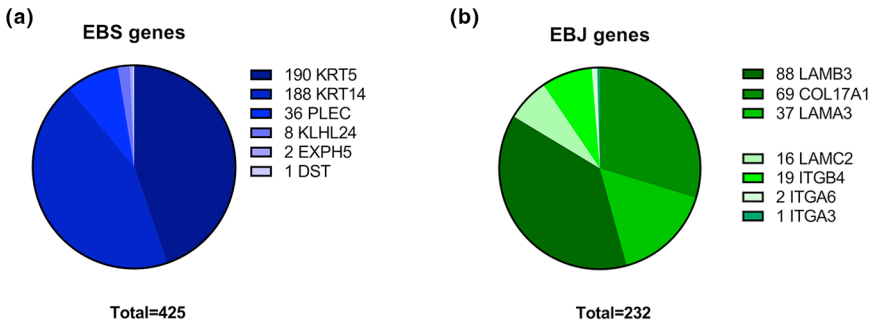


**FIGURE 2** Genetic basis of epidermolysis bullosa in Germany. (a) Genetic heterogeneity of EB simplex. (b) Genetic heterogeneity of junctional EB.

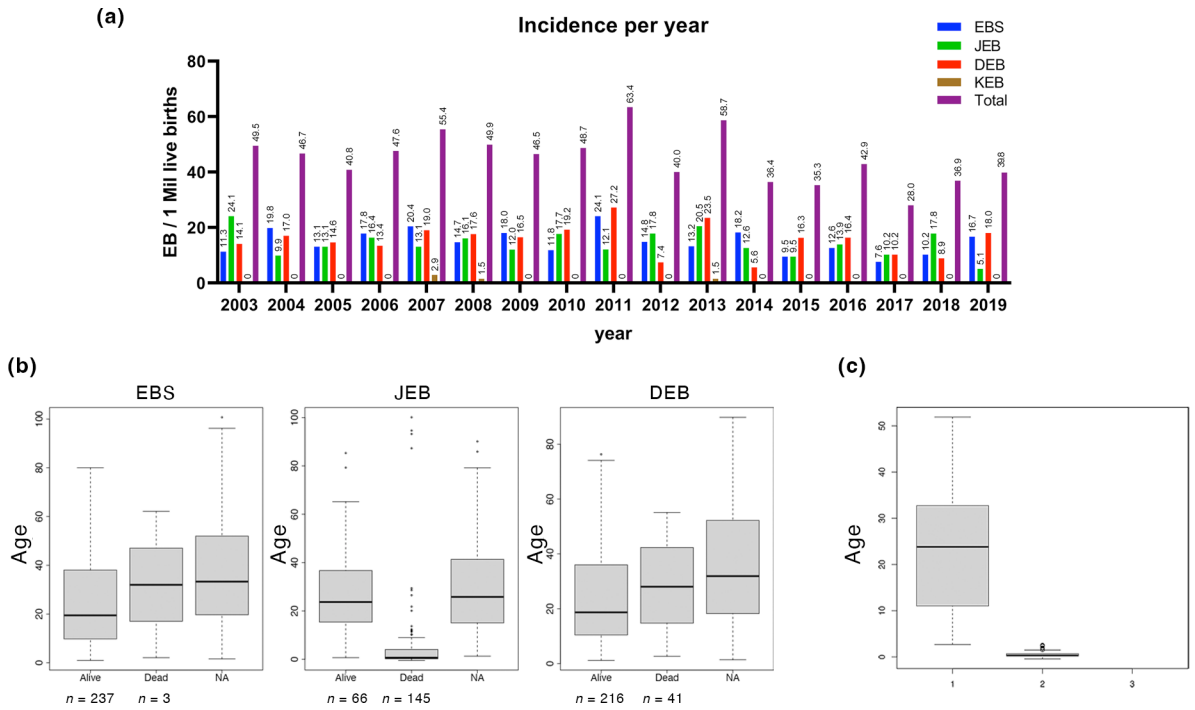


**FIGURE 3** Incidence and mortality of epidermolysis bullosa (EB) in Germany. (a) Incidence of EB and main EB types per year between 2003 and 2019. (b). The box plot graphs (median, 1st and 3rd Q, min, max) represent the age distribution related to vital status, alive or death, for each main EB type. NA, information on vital status was not available; N, number of cases. The age is at April 1st 2022 for alive and NA patients, and at time of death for deceased patients. (c) The box plot graph represents the distribution of the age at death in severe EB subtypes: 1, severe recessive dystrophic EB, severe junctional EB; 3, severe EB simplex.

but also due to several structural factors,[17] and to the lack of a national healthcare registry. In the past 20 years, clinical care, molecular genetic diagnostics, research and awareness about EB have been promoted in Germany mainly through the effort of clinicians and researchers who focused on EB, but also through the patient organization IEB, and more recently by the support of national and European rare disease programs.

Against this background, collecting the epidemiologic data on EB implied a joint effort of academic hospitals, diagnostic laboratories and the patient organization. Data protection issues were a limiting factor, hindering some centres known to care for a relevant number of EB patients to participate. An alternative data-source would have been databases of health insurances. However, these are not readily available and bear additional challenges, such as a dual system of private and state insurances, a high number of companies, and an inaccurate depiction of EB types in ICD-10-encodings. The large number of cases that remained "suspected" or not otherwise classified mirrors the failure and lack of systematic coordination of the national healthcare system for rare diseases. Indeed, 6% of all collected cases were lost from follow-up and the diagnosis of EB was not validated. In 33% of the patients considered to have EBS, no further characterization of the disease was possible. More precise and complete data were obtained on JEB and DEB, the EB types that mainly require molecular diagnostics and medical care in specialized centres.

Our study indicates an EB incidence of 45 per million live births in Germany, which is close to the Dutch incidence of 41.3[8] and lower than the United Kingdom (UK) incidence of 67.8.[10] With 14.23 per million live births, JEB reaches higher levels in Germany than in the aforementioned countries (Table 1), possibly reflecting differences in the genetic pool of Germany or other sources of diagnostic bias. DEB incidence, with 15.58 cases per million live births, was comparable with the figures published from the Netherlands,[8] but lower than in the UK[10] and the modelled incidences for the USA.[26] This could be explained by geographical, but also methodological factors. The relatively low incidence found for EBS (14.93 per million live births) is likely related to the fact that it is underreported and the diagnosis is often established later in life.

Even though a degree of uncertainty in incidence numbers remains, we are confident that our data are reliable, as they are derived from the main EB diagnostic laboratories. Calculations of point prevalence and mortality for EB and its subtypes are subject to more uncertainty, as Germany lacks a national health register that provides such data in other countries, such as Denmark[27] or the UK.[10] To compensate for this limitation, the capture–recapture model in combination with log-linear models and correction with random effects represents a solid epidemiologic model and was also applied in rare disease epidemiology studies in other countries.[22,28,29] The prevalence estimates derived from our data

(54 per million for all EB types, 28.44 per million for EBS, 2.44 per million for JEB and 12.16 per million for DEB) should be understood as upper limits to account for presumptive high rate of unreported or undiagnosed cases, and they compare to previously reported data from other countries (Table 1).

Our mortality data for JEB resembles the numbers found in the literature.[8] For DEB, the mean age at death of 28.03 years in our cohort is in line with a previous report from Australia,[13] but higher than in the Netherlands.[8] Our results could be due to the fact that the main German EB centre manages mainly adults, or it could be biased towards a false-high age, as they rely on the feedback of families to report on the decease of their relatives, or on reports of physicians outsides of dermatology.

To put the figures into context, we are dealing with maximum numbers of about 2400 individuals with EBS, 200 with JEB and 1000 with DEB within a population of 82 million in Germany. These patients and their families are often confronted with very high administrative hurdles to obtain support, such as bandages, antiseptics or wheelchairs, or to be assisted in their struggle to obtain an appropriate working place. Although no cure for EB is available to date, new therapeutics are currently evaluated in clinical trials.[30,31] To fulfil this way, pharmaceutical companies and regulatory authorities require precise information on the numbers of EB patients and their needs.

As is characteristic for rare diseases, the number of affected persons is very low compared with the country's total population, and the options for optimal disease management reflect the quality of public health and social system. Future efforts should place the needs of individuals with rare diseases such as EB into the centre of the national and international policies. These efforts are supported by the European Network for Rare Skin disease (ERN-Skin, https://ern-skin.eu/) and the patient organization Debra International (https://www.debra-international.org/), which are jointly working on improving registries and on supporting local infrastructures, giving hope for ongoing improvements for people living with EB.

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## CONFLICT OF INTEREST

None to declare.

## DATA AVAILABILITY STATEMENT

Data are available on request due to privacy/ethical restrictions.

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