

# The Epidemiology of Guillain-Barré Syndrome Worldwide

## A Systematic Literature Review

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### Key Words

Epidemiology · Guillain-Barré syndrome · Incidence · Systematic review

### Abstract

**Background:** This systematic literature review of the epidemiology of Guillain-Barré syndrome (GBS) identifies trends in incidence rates by age, study method and cause of disease. It is important to have a reliable estimate of incidence to determine and investigate any changes: no previous systematic reviews of GBS have been found. **Methods:** After critical assessment of the reliability of the reported data, incidence rates were extracted from all relevant papers published between 1980 and 2008, identified through searches of Medline, Embase and Science Direct. **Results:** Sixty-three papers were included in this review; these studies were prospective, retrospective reviews of medical records or retrospective database studies. Ten studies reported on the incidence in children (0–15 years old), and found the annual incidence to be between 0.34 and 1.34/100,000. Most studies investigated populations in Europe and North America and reported similar annual incidence rates, i.e. between 0.84 and 1.91/100,000. A decrease in incidence over the time between the 1980s and 1990s was found. Up to 70% of cases of GBS were caused by antecedent infections. **Conclusions:** Our best estimate of the overall incidence of GBS

was between 1.1/100,000/year and 1.8/100,000/year. The incidence of GBS increased with age after 50 years from 1.7/100,000/year to 3.3/100,000/year.

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### Introduction

Guillain-Barré syndrome (GBS) is a peripheral neuropathy with acute onset, and characterised by rapidly developing motor weakness [1–3]. The disease is thought to be autoimmune and triggered by a preceding infection in two thirds of cases, most frequently respiratory or gastrointestinal infections [3, 4]. Possible links between vaccinations and the occurrence of cases of GBS have been proposed, although the evidence for this link is not strong. An increase in GBS incidence of about 1 case per million above background incidence has been associated with the 1976 New Jersey swine influenza vaccination programme, and of about 1 case per thousand associated with rabies vaccinations [3, 5].

GBS can be divided into at least 4 main subtypes of disease: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the axonal subtypes, i.e. acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome, the main symptoms of which are oculomotor

dysfunction, ataxia and areflexia. In North America and Europe, around 5% of patients with GBS have the axonal subtypes, whereas in Central and South America, Japan and China axonal subtypes account for 30–47% of cases [5]; Miller-Fisher syndrome has been found to account for around 5% of cases of GBS [3, 5]. Standard criteria for the diagnosis of GBS were published in 1978 by a National Institute of Neurological and Communicative Diseases (NINCDS) committee. The criteria include clinical features such as progression, relative symmetry and mild sensory symptoms or signs as well as levels of protein in cerebrospinal fluid, and electrodiagnostic features, such as nerve conduction slowing or blocking [2]. Typical treatment regimens for GBS include plasma exchange and intravenous immunoglobulin. Both treatments are thought to be equally efficacious, but Tsai et al. [6] showed that intravenous immunoglobulin may be cheaper due to patients having fewer complications and requiring a shorter stay in hospital; direct health care costs were estimated to be approximately USD 110,000 in the USA.

Insight into the incidence of disease is important for the identification of trends in relation to patient characteristics, such as age and geographical location, and to determine any changes in incidence following exposure to new environmental factors. Previous reviews evaluating the incidence of GBS have found rates to be between 0.16 and 4.0/100,000/year in individuals of all ages [3, 4] and between 0.5 and 1.5/100,000/year in those under 18 years [7]. The highest rates have been reported in adults, especially those aged over 75 years [4, 5]. Unusually for an autoimmune disease, higher incidence rates have been reported in males than females [4].

To our knowledge, no systematic evaluation of published studies of the incidence of GBS has been published. Previous epidemiological reviews of GBS include: Sladky [7] who reported on incidence of GBS in children, Govoni and Granieri [3] who included studies published between 1978 and 2000 and described overall trends in incidence rates, and Hughes and Rees [4] who tabulated rates from 35 studies published between 1958 and 1996. The objectives of this literature review were to identify reliable estimates of GBS incidence, to compare rates by age and geography, and to examine any changes in incidence over time.

## Method

Searches of the Medline (1980–2008), EMBASE (1980–2008) and Science Direct (1980–2008) databases were carried out using the keywords ‘Guillain-Barré Syndrome’ or ‘polyradiculoneurop-

athy’ and ‘incidence’ or ‘epidemiology’. The 2 disease terms were used because the MeSH term ‘Guillain-Barré syndrome’ was only used in Medline from 1998.

The inclusion criteria were that the studies reported original work, that a reasonable effort had been made by the authors to include all incident cases and that the estimates of population size and person-time contributed during the study period were accurate. When assessing the likelihood of missing incident cases, papers were evaluated as follows: (1) for case-finding studies, did the authors ensure that all of the subjects contributing person-time to the denominator data were available as potential cases and did the authors check all relevant medical records? (2) for all studies, were cases checked to ensure that they were incident and not prevalent? (3) for all studies, did the authors ensure that the cause of GBS was autoimmune and it was not secondary to another disease?

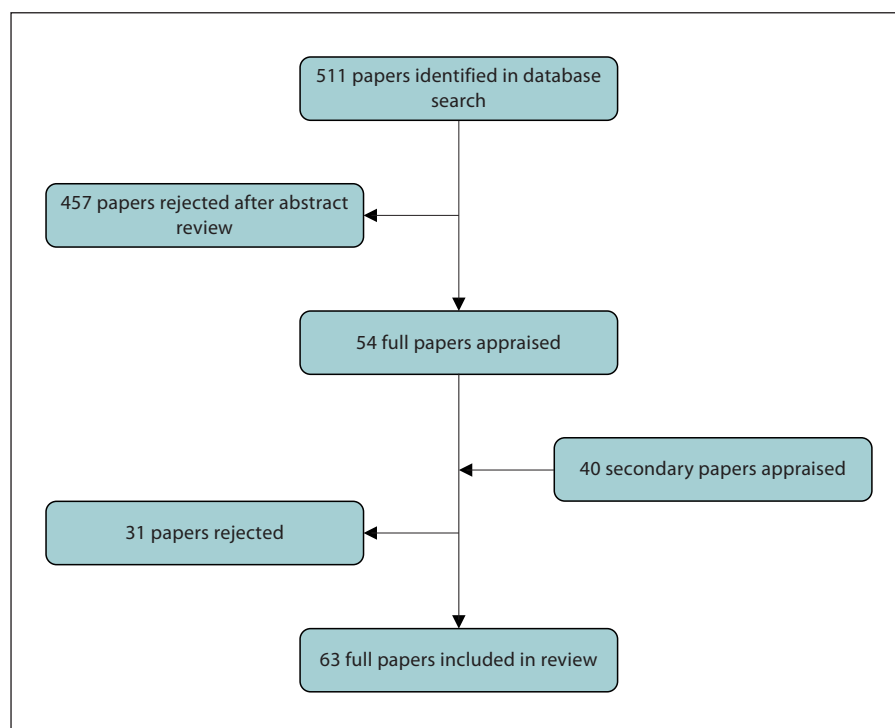
The titles and abstracts (where available) of all of the studies identified by the searches were reviewed by 2 investigators. Studies published in English, French, German, Spanish or Dutch were included. The full text of all potentially relevant papers was appraised and decisions about inclusion of papers were discussed by all authors. Review papers were searched for secondary references reporting on original research; secondary references found from any of the other papers reviewed were also included.

A standard data abstraction form was used to record all details of the papers reviewed (appendix 1). Each study was classified as being at low, medium or high risk of under- or overestimation of reported incidence rates by considering the reliability of numerator and denominator data. For instance, inclusion of prevalent cases or those thought not to be caused by autoimmunity will have led to overestimated rates, as will underestimated denominator data. Conversely, missing cases or an overestimated denominator (e.g. a catchment area from which not all inhabitants had access to hospital services) would be considered to result in underestimated incidence rates. Explanations provided by the papers’ authors as to why incidence rates were as expected or whether they were considered to be an over- or underestimate of the true incidence rate were taken into account in this process. If the extent of likely error was considered to be very great, the study was excluded. To minimise subjectivity, this assessment was agreed between the authors and random checks were performed to ensure consistency. Rates are presented as the number of cases/100,000/year and where sufficient data were given in the paper, rates were checked for accuracy.

## Results

Figure 1 shows the results of the database searches and subsequent filtering of search results. A list of all of the references considered for this study but excluded is available on request from the authors.

Of the 457 papers rejected at the abstract review stage, nearly half did not focus on GBS as the subject of the paper and one fifth did not investigate incidence of GBS; other key reasons for rejecting papers at this stage included those reviewing the disease, case series, those investigating outcomes of vaccinations and those reporting on incidence of a disease other than GBS. Following review



**Fig. 1.** Results from Medline search.

of the full papers, 31 papers were rejected; key reasons for this included papers that reviewed the disease and did not provide primary data on incidence, papers reporting data given in other papers already included, incidence rates not presented and too few data given to calculate incidence rates and papers reporting incidence data thought to be very unreliable. Each of the 63 studies included in this review is described in table 1, first for children and then for adults grouped by continent. Incidence rates broken down by age band are given in table 2.

#### *Incidence Rates*

The incidence rates found for GBS varied between 0.38/100,000/year (95% CI 0.25–0.56) in Finland [8] and 2.53/100,000/year (95% CI 1.87–3.35) in Curaçao [9] (table 1).

#### *Geographical Variation*

Most of the studies included in this review were from Europe and North America where the majority of incidence rates were between 0.84/100,000/year (Finland) [10] and 1.91/100,000/year (Italy) [11]. For other parts of the world, very few studies were found, and therefore it is difficult to comment on any geographical trends. For the data presented, a comparison of these rates with those of Europe

and North America suggest that incidence was lower in China [12, 13], Hong Kong [14] and Brazil [15], similar in Tanzania [21], Australia [16, 17] and Japan [18] and slightly higher in the Middle East [19, 20] and Curaçao [9].

#### *Variation over Time*

Most studies covered time periods between 1980 and 2000 [9–19, 21–43]. Between 1980 and 2000, the incidence was between 1.0/100,000/year and 1.8/100,000/year. Only 3 studies reported rates from 2000 onwards, and these were thought to be unreliable [20, 44, 45].

#### *Variation with Age*

In the majority of studies that included incidence rates broken down by age, increases in rates were observed in most studies of people aged 50 years or more [11, 17, 22, 26, 31–33, 35–39, 46–49], with some showing a decrease in the highest age group of  $\geq 80$  years [22, 26, 31, 35–38, 47–49].

Overall incidence rates in children ranged from 0.34/100,000/year to 1.34/100,000/year [31, 34]. In the studies that investigated incidence in children (0–9 years) and teenagers (10–19 years), most showed an increase in incidence with increasing age [19, 37, 38, 48–51], although some demonstrated decreases [12, 13, 17, 46, 47].

**Table 1.** Description of studies and overall incidence by continent

Study	Location	Study method	Diagnostic criteria	Cases n	Antecedent infection, %	Period	Age	Rate 100,000/year
<b>Children</b>								
Hung et al. [60] RUE: ** ROE: *	Taiwan	medical record review by paediatric neurologists	NINCDS	72	all: 83 URI: 68 GI: 7 other: 7	1986–90	0–16	0.66
Rantala et al. [8] RUE: * ROE: *	Finland	hospital discharge database; diagnoses of cases reviewed	not given	27	all: 85 URI: 67	1980–86	≤15	0.38 (0.25–0.56) <sup>1</sup>
Artan [61] RUE: * ROE: *	Antalya, Turkey	retrospective study of cases of acute paralysis reported to Ministry of Health	Asbury and Cornblath	11	URI: 63	1990–96	1–14	0.54
Barzegar et al. [53] RUE: ** ROE: *	Eastern Azerbaijan, Iran	systematic registration of children with acute flaccid paralysis; all cases referred.	Asbury and Cornblath	143	all: 69 URI: 52 GI: 14 other: 3	2001–06	0–15	2.27
Ismail et al. [67] RUE: ** ROE: *	Kuwait	retrospective review of medical records identifying hospital discharges coded for GBS; records reviewed	Asbury and Cornblath	19	all: 79 URI: 68 GI: 11	1992–97	≤12	0.95 (0.52–1.37) <sup>1,2</sup>
Molinero et al. [57] RUE: ** ROE: ***	Honduras	prospective hospital-based study	Asbury and Cornblath	394	not given	1989–99	<16	1.37 (1.22–1.49) <sup>1,2</sup>
Rantala et al. [68] RUE: * ROE: *	Los Angeles and Orange Counties, USA	medical records of those discharged from children's hospitals; case histories reviewed by paediatric neurologist	review of cases with ICD 356.0–357.9	93	all: 76 URI: 48 GI: 12 other: 11	1980–86	≤15	0.60 (0.48–0.73) <sup>1</sup>
Olive et al. [58] RUE: * ROE: **	South America	all cases of acute flaccid paralysis must be reported for surveillance; active searches: door to door survey, hospital admissions, death certificates; more detailed studies in 7 countries	NINCDS	3,112	all: 67	1989–91	<15	0.67
Dias-Tosta et al. [54] RUE: * ROE: **	Brazil	cases identified from the Fundação Nacional de Saúde of the Brazilian Ministry of Health; data collected during a poliomyelitis surveillance programme reviewed and 60-day follow-up	Asbury and Cornblath	1,678	not given	1990–96	<15	0.46
Hart et al. [59] RUE: * ROE: *	Paraguay	compulsory reporting of GBS cases to the Ministry of Health; cases also identified through door-to-door vaccination programs and a notification agreement with neighbouring countries; records reviewed	NINCDS	37	all: 54 URI: 32 GI: 8 other: 14	1990–91	<15	1.06 (0.72–1.40) <sup>1,2</sup>
<b>All ages</b>								
<i>Africa</i>								
Howlett et al. [21] RUE: ** ROE: *	Kilimanjaro, Tanzania	retrospective hospital-based study with review of medical records (ICD 357.0)	NINCDS	45	all: 40.6	1984–92	≥12	0.83
<i>Asia</i>								
Cheng et al. [12] RUE: * ROE: *	Harbin, China	prospective reporting of new cases by hospitals and clinics; cases and admission registers checked	NINCDS	36	all: 75 URI: 58 GI: 11 other: 6	1997–98	all	0.66 (0.46–0.91) <sup>3</sup>
Zhang et al. [13] RUE: * ROE: *	Harbin, China	surveillance system: new cases were reported to the study; checks for missing cases also conducted	Asbury and Cornblath	72	all: 71 URI: 58 GI: 4 URI and GI: 9	1997–99	all	0.69 <sup>3</sup>
Hui et al. [14] RUE: ** ROE: **	Hong Kong, China	retrospective review of admission and discharge records; clinical variants included	ICD-9 codes 357.0, 356.4, 356.8, 356.9	20	GI: 25	1993–98	>15	0.44 (0.25–0.64) <sup>1,2</sup>
Kusumi et al. [18] RUE: ** ROE: *	Tottori Prefecture, Japan	patient records at the university hospital; questionnaires sent to general hospitals	NINCDS	35	not given	1988–92	all	1.14

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**Table 1** (continued)

Study	Location	Study method	Diagnostic criteria	Cases n	Antecedent infection, %	Period	Age	Rate 100,000/year
<i>Australasia</i>								
Storey et al. [16] RUE: ** ROE: *	Victoria, Australia	medical record systems in teaching hospitals; all cases reviewed	criteria not given	110	URI: 34 GI: 12	1980–84	≥15	0.90 <sup>3</sup>
Hankey [17] RUE: ** ROE: *	Western Australia	case record search for GBS, polyneuritis or polyneuropathy codes	Asbury	109	all: 58	1980–85	all	1.35 (1.10–1.61) <sup>1,2</sup>
<i>The Caribbean</i>								
van Koningsveld et al. [9] RUE: * ROE: *	Curaçao	medical records with relevant ICD-9 codes; cases reviewed	NINCDS	49	all: 92 URI: 5 influenza: 25 GI: 55 other: 7	1987–96	all	2.53 (1.87–3.35) <sup>1</sup>
<i>Europe</i>								
Bak [62] RUE: * ROE: **	Ringkøbing County, Denmark	record review for patients admitted to all hospitals in the county.	Danish ICD code for GBS (ICD adaptation)	51	all: 41	1965–82	all	1.14 <sup>3</sup>
Halls et al. [63] RUE: ** ROE: **	Copenhagen county, Denmark	record review of those with a diagnosis of neuropathy, to find cases of GBS	criteria not given	34	not given	1977–84	all	1.50 (0.90–2.30) <sup>3</sup>
Hughes et al. [22] RUE: * ROE: *	UK	population-based study using General Practice Research database	codes for GBS or infective neuritis used	228	not given	1992–2000	all	1.33 (1.15–1.50) <sup>1,3</sup>
MacDonald et al. [23] RUE: * ROE: **	London, England	case ascertainment using referrals, databases, clinic records and patient medical records	diagnostic criteria not given	not given	not given	1995–96	all	3.0 (1.0–6.0) <sup>1,4</sup>
Haberman et al. [64] RUE: ** ROE: *	North-West Thames, England	retrospective review of hospital activity analysis	ICD-8 code 354.9, clinical features, diagnosed by a neurologist	39	not given	1978	all	1.10 (0.77–1.48) <sup>1</sup>
Winner et al. [46] RUE: * ROE: *	Oxfordshire, England	hospital records and those from record linkage study used with discharge codes for GBS or acute infective polyneuritis (ICD-8 354, ICD-9 357.0, 357.9)	NINCDS, MF also included (Asbury)	72	not given	1978	all	1.10 (0.80–1.40) <sup>1</sup>
Rees et al. [24] RUE: ** ROE: *	south-east England	prospective reporting of cases, hospital activity analysis, research database and death certificates	Asbury and Cornblath criteria used	79	not given	1993–94	all	1.20 (0.90–1.40) <sup>1</sup>
Kinnunen et al. [10] RUE: * ROE: **	Finland	cases with diagnosis of polyradiculitis found from hospital discharge database and reviewed by a neurologist	Asbury and Poser criteria used	247	all: 67	1981–86	all	0.84 (0.56–1.25) <sup>1</sup>
Lehmann [44] RUE: ** ROE: ***	Germany	nationwide administrative database from reimbursement scheme implementation	ICD-10 code G61.0 used to find cases	4,349	not given	2003 2004 2005	all	1.78 <sup>2</sup> 1.6 <sup>2</sup> 1.89 <sup>2</sup>
Markoula et al. [25] RUE: ** ROE: *	north-west Greece	records of patients admitted to neurology inpatients reviewed; variants were included	NINCDS	46	all: 61 URI: 30 GI: 26	1996–2005	all	1.22
Chroni et al. [26] RUE: * ROE: *	south-west Greece	retrospective review of medical records; many cases followed up after 14 months.	NINCDS	105	all: 50 URI: 29 GI: 7 other: 14	1989–2001	all	0.99 (0.81–1.19) <sup>1</sup>
Anon [27, 47] RUE: * ROE: *	Emilia-Romagna, Italy	prospective study of all neurological units and relevant departments; discharges using ICD codes were also checked	not given	105	all: 70 URI: 46 influenza: 13 GI: 11	1992–93 NINCDS	all	1.11 (0.89–1.36) <sup>1</sup> 1.2 (0.96–1.46) <sup>1,3</sup>
Paolino et al. [28] RUE: * ROE: *	Ferrara, Italy	medical records from relevant departments searched; diagnosis of GBS and related disorders checked	NINCDS	16	all: 38 URI: 19 GI: 6 other: 13	1981–87	all	1.26 (0.65–1.88) <sup>1,2</sup>

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**Table 1** (continued)

Study	Location	Study method	Diagnostic criteria	Cases n	Antecedent infection, %	Period	Age	Rate 100,000/year
Govoni et al. [11, 29] RUE: * ROE: *	Ferrara, Italy	prospective identification of patients referred to neurological wards; retrospective review of medical records and discharge records (ICD-9 356.9, 357.0, 356.4, 356.8)	NINCDS (GBS); Asbury and Cornblath (variants)	43 [29], 26 [11]	all: 54 URI: 23 GI: 9 other: 22	1981–93 [29], 1994–2001 [11]	all	1.66 <sup>3</sup> 1.91 (1.49–2.43)
Beghi et al. [30] RUE: * ROE: *	Lombardy, Italy	prospective hospital-based survey; patients were interviewed and atypical cases discussed	NINCDS (GBS); Ropper (variants)	109	not given	1994–95	all	0.92 (0.75–1.09) <sup>1</sup>
Bogliun et al. [31] RUE: ** ROE: *	Lombardy, Italy	cases traced through hospital, prospective regional registry started in 1994; hospital discharges also checked for ICD-9 code 357.0	NINCDS (GBS); Asbury and Ropper (variants)	138	all: 30 URI: 13 GI: 7 influenza: 10	1993–96	all	1.43 (1.16–1.74) <sup>1</sup>
D'Ambrosio et al. [52] RUE: *** ROE: *	Naples and province, Italy	admission diagnoses reviewed and records examined	NINCDS	46	not given	1971–80	all	0.16 (0.11–0.21) <sup>1,2</sup>
Chio et al. [32] RUE: * ROE: *	Piedmont and Valle d'Aosta, Italy	prospective recording in registry of cases found in neurology departments; hospital discharge databases also checked for ICD-9 codes 357.0, 357.8 and 357.9; cases verified	NINCDS	120	all: 58 URI/influenza: 41 GI: 14 other: 4	1995–96	all	1.28 (1.04–1.51) <sup>5</sup>
Congia et al. [55] RUE: *** ROE: *	Sardinia, Italy	retrospective review of medical records and hospitalisations	NINCDS	120	all: 36	1961–80	all	0.40 (0.33–0.47) <sup>1,2</sup>
van Koningsveld et al. [33] RUE: * ROE: *	south-west Netherlands	retrospective review of medical records checking for ICD-9 codes 357.0, 357.8 and 357.9; cases re-evaluated by neurologist	NINCDS	476	all: 79 URI: 22 GI: 20 influenza: 25 other: 12	1987–96		1.14 (1.04–1.24) <sup>3</sup>
Larson et al. [56] RUE: * ROE: *	western Norway	hospital records searched for cases	NINCDS	109	all: 57	1957–82	all	1.19 <sup>3</sup>
Sridharan et al. [34] RUE: * ROE: *	Grampian, Orkney and Shetland, Scotland	retrospective search of hospital records and morbidity records using ICD-8 354, ICD-9 357.0 and 357.9 codes; diagnosis confirmed by neurologist	NINCDS	36	influenza: 42	1980–88	all	1.1 (0.8–1.4) <sup>1</sup>
Cuadrado et al. [35] RUE: * ROE: *	Spain	retrospective review of hospital records, laboratory records and discharge files	NINCDS	337	URI: 31 GI: 12	1985–97	>19	0.86 <sup>3</sup>
Cuadrado et al. [36] RUE: * ROE: *	Spain	prospective population-based study with cases reported to central units; records of cases checked by neurologist	NINCDS	98	all: 62 URI: 43 GI: 10 other: 9	1998–99	>19	1.26 <sup>3</sup>
Sedano et al. [50] RUE: * ROE: **	Cantabria, Spain	hospital medical records searched for ICD-8 code 354	NINCDS	69	all: 36 URI: 23 GI: 9 other: 4	1975–88	all	0.95 (0.73–1.18) <sup>2,3</sup>
Jiang et al. [37] RUE: * ROE: **	Sweden	cases discharged from a first hospital stay	ICD-9 code 357A	2,257	not given	1978–93	all	1.77 <sup>3,6</sup>
Cheng et al. [38] RUE: * ROE: *	Sweden	prospective data collection of newly reported cases identified by neurologists; inpatient registries checked for those with ICD-9 code 357A	NINCDS	73	not given	1996	all	1.51 (1.18–1.90) <sup>3</sup>
Jiang et al. [48] RUE: * ROE: *	Stockholm County, Sweden	medical records searched for appropriate ICD codes	codes ICD-8 354.01 ICD-9 357A	556	not given	1973–91	all	1.89 (1.72–2.03) <sup>1,2</sup>
Jiang et al. [49] RUE: * ROE: *	south-west Stockholm, Sweden	as above	as above	84	not given	1973–91	all	1.56 (1.24–1.93) <sup>3</sup>

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**Table 1** (continued)

Study	Location	Study method	Diagnostic criteria	Cases n	Antecedent infection, %	Period	Age	Rate 100,000/year
<i>The Middle East</i>								
Arami et al. [20] RUE: ** ROE: *	Eastern Azerbaijan, Iran	prospective survey of all new cases of GBS admitted to 3 referral centres	NINCDS	76	all: 65.8 URI: 50 GI: 16	2003	all	2.11 (1.64–2.59) <sup>2,3</sup>
Radhakrishnan et al. [19] RUE: * ROE: **	Benghazi, Libya	screening through clinics, hospitals and other centres identified cases	not given	27	all: 26	1983–85	all	1.73 <sup>3</sup>
<i>North America and Canada</i>								
Hauck et al. [39] RUE: ** ROE: **	Alberta, Canada	administrative sources maintained by the Ministry of Health and Wellness of the Government of Alberta	codes used to find cases	496	not given	1994–04	all	1.14
McLean et al. [40] RUE: * ROE: *	Quebec and Ontario, Canada	hospital discharge databases searched; sample of cases checked by 2 neurologists	ICD-9 codes 357.0, 357.8, 357.9 and 375.0	2,333	not given	1983–89 Ontario Quebec	all	1.51 1.78
Alshekhlee et al. [45] RUE: *** ROE: ***	USA	identified cohort from the Nationwide Inpatient Sample which records data from approx. 20% of community hospitals	included: ICD-9 codes for GBS (357.0); excluded: 357.81, 357.82, 359.81, 357.4, 045, 045.1, 358.0, 358.01, 358.1, 358.8, 323, 303.0, 960, 979	4,956	not given	2000–04	>17	1.72 <sup>2</sup>
Kaplan et al. [65] RUE: * ROE: *	Colorado, USA	retrospective review of medical records	diagnosed by a neurologist; records with ICD-9 357.0 reviewed	48	all (Larimer County): 86 URI 53 GI 23 other 10	1975–83 Larimer County Weld County	all	2.20 (1.41–3.02) <sup>1,2</sup> 1.80 (0.97–2.55) <sup>1,2</sup>
Church Potter et al. [41] RUE: * ROE: ***	Michigan, USA	data on GBS cases collected retrospectively from the community health reportable disease database and GBS registry	diagnostic criteria not given	471	not given	1992–99		0.63
Beghi et al. [66] RUE: * ROE: *	Olmsted county, USA	retrospective review of medical records of the Mayo Clinic record-linkage system; records evaluated and diagnosis confirmed by neurologists	codes identified included GBS, polyradiculitis, peripheral neuritis or neuronitis	48	all 65	1935–80	all	1.77 <sup>3</sup>
Hoppock et al. [42] RUE: * ROE: **	Sedgwick County, Kansas, USA	hospital records were reviewed	ICD code 357.0 and clinical features	43	all: 73 URI: 47 GI: 21 URI and GI: 5	1984–88	all	2.2
Koobatian et al. [43] RUE: * ROE: *	Vermont, USA	computer discharge abstracts from all hospitals searched for GBS ICD-9 code 357.0	NINCDS	51	all: 57	1980–85		1.6
Riggs et al. [51] RUE: ** ROE: *	West Virginia, USA	medical records of patients admitted with acute neuropathies reviewed	not given	92	not given	1967–87	all	1.7 <sup>3</sup>
<i>South America</i>								
Rocha et al. [15] RUE: *** ROE: *	Sao Paulo, Brazil	medical record review (1995–1999) and clinical registration of cases (2000–2002); all cases examined by neurological staff	Asbury and Cornblath	95	all: 58 URI: 46 GI: 12	1995–2002	all	0.40 (0.32–0.48) <sup>1,2</sup>

Figures in parentheses are 95% CI.  
 RUE = Risk of underestimation; ROE = risk of overestimation; \* = low; \*\* = medium; \*\*\* = high; MF = Miller-Fisher; URI = upper respiratory tract infection; GI = gastrointestinal infection.  
<sup>1</sup> Rate checked and confirmed. <sup>2</sup> CI added. <sup>3</sup> Standardised rate. <sup>4</sup> Date used in incidence calculations is date of diagnosis. <sup>5</sup> Rate calculated from number of cases and population data provided in the paper. <sup>6</sup> Date used in incidence calculations is date of first admission to hospital.

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### *Clinical Variants of GBS*

Very few studies included in this review gave information about incidence of the clinical variants of GBS – of those studies that did, the main variant of GBS, Miller-Fisher syndrome, was much less common than GBS. If cases of these diseases were included in any studies of GBS incidence, then the overall incidence rate would only be overestimated by a small amount.

### *Antecedent Infection*

A number of the studies included in this review gave details of numbers of cases reporting an antecedent infection, usually less than 4 weeks, before onset of GBS. These data have been recorded in table 1 along with a breakdown of the type of infection, where given. In most studies reporting this information, 40–70% of cases recorded an infection before onset with 22–53% having an upper respiratory tract infection and 6–26% a gastrointestinal infection. Children's rates were higher, with 67–85% of all cases reporting an infection: 50–70% were respiratory infections and 7–14% gastrointestinal infections.

### *Seasonal Variation*

The issue of seasonal variation in incidence was raised in some studies although none reported significant differences in levels of onset of GBS between seasons [16, 28, 29, 50, 52–54]. Some found more cases in colder months [9, 19, 20, 46, 55, 56] although a cluster of cases was reported in spring and summer in Brazil [15], during the winter and June in the Netherlands [33] and during autumn in Sweden [37].

### *Study Method*

Study design is an important consideration when comparing incidence rates between different studies. In this review, the studies included were of 3 types: prospective [11–13, 20, 24, 27, 29–32, 36, 38, 47, 53, 54, 57–59], retrospective medical record review [9, 14–19, 21, 25, 26, 33–35, 41, 46, 50–52, 55, 56, 60–66] and retrospective database studies with [8, 10, 40, 67, 68] or without [22, 23, 37, 39, 42–45, 48, 49] the review of cases by a clinician. At first glance, it would appear that study design did not have a sizeable effect as the incidence rates found were similar. However, when incidence rates were compared by type of study, some trends became apparent. For the prospective studies, the majority of incidence rates were between 1.11/100,000/year and 1.66/100,000/year; for the retrospective record review studies and the database studies with record review, most were between 0.83/100,000/year and 1.77/100,000/year and for the database

studies where a review of cases was not performed, 1.14/100,000/year to 2.2/100,000/year. Prospective studies are usually the most reliable; using this as the standard suggests that some of the database studies overestimated incidence rate and some of the retrospective record review studies underestimated rates.

Most patients diagnosed with GBS will be hospitalised due to the nature of the disease [8, 26, 32, 33, 35–37, 64]: 3 studies reported small numbers of outpatient or community patients identified in their studies compared with numbers of hospitalised GBS cases [12, 32, 38]. Ten studies noted the inclusion of mild cases in their studies [16, 24, 29, 33, 38, 45, 46, 50, 57, 59] and the design of other studies implied the inclusion of mild cases: 2 studies using general practitioner records [22, 23], a surveillance study [54], a door-to-door survey [58] and the record linkage system used by the Mayo Clinic [66]. Of those studies that used mainly hospital records, 2 noted that all patients were given intravenous immunoglobulin or plasma exchange therapy [20, 67], and this implies that only serious cases were included, whereas others reported proportions of patients receiving these therapies of between 24 and 49% for intravenous immunoglobulin and 34–51% receiving plasma exchange [26, 27, 30, 47, 61]. Ten studies reported missing mild cases [12, 32, 36, 64, 69, 70] or reported finding it difficult to detect mild cases if they had not been admitted to hospital [17, 25, 37, 62].

## **Discussion**

Most of the incidence rates of GBS reported were between 1.1/100,000/year and 1.8/100,000/year with lower rates reported in children (<16 years) of 0.4/100,000/year to 1.4/100,000/year. Most of the studies included were from Europe and North America where the rates found were similar.

A number of studies have commented on a bimodal pattern of incidence by age, with peaks occurring in young adults and the elderly [3, 24, 71]. In this review, only 1 study [19] (out of 24) found a peak in incidence in young adults, although the rates were not adjusted and a high proportion of young adults in this area could have biased the incidence rates found.

The majority of studies used the recognised NINCDS criteria or a comparable set of diagnostic criteria, and this allowed comparisons to be made between studies. One important difference between studies that should be highlighted is the study method used. In this review, the overall incidence rates found by the prospective studies



**Table 2.** Incidence of GBS by age band (only those studies that gave incidence by age band are included in the table)

Study	Sex	Age bands and incidence rates/																	
Chroni et al. [26]	both	0-5	6-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
		0.83 <sup>1,2</sup>	1.17 <sup>1,2</sup>	0.67 <sup>1,2</sup>	0.42 <sup>1,2</sup>	0.58 <sup>1,2</sup>	0.67 <sup>1,2</sup>	0.42 <sup>1,2</sup>	0.75 <sup>1,2</sup>	0.83 <sup>1,2</sup>	1.33 <sup>1,2</sup>	0.67 <sup>1,2</sup>	3.33 <sup>1,2</sup>	0.5 <sup>1,2</sup>	2 <sup>1,2</sup>	2.17 <sup>1,2</sup>	2.67 <sup>1,2</sup>	1.83 <sup>1,2</sup>	0 <sup>1,2</sup>
van Koningsveld et al. [33]	both	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	
		0.58 <sup>2,3</sup>	0.74 <sup>2,3</sup>	0.22 <sup>2,3</sup>	0.66 <sup>2,3</sup>	0.74 <sup>2,3</sup>	0.99 <sup>2,3</sup>	0.97 <sup>2,3</sup>	0.92 <sup>2,3</sup>	0.92 <sup>2,3</sup>	1.08 <sup>2,3</sup>	1.14 <sup>2,3</sup>	1.47 <sup>2,3</sup>	1.42 <sup>2,3</sup>	1.99 <sup>2,3</sup>	2.2 <sup>2,3</sup>	1.82 <sup>2,3</sup>	1.91 <sup>2,3</sup>	
Jiang et al. [37]	both	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+	
		0.61 <sup>2,4</sup>	0.79 <sup>2,4</sup>	0.85 <sup>2,4</sup>	1.33 <sup>2,4</sup>	1.58 <sup>2,4</sup>	1.45 <sup>2,4</sup>	1.45 <sup>2,4</sup>	1.27 <sup>2,4</sup>	1.58 <sup>2,4</sup>	1.45 <sup>2,4</sup>	2.48 <sup>2,4</sup>	2.55 <sup>2,4</sup>	3.09 <sup>2,4</sup>	3.64 <sup>2,4</sup>	4.24 <sup>2,4</sup>	3.64 <sup>2,4</sup>	2.42 <sup>2,4</sup>	
Hughes et al. [22]	male	0-14		15-24		25-34		35-44		45-54		55-64		65-74		75-84		85-100	
	female	0.47		0.63		0.87		1		1.98		3.15		3.86		2.85		2.26	
Winner and Evans [46]	both	0-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75+									
	both	0.50	0.60	1.10	1.61	1.32	0.68	2.07	1.90	1.90	1.90	2.00	2.00	1.80	1.80	1.90	1.90	1.90	1.90
Haberman et al. [64]	both	0-4	5-14	15-44	20-29	30-39	40-49	50-59	60-69	70-79	80-90								
	both	0.00-1.30 <sup>5,6</sup>	0.00-1.30 <sup>5,6</sup>	1.10 (0.60-1.60) <sup>5,6</sup>	1.61	1.32	0.68	2.07	2.6	1.77	3.30								
Hankey [17]	both	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-90									
	both	1.13	0.62	1.61	1.32	0.68	2.07	2.6	1.77	3.30									
Cheng et al. [12]	both	0-9	10-19	20-29	30-39	40-49	50-59	60+											
	both	1.15	0.74	0.61	0.4	0.75	0.44	0.50	0.50	0.50									
Zhang et al. [13]	both	0-9	10-19	20-29	30-39	40-49	50-59	60+											
	both	0.89 <sup>2</sup>	0.74 <sup>2</sup>	0.49 <sup>2</sup>	0.67 <sup>2</sup>	0.85 <sup>2</sup>	0.60 <sup>2</sup>	0.48 <sup>2</sup>											
Kusumi et al. [18]	male	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+										
	female	2.62 <sup>2,3</sup>	2.30 <sup>2,3</sup>	9.84 <sup>2,3</sup>	7.70 <sup>2,3</sup>	6.39 <sup>2,3</sup>	2.62 <sup>2,3</sup>	5.57 <sup>2,3</sup>	3.77 <sup>2,3</sup>	6.56 <sup>2,3</sup>									
Anon [47]	both	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+										
	both	0.73	0.36	0.94	0.83	0.94	1.30	2.34	1.85										
Paolino et al. [28]	both	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79										
	both	0.86	0.00	0.00	0.58	3.25	0.50	3.98	0.72										
Chio et al. [32]	male	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+									
	female	1.13 <sup>2,3</sup>	1.44 <sup>2,3</sup>	1.06 <sup>2,3</sup>	1.25 <sup>2,3</sup>	1.31 <sup>2,3</sup>	2.94 <sup>2,3</sup>	3.13 <sup>2,3</sup>	1.75 <sup>2,3</sup>	2.38 <sup>2,3</sup>									
Sedano et al. [50]	both	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+										
	both	0.59	1.57	0.79	0.64	1.05	1.41	1.23	0.32										
Cuadrado et al. [35]	both	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+									
	both	0.59	1.57	0.79	0.64	1.05	1.41	1.23	0.32										
Cuadrado et al. [36]	both	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+									
	both	0.59	1.57	0.79	0.64	1.05	1.41	1.23	0.32										

Jiang et al. [49]	both	0-9 1.07 (0.37-1.76) <sup>5,6</sup>	10-19 1.35 (0.59-2.12) <sup>5,6</sup>	20-29 1.59 (0.79-2.40) <sup>5,6</sup>	30-39 0.78 (0.16-1.41) <sup>5,6</sup>	40-49 3.38 (1.86-4.90) <sup>5,6</sup>	50-59 2.49 (1.02-3.96) <sup>5,6</sup>	60-69 2.93 (0.9-4.97) <sup>5,6</sup>	70-79 1.87 (0.00-4.46) <sup>5,6</sup>	80+ 1.49 (1.19-1.85) <sup>5,6</sup>
Jiang et al. [48]	both	0-9 0.81	10-19 1.68	20-29 1.78	30-39 1.51	40-49 1.46	50-59 2.92	60-69 3.08	70-79 4.05	80+ 1.35
Cheng et al. [38]	both	0-9 1.02 (0.20-1.83) <sup>5,6</sup>	10-19 1.21 (0.24-2.18) <sup>5,6</sup>	20-29 1.25 (0.38-2.11) <sup>5,6</sup>	30-39 1.24 (0.38-2.10) <sup>5,6</sup>	40-49 1.27 (0.39-2.15) <sup>5,6</sup>	50-59 0.94 (0.12-1.76) <sup>5,6</sup>	60-69 3.10 (1.35-4.86) <sup>5,6</sup>	70-79 4.48 (2.29-6.68) <sup>5,6</sup>	80+ 1.98 (0.04-3.91) <sup>5,6</sup>
Radhakrishnan et al. [19]	both	0-9 0.30	10-19 1.80	20-29 3.10	30-39 5.90	40-49 1.70	50-59 1.50	60+ 1.10		
Riggs et al. [51]	both	0-9 1.30 <sup>1</sup>	10-19 1.80 <sup>1</sup>	20-29 2.20 <sup>1</sup>	30-39 1.70 <sup>1</sup>	40-49 0.90 <sup>1</sup>	50-59 2.20 <sup>1</sup>	60-69 2.40 <sup>1</sup>	70+ 1.40 <sup>1</sup>	
Hauck et al. [39]	male female	0-9 0.91 <sup>2</sup> 0.42 <sup>2</sup>	10-19 1.12 <sup>2</sup> 0.42 <sup>2</sup>	20-29 1.26 <sup>2</sup> 0.84 <sup>2</sup>	30-39 1.47 <sup>2</sup> 0.98 <sup>2</sup>	40-49 1.67 <sup>2</sup> 1.26 <sup>2</sup>	50-59 2.02 <sup>2</sup> 1.53 <sup>2</sup>	60-69 5.02 <sup>2</sup> 2.79 <sup>2</sup>	70-79 4.88 <sup>2</sup> 4.05 <sup>2</sup>	80+ 4.19 <sup>2</sup> 2.72 <sup>2</sup>
Govoni et al. [11]	both	0-19 0.53	20-39 0.98		40-59 2.01		60-79 3.24		80+ 4.30	
Larson et al. [56]	both	0-19 0.84	20-39 1.12	19-49 0.67	40-59 1.51		60+ 1.24			
Howlett et al. [21]	both		12-29 0.70		30-49 1.30		50+ 0.50			
Kinnunen et al. [10]	both	0-18 0.58		19-49 0.67			50+ 1.35			
Govoni et al. [29]	both	0-29 0.89 (0.23-1.55) <sup>5,6</sup>			30-59 1.61 (0.82-2.40) <sup>5,6</sup>		60+ 3.82 (2.15-5.50) <sup>5,6</sup>			
Beghi and Boghun [30]	both	0-14 0.34	15-34 0.57		35-54 0.91		55+ 1.91			
Boghun and Beghi [31]	both	0-34 0.79 (0.55-1.10) <sup>1</sup>			35-54 1.33 (0.92-1.85) <sup>1</sup>		55-74 3.22 (2.76-7.38) <sup>1</sup>	75+ 4.67 (2.77-7.38) <sup>1</sup>	80+ 2.52 (1.16-4.78) <sup>1</sup>	
Sridharan et al. [34]	both	0-18 1.34 (0.72-1.95)	19-60 0.80 (0.46-1.15)				61+ 1.62 (0.80-2.43) <sup>5</sup>			
Beghi et al. [66]	both	0-17 0.81 (0.25-1.37) <sup>5,6</sup>	18-39 1.34 (0.61-2.07) <sup>5,6</sup>			40-59 2.84 (1.45-4.23) <sup>5,6</sup>	60+ 3.25 (1.33-5.18) <sup>5,6</sup>			
Koobatian et al. [43]	both	0-24 0.86		25-44 0.97		45-64 2.52	65+ 4.73			
Cheng et al. [74]	both	<40 1.23			40+ 2.04					
Arami et al. [20]	both	0-15 2.28 <sup>1</sup>	15+ 2.06 <sup>1</sup>							

Data are presented as incidence rates per 100,000 people/year, with 95% CI in parentheses. <sup>1</sup> Standardised rate. <sup>2</sup> Rate read from graph. <sup>3</sup> Rate calculated from number of cases and population data provided in the paper. <sup>4</sup> Date used in incidence calculations is date of first admission to hospital. <sup>5</sup> CI added. <sup>6</sup> Rate checked and confirmed.

and the database studies that did not review cases were higher than those found by the retrospective studies that reviewed medical records. Prospective studies of incidence are thought to be the most accurate provided the ascertainment of cases and determination of denominator are reliable. This is thought to be true of the prospective studies included in this review, so the incidence rates from these are likely to be the best approximation available for the true incidence of GBS. The range of incidence rates found by the retrospective studies where medical records were reviewed produced slightly lower incidence rates, which indicates that some cases may have been missed by these studies. Conversely, it is possible that the studies using databases where medical records were not reviewed overestimated the incidence rates. Bogliun et al. [72] compared case ascertainment between a hospital discharge database and a registry, and found that over half of the 'cases' identified in the discharge database had either not had their diagnosis confirmed or had been double-counted through re-admission to hospital. The possibility of inaccurate coding could also contribute to overestimation of cases in this type of study. The database studies did not provide any indication of the criteria used when the original diagnosis was made, which is more likely to be a feature of this particular study method than a lack of regard for set diagnostic guidelines.

The identity of GBS as a single homogenous clinical entity is evolving and reference to GBS as a term covering the disease subtypes AIDP, AMAN, AMSAN and Miller-Fisher syndrome is becoming more common [71, 73]. GBS also has links with chronic diseases, including chronic inflammatory demyelinating neuropathy and subacute demyelinating polyneuropathy [71]. Possible implications for interpretation of incidence rates in epidemiological studies of GBS are that most of the studies included in this review used the NINCDS criteria, which do not include the symptoms of Miller-Fisher syndrome but do include AIDP, AMAN and AMSAN. Therefore, if Miller-Fisher syndrome is to be included in the definition, then some of the rates reported here derived from studies using NINCDS criteria will be slight underestimates of the true incidence. Geographical patterns of incidence of AIDP, AMAN and AMSAN have been reported [5, 73]. Very few studies in this review included information on the incidence of variants of GBS, and those that did concentrated on whether cases of Miller-Fisher syndrome were included; it was not possible to determine whether there was a geographical difference between incidence of AIDP, AMAN and AMSAN. A link between the incidence of clinical variants and preceding infection

was made by Govoni et al. [29] who compared GBS incidence with clinical variants of GBS including Miller-Fisher syndrome, polyneuritis cranialis, sensory form, acute pandysautonomia and chronic inflammatory demyelinating polyneuropathy. They found that a higher number of cases with preceding infection amongst individuals with clinical variants than amongst those with GBS (88% compared with 54% in their study), and that the disease was milder at nadir for clinical variants of GBS. Some investigators recommend that the NINCDS criteria are widened to include clinical variants and this might result in more cases being identified [29, 66].

The association with antecedent viral and upper respiratory infections before onset of GBS has been known for over 100 years, although the suggested link between *Campylobacter jejuni* and GBS is much more recent [73]. Potential links have been reported between *Campylobacter jejuni* and axonal forms of GBS [73]. It is acknowledged that the reporting of antecedent infections is likely to be more accurate in prospective than in retrospective studies; for example less than 40% of cases of GBS were reported to be preceded by an infection in 3 retrospective studies in Italy [28, 31, 55] whereas a prospective study from Italy reported a rate of preceding infection of 70% [27, 47]. It is therefore reasonable to assume that most cases of GBS are triggered by antecedent infection, although no indications were given as to the likely cause of the majority of the remaining cases. Hughes and Rees [4] noted that the lack of obvious seasonal changes in incidence may be because the infections found most frequently to trigger this disease, respiratory and enteric infections, have opposite seasonality of occurrence. Two studies investigated potential seasonal variations in cases for those who reported an antecedent infection before onset of GBS: Larson et al. [56] found seasonal variation to be more pronounced in this group, but Paolino et al. [28] did not find a significant association with onset in cold or warm months.

## Conclusions

Overall the best estimate of the incidence of GBS is between 1.1/100,000/year and 1.8/100,000/year with lower rates reported in children (<16 years) of around 0.6/100,000/year. The review reported mostly on studies from Europe and North America. Few rates were presented from other parts of the world, particularly Asia and Africa, and this makes it difficult to comment on possible geographical variations. Incidence increased

with age from 50 years; we were unable to confirm the suggestion that bimodality exists in the incidence of GBS. Antecedent infections, mainly upper respiratory and gastrointestinal infections, preceded up to 70% of cases reported.

The widespread use of the NINCDS criteria provides consistency across studies. Differences in incidence rates between studies with different methods were found: pro-

spective studies were thought to be the most reliable; however, large differences in incidence rates between the various types of studies were not found.

### Acknowledgements

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## Appendix

Data abstraction forms:

Ref Manager ID <input type="text"/>	Case definition <input type="text"/>	Risk of missing cases <input type="checkbox"/> Low <input type="checkbox"/> Medium <input type="checkbox"/> High	Reasons <input type="text"/>
Year published <input type="text"/>	Number of cases <input type="text"/>	Risk of overestimating cases <input type="text"/>	
Reviewer <input type="text"/>	Base population: person years <input type="text"/>	Secondary references <input type="text"/>	
Original in English? <input type="checkbox"/>	Base population: number of people <input type="text"/>	Notes <input type="text"/>	
Translation <input type="text"/>	Source of case identification <input type="text"/>		
Excluded? <input type="checkbox"/>	Study dates <input type="text"/>		
Reason for exclusion <input type="text"/>	Country <input type="text"/>		
	Region <input type="text"/>		
	Ethnic distribution <input type="text"/>		
Ref Manager ID <input type="text"/>	Type of rate <input type="text"/>		
Race <input type="text"/>	Incidence <input type="text"/>		
Other ethnic origin <input type="text"/>	Units <input type="text"/>		
Gender <input type="text"/>	Lower CI <input type="text"/>		
Multiple locations? <input type="text"/>	Upper CI <input type="text"/>		
Time period <input type="text"/>	Figures checked? <input type="checkbox"/>		
Other descriptor <input type="text"/>	Figures correct? <input type="text"/>		
Age range <input type="text"/>	Notes <input type="text"/>		

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