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Incidence rates of adverse events of special interest: Guillain-Barré syndrome and Bell's palsy

DRAFT Report for IMS® Disease Analyzer databases (France and Germany)

Details	
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Executive summary	To support the assessment of suspected adverse reactions following vaccination for COVID-19, there is a need to identify background incidence rates for events of interest. To test the ability of inhouse dataset to generate such background rates, a feasibility study was done to see if useful, accurate results could be generated within a short timeframe. As an exemplar, the IMS® Disease Analyzer France and Germany databases were used to calculate the incidence rate of Guillain-Barré syndrome and Bell's palsy, using a methodology similar to that employed by the ACCESS consortium. For Guillain-Barré syndrome, there was an overall incidence rate of 1.4 (95% CI 0.9-2.0) per 100,000 person-years in France and 4.5 (95% CI 4.0-5.0) per 100,000 person-years in Germany. Both in Germany and France, the incidence rate peaked in the 60-79 years age group. In Germany but not in France the incidence rate was also numerically but not statistically significantly higher for males than females. The incidence rate of Guillain-Barré syndrome in Germany was comparatively high whereas it was similar in France in relation to those reported elsewhere. For Bell's palsy, there was an overall incidence of 24.2 (95% CI 22.1-26.5) per 100,000 person-years in France and 67.2 (95% CI 65.2-69.2) per 100,000 person-years in Germany. In France the incidence rate peaked at between 40-49 years and 60-69 years whereas in Germany the incidence rate peaked in the oldest age group. Incidence rates were similar in males and females in France whereas

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Details	
	males had a higher rate than females in Germany. The incidence rate for Bell's palsy was again comparatively high in Germany and similar in France in relation to those reported elsewhere.

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1. Rationale and background

Background rates of adverse events of special interest (AESIs) are important in order to be able to determine if an event rate in patients with a certain drug exposure is higher than expected in the general, non-exposed population. Such background rates can then serve as comparator data when reports of suspected adverse reactions are reviewed, for example in the case of immune-mediated or neurologic events for COVID-19 vaccines.

This study assesses the feasibility of generating background rates of events of interest in the IMS® Disease Analyzer databases, using two AESIs as a case study: Guillain-Barré syndrome (GBS) and Bell's palsy. The present study has obtained event rates for Guillain-Barré syndrome and Bell's palsy using similar methods as in the ACCESS protocol (EUPAS study 37274) [1, 2]. Results from this study will be compared to results from ACCESS and from the ADVANCE project [3, 4], which published incidence rates of autoimmune diseases in European healthcare databases [4] between 2003 and 2014. This study also serves as a pilot to define a process for rapid generation of background rates should data be promptly required to address potential safety concerns emerging from the COVID-19 vaccination campaigns.

2. Research question and objectives

This study has addressed the following objectives:

1) To obtain yearly incidence rates for Guillain-Barré syndrome and Bell's palsy between 2017 and 2019 as pre-COVID-19 event rates in France and Germany;

2) To stratify the yearly incidence rates for Guillain-Barré syndrome and Bell's palsy between 2017 and 2019 in France and Germany by gender and age group.

3. Research Methods

3.1. Study Design

A cohort of patients in GP practices with a minimum observation time of 365 days was established. For each year of the study, patient time denominators were then established. For this feasibility assessment, patients were required to have a minimum observation time of 365 days prior to entering each yearly period in order to establish whether events were incident (new) cases. In this cohort, patient follow-up time within each yearly time period was established with a minimum of one and a maximum of 365 follow-up days. For the specific event type patients in the denominator were required to have no history of the event. The numerator consisted of patients with no history of the event that experienced the event during the yearly time period. The first recorded event date during the time period was captured in these patients. Patient follow-up time was truncated at the occurrence of the first event. For Bell's palsy a "narrow" and "broad" case definition was defined, to reflect the uncertainty of diagnostic coding.

3.2. Study period

The study period was between 2017 and 2019.

3.3. Setting

The study population included GP patients in the IMS® Disease Analyzer databases that had at least 365 days of observation prior to entering the yearly period and were observable during the yearly period, please see section 3.4.

3.4. Variables

Results were stratified by year, sex, age group and quarter. The age groups were 0-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, and ≥80 years.

3.4.1. Outcomes

- Bell's palsy, narrow definition: ICD 10 code G51.0 (Bell palsy)
- Bell's palsy, broad definition: ICD 10 codes G51.0 (Bell palsy), G51.8 (Other disorders of facial nerve) and G51.9 (Disorder of facial nerve, unspecified)
- Guillain-Barré syndrome: ICD 10 code G61.0 (Guillain-Barré syndrome)

3.4.2. Denominators

Patients needed to have a minimum of 365 days of observation prior to entering the time period. The last consultation date for the patient could not be earlier than the start of the time period. Patients also needed to have at least one consultation between 365 days prior to start of the period and 365 days after the end of the period (±365-day time window) to be considered observable during the time period. A patient was considered observable for a maximum of 365 days before and after a consultation but was not considered observable after the last consultation date.

To be included in the incidence calculations, patients were also required to have no prior history of the event at the start of the time period.

Patients with unknown age were excluded from the analyses.

The period of eligibility for the patient was between 365 days after the first consultation and up to the last consultation. Start and end dates for the period were then determined based on the period of eligibility.

3.4.2.1. Start of time period during period of eligibility

Based on consultations during the period of eligibility the observation period for the patient started on the first date of the period if the patient had a consultation within 365 days of the period start date. Otherwise the observation period started 365 days before the most recent consultation within the ±365-day time window.

3.4.2.2. End of time period during period of eligibility

Based on consultations during the period of eligibility the observation period for the patient ended on the last date of the period if the last consultation date for the patient was on or after the period end date and the patient had a consultation within 365 days of the period end date. Otherwise the observation period ended at the earliest of the last consultation date for the patient or 365 days after the most recent consultation within the ±365-day time window.

3.5. Database

The following databases were included in the study:

- IMS® Disease Analyzer France version September 2020
- IMS® Disease Analyzer Germany version June 2020

3.5.1. IMS® Disease Analyzer France

IMS® Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2 % of physicians, and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). The age distribution of patients has been shown to be similar to France social security data (SNIIRAM).

3.5.2. IMS® Disease Analyzer Germany

The IMS® Disease Analyzer Germany database contains anonymised electronic medical record data from a representative panel of physicians since 1992 (general practitioners (GPs) and specialists). The sampling of participating physicians is stratified for specialist groups, regions, and age of the physician. IMS® Disease Analyzer Germany contains patient records including diagnoses, prescriptions, referrals, hospitalisations and sick notes. The sampling of physicians ensures that patients are representative for each speciality across regions in Germany with 83% of practices being single physician practices. As registration with a GP is not a requirement in Germany, patients with a consultation during the time period will be used as denominator in prevalence calculations. The GP patient population is broadly representative of the German population in terms of gender and age distribution [5, 6], except for children as parents may choose to visit a paediatrician directly. The patient age is only available for patients up to an age of 99 years at the time of the database creation (June 2020).

3.6. Analysis

3.6.1. Incidence rate calculation

In patients without an outcome event during the time period the follow-up time in years was calculated with the following formula: $follow\ up\ time = \frac{(\text{End date for the period} - \text{start date for the period} + 1)}{365.25}$

In patients with an outcome event during the time period, the date of the outcome was used instead of the end date for the period. The incidence rate was calculated as the number of patients with an outcome event per 100,000 person-years.

Incidence rates were also calculated for the entire population as well as stratified by gender and age group. Analyses of yearly incidence rates were performed using SAS. Confidence intervals around incidence rates were calculated using exact method [7].

3.7. Results for the French dataset

3.7.1. Bell's palsy narrow and broad definition

The incidence rate of Bell's palsy narrow definition per 100,000 person-years is shown in Table 1. A total of 1319 patients were excluded from the denominators due to a prior history of Bell's palsy (narrow definition) and 1,037,771 patients contributed follow-up time for the analysis.

The incidence rate of Bell's palsy broad definition per 100,000 person-years is shown in Table 2. A total of 3,685 patients were excluded from the denominators due to a prior history of Bell's palsy (broad definition) and 1,035,834 patients contributed follow-up time for the analysis.

Results show that more than twice as many cases were identified using the broader as opposed to the narrow definition. The overall incidence was 24.2 (95% CI 22.1-26.5) per 100,000 person-years for the narrow definition and 61.3 (95% CI 57.9-64.9) per 100,000 person-years for the broad definition. However, the broader set of codes also captures other conditions besides Bell's palsy. There was no significant difference in incidence rates between genders for the narrow definition whereas the broad definition has a higher incidence rate in females compared to males. Results by age group showed the highest incidence rates in adults 40-49 years and 60-69 years. There was no clear evidence of seasonality.

Table 1 Incidence rate of Bell's palsy per 100,000 person-years in IMS® Disease Analyzer France (narrow definition[1])

Bell's palsy narrow			
Strata	Events	Follow-up time (person-years)	Rate per 100,000 (95% CI)
Overall	472	1,948,634	24.2 (22.1-26.5)
2017	138	665,957	20.7 (17.4-24.5)
2018	177	676,087	26.2 (22.5-30.3)
2019	157	606,591	25.9 (22.0-30.3)
First quarter	121	491,878	24.6 (20.4-29.4)
Second quarter	129	492,783	26.2 (21.9-31.1)
Third quarter	109	489,088	22.3 (18.3-26.9)
Fourth quarter	113	474,885	23.8 (19.6-28.6)
<20 years	35	437,521	8.0 (5.6-11.1)
20-29 years	40	194,854	20.5 (14.7-28.0)
30-39 years	57	230,222	24.2 (18.8-32.1)
40-49 years	92	264,175	34.8 (28.1-42.7)
50-59 years	73	273,424	26.7 (20.9-33.6)
60-69 years	85	249,185	34.1 (27.2-42.2)
70-79 years	53	178,525	29.7 (22.2-38.8)
≥80 years	37	120,727	30.6 (21.6-42.2)
Male	223	908,617	24.5 (21.4-28.0)
Female	249	1,040,009	23.9 (21.1-27.1)

[1] ICD 10 code G51.0

Table 2 Incidence rate of Bell's palsy per 100,000 person-years in IMS® Disease Analyzer France (broad definition[1])

Bell's palsy broad			
Strata	Events	Follow-up time (person-years)	Rate per 100,000 (95% CI)
Overall	1191	1,942,977	61.3 (57.9-64.9)
2017	372	664,124	56.0 (50.5-62.0)
2018	420	674,144	62.3 (56.5-68.6)
2019	399	604,708	66.0 (59.7-72.8)
First quarter	298	490,480	60.8 (54.1-68.1)
Second quarter	312	491,366	63.5 (56.6-70.9)
Third quarter	285	487,662	58.4 (51.9-65.6)
Fourth quarter	296	473,469	62.5 (55.6-70.1)
<20 years	50	437,492	11.4 (8.5-15.1)
20-29 years	84	194,698	43.1 (34.4-53.4)
30-39 years	159	229,649	69.2 (58.9-80.9)
40-49 years	241	263,072	91.6 (80.4-103.9)
50-59 years	217	272,218	79.7 (69.5-91.1)
60-69 years	196	248,150	79.0 (68.3-90.9)
70-79 years	143	177,629	80.5 (67.9-94.8)
≥80 years	101	120,070	84.1 (68.5-102.2)
Male	458	906,717	50.5 (46.0-55.4)
Female	733	1,036,250	70.7 (65.7-76.0)

[1] ICD 10 codes G51.0, G51.8, G51.9

3.7.1.1. Guillain-Barré syndrome

The incidence rate of Guillain-Barré syndrome per 100,000 person-years is shown in Table 3. A total of 78 patients were excluded from the denominators due to a prior history of Guillain-Barré syndrome and 1,038,766 patients contributed follow-up time for the analysis.

A total of 27 incident cases were observed. The overall incidence was 1.4 (95% CI 0.9-2.0) per 100,000 person-years. The highest yearly incidence, 1.8 per 100,000 person-years, was observed in 2017. The incidence rate was highest in the age group 60-69 years.

Table 3 Incidence rate of Guillain-Barré syndrome per 100,000 person-years in IMS® Disease Analyzer France [1]

Guillain-Barré syndrome			
Strata	Events	Follow-up time (person-years)	Rate per 100,000 (95% CI)
Overall	27	1,951,447	1.4 (0.9-2.0)
2017	<20	666,861	1.8 (0.9-3.1)
2018	<20	677,053	1.0 (0.4-2.1)
2019	<20	607,533	1.3 (0.6-2.6)
First quarter	<20	492,570	2.0 (1.0-3.7)
Second quarter	<20	493,486	1.0 (0.3-2.4)
Third quarter	<20	489,799	0.8 (0.2-2.1)
Fourth quarter	<20	475,591	1.7 (0.7-3.3)
<20 years	0	437,619	0.0 (0.0-0.8)
20-29 years	<20	195,047	1.0 (0.1-3.7)
30-39 years	<20	230,513	0.9 (0.1-3.1)
40-49 years	<20	264,653	1.5 (0.4-3.9)
50-59 years	<20	273,989	1.5 (0.4-3.7)
60-69 years	<20	249,765	3.6 (1.6-6.8)
70-79 years	<20	178,878	2.2 (0.6-5.7)
≥80 years	<20	120,982	1.7 (0.2-6.0)
Male	<20	910,028	1.3 (0.7-2.3)
Female	<20	1,041,410	1.4 (0.8-2.4)

[1] ICD 10 code G61.0

3.8. Results for the German dataset

3.8.1. Bell's palsy narrow and broad definition

The incidence rate of Bell's palsy narrow definition per 100,000 person-years is shown in Table 4. A total of 13,325 patients were excluded from the denominators due to a prior history of Bell's palsy (narrow definition) and 3,327,497 patients contributed follow-up time for the analysis.

For the Bell's palsy broad definition results are shown in Table 5. A total of 14,099 patients were excluded from the denominators due to a prior history of Bell's palsy (broad definition) and 3,326,871 patients contributed follow-up time for the analysis.

Results using a narrow or a broad definition were similar. The overall incidence was 67.2 (95% CI 65.2-69.2) per 100,000 person-years for the narrow definition and 70.9 (95% CI 68.9-72.9) per 100,000 person-years for the broad definition. For both definitions the incidence rate was higher in males compared to females. The incidence rate also increased with increasing age. The incidence rate was higher in the first quarter compared to the fourth quarter.

Table 4 Incidence rate of Bell's palsy per 100,000 person-years in IMS® Disease Analyzer Germany (narrow definition[1])

Bell's palsy narrow			
Strata	Events	Follow-up time (person-years)	Rate per 100,000 (95% CI)
Overall	4,529	6,741,919	67.2 (65.2-69.2)
2017	1,453	2,177,820	66.7 (63.3-70.2)
2018	1,504	2,356,353	63.8 (60.6-67.1)
2019	1,572	2,207,745	71.2 (67.7-74.8)
First quarter	1,195	1,667,856	71.6 (67.6-75.8)
Second quarter	1,117	1,692,375	66.0 (62.2-70.0)
Third quarter	1,147	1,705,396	67.3 (63.4-71.3)
Fourth quarter	1,070	1,676,291	63.8 (60.1-67.8)
<20 years	116	448,089	25.9 (21.4-31.0)
20-29 years	343	710,238	48.3 (43.3-53.7)
30-39 years	462	822,028	56.2 (51.2-61.6)
40-49 years	480	913,181	52.6 (48.0-57.5)
50-59 years	831	1,277,379	65.1 (60.7-69.6)
60-69 years	797	1,066,207	74.8 (69.7-80.1)
70-79 years	783	857,519	91.3 (85.0-97.9)
≥80 years	717	647,277	110.8 (102.8-119.2)
Male	2,254	3,168,786	71.1 (68.2-74.1)
Female	2,265	3,560,117	63.6 (61.0-66.3)

[1] ICD 10 code G51.0

Table 5 Incidence rate of Bell's palsy per 100,000 person-years in IMS® Disease Analyzer Germany (broad definition[1])

Bell's palsy broad			
Strata	Events	Follow-up time (person-years)	Rate per 100,000 (95% CI)
Overall	4,777	6,740,043	70.9 (68.9-72.9)
2017	1,531	2,177,257	70.3 (66.8-73.9)
2018	1,587	2,355,722	67.4 (64.1-70.8)
2019	1,659	2,207,064	75.2 (71.6-78.9)
First quarter	1,273	1,667,408	76.3 (72.2-80.7)
Second quarter	1,174	1,691,911	69.4 (65.5-73.5)
Third quarter	1,201	1,704,917	70.4 (66.5-74.5)
Fourth quarter	1,129	1,675,807	67.4 (63.5-71.4)
<20 years	120	448,074	26.8 (22.2-32.0)
20-29 years	364	710,238	51.3 (46.1-56.8)
30-39 years	497	821,833	60.5 (55.3-66.0)
40-49 years	511	912,964	56.0 (51.2-61.0)
50-59 years	889	1,276,956	69.6 (65.1-74.3)
60-69 years	833	1,065,823	78.2 (72.9-83.6)
70-79 years	822	857,183	95.9 (89.5-102.7)
≥80 years	741	647,046	114.5 (106.4-123.1)
Male	2,350	3,168,084	74.2 (71.2-77.2)
Female	2,414	3,558,959	67.8 (65.1-70.6)

[1] ICD 10 codes G51.0, G51.8, G51.9

3.8.1.1. Guillain-Barré syndrome

The incidence rate of Guillain-Barré syndrome per 100,000 person-years is shown in Table 6. A total of 1,117 patients were excluded from the denominators due to a prior history of Guillain-Barré syndrome and 3,337,278 patients contributed follow-up time for the analysis.

The overall incidence rate of Guillain-Barré syndrome was 4.5 (95% CI 4.0-5.0) per 100,000 person-years. The incidence rate was numerically higher in males compared to females, but confidence

intervals were slightly overlapping. The incidence rate increased with increasing age up to the age group 60-69 years and 70-79 years. There was no clear evidence of seasonality.

Table 6 Incidence rate of Guillain-Barré syndrome per 100,000 person-years in IMS® Disease Analyzer Germany [1]

Guillain-Barré syndrome			
Strata	Events	Follow-up time (person-years)	Rate per 100,000 (95% CI)
Overall	305	6,770,517	4.5 (4.0-5.0)
2017	103	2,186,582	4.7 (3.8-5.7)
2018	103	2,366,082	4.4 (3.6-5.3)
2019	99	2,217,853	4.5 (3.6-5.4)
First quarter	91	1,674,738	5.4 (4.4-6.7)
Second quarter	86	1,699,462	5.1 (4.0-6.2)
Third quarter	65	1,712,684	3.8 (2.9-4.8)
Fourth quarter	63	1,683,634	3.7 (2.9-4.8)
<20 years	9	448,510	2.0 (0.9-3.8)
20-29 years	13	711,594	1.8 (1.0-3.1)
30-39 years	19	824,481	2.3 (1.4-3.6)
40-49 years	30	916,323	3.3 (2.2-4.7)
50-59 years	62	1,282,674	4.8 (3.7-6.2)
60-69 years	77	1,071,673	7.2 (5.7-9.0)
70-79 years	62	862,995	7.2 (5.5-9.2)
≥80 years	33	652,266	5.1 (3.5-7.1)
Male	164	3,182,533	5.2 (4.4-6.0)
Female	141	3,574,939	3.9 (3.3-4.7)

[1] ICD 10 code G61.0

4. Interpretation of the results and discussion

When interpreting incidence rates obtained from IMS® Disease Analyzer France and Germany it should be considered that denominators are not based on true population denominators. Instead they are based on patients with health encounters, where patients are considered observable for as long as they have a minimum consultation frequency of one visit per year. When establishing denominators, future visits after the yearly time period are considered. Due to the fact that the last visit of the patient

during the time period is more likely to represent the last visit ever of the patient as the end date of data availability approaches, the denominators shrink towards the end of data availability whereas numerators stay the same.

Also, for France and Germany, patients do not need to register with a primary care provider and do not need to always visit the same GP, although it is expected that patients do visit the same GP to a large extent. This makes the information about the patient in the IMS® Disease Analyzer France and Germany databases patchy because the same person cannot be identified uniquely across practices.

In France it is also not required for GPs to record a diagnosis as a reason for a patient visit, which means that diagnoses can be under-recorded in IMS® Disease Analyzer France.

In Germany, the age distribution for patients visiting GPs show an under-representation of young children because it is common practice for parents to visit a paediatrician rather than a GP for the care of younger children. In IMS® Disease Analyzer Germany, the age of patients is not provided in patients older than 99 years at the time of the database creation. As we only included patients with known age, the very oldest patients were excluded from our analyses.

Another consideration of importance for the estimation of incidence rates is the extent to which a patient is diagnosed with the condition in primary care, i.e. whether the diagnosis is captured directly in primary care or if the diagnosis needs to be transferred from secondary care, a process which may be incomplete. Also, as with all diagnoses, it can be uncertain whether a recorded diagnosis represents the occurrence of a new diagnosis or if the patient had instead consulted the physician due to sequelae related to an existing diagnosis.

The expected impact of the above considerations on incidence rates would be:

- An overestimation of incidence rates due to underestimation of the true population denominator, especially at the end of data availability.
- An overestimation of incidence rates due to patchy data: It is possible that events in the history of the patient are missing in the patient records resulting in misclassification of person-time as incident. This overestimates incidence rates because rates are higher in non-incident patients.
- An underestimation of incidence rates due to patchy data including incomplete transfer of diagnosis data from secondary care: For example, Bell's palsy may be confused with stroke and may lead to the patient seeking acute secondary care instead of primary care.
- Possible underestimation of incidence rates in IMS® Disease Analyzer France due to under-recording of diagnoses.
- Risk of bias in younger children in IMS® Disease Analyzer Germany with unknown impact on estimation of incidence rates due to limited and possibly skewed patient population. Reduced representation of younger children results in higher overall estimates for incidence rates that increase with increasing age.

4.1. Published incidence rates of Bell's palsy

Bell's palsy is expected to have an annual incidence rate of 15-30 per 100,000 population [4, 8-11], but in a Korean population the annual incidence rate was 57 per 100,000 population [12] and in the Swiss population the annual incidence rate was also around 50 per 100,000 population [13]. A published review of the literature stated that although most incidence estimates varied between 11 and 40 cases per 100,000 population per year, figures as low as 8 and as high as 240 cases per

100,000 population per year were found in the literature [14]. Bell's palsy is considered to be most common between ages 15 to 40 [15]. The incidence may be higher in the winter compared to summer months [16], with a possible association to respiratory infections [17]. In Italy, a higher occurrence of Bell's palsy was observed during the COVID-19 outbreak compared to the year before [18].

4.2. Incidence rates of Bell's palsy from the ADVANCE study

Results from the ADVANCE study showed an overall incidence rate per 100,000 person-years of Bell's palsy of 23.84 (95% confidence interval 23.64-24.05). The ADVANCE study, where based on ICD 10 codes, used the narrow definition of Bell's palsy. Results by database showed the following incidence rates (95% confidence intervals) per 100,000 person-years (results from Italy are significantly lower compared to the other participating countries):

- THIN UK: 32.1 (31.65–32.58)
- ARS Italy: 6.7 (6.47–6.97)
- BIFAP Spain: 42.4 (41.62–43.10)
- Denmark: 19.6 (19.28–19.93)

4.3. Discussion of results of Bell's palsy from IMS® Disease Analyzer France and Germany

Using the same definition of Bell's palsy as in the ADVANCE/ACCESS study, overall estimates per 100,000 person-years (95% confidence intervals) were:

- IMS® Disease Analyzer France: 24.2 (22.1-26.5)
- IMS® Disease Analyzer Germany: 67.2 (65.2-69.2)

The French data seem more compatible with the published literature in that adult middle-aged patients had the highest incidence rates, whereas the German data show incidence rates that continue to increase with age up to the oldest age group. This is not expected for Bell's palsy and may indicate some misclassification of stroke as Bell's palsy. However, this is not expected to have an impact on incidence rates in younger patients as stroke is less likely in these patients. Nevertheless, it would be expected to have an impact on the overall incidence rates.

The French data also fall within the range of the estimates from the ADVANCE study whereas the estimates from Germany are higher. Both rates are subject to a risk of overestimation due to underestimation of denominators. The French rate is also subject to a risk of underestimation due to possible under-recording of diagnoses. In addition, there is an unknown risk of misclassification of the diagnosis and a possibility of incomplete transfer of the diagnosis from other caregivers.

Using the broad definition of Bell's palsy had a marked effect on the incidence rates in France and little effect on the incidence rates in Germany. In order to reduce the risk of misclassification it is considered preferable to use the narrow definition of Bell's palsy.

Quarterly results show no clear seasonal pattern in the French data with lowest incidence rates in the first quarter. In the German data the incidence rate was higher during the first quarter compared to the fourth quarter.

4.4. Published incidence rates of Guillain-Barré syndrome

In a meta-analysis of published studies [19] crude incidences per 100,000 were stated to range from 0.81 to 1.89. The incidence rate increased with increasing age (from 0.62 to 2.66) [19]. The variation between incidence estimates in different studies was larger in older compared to younger patients [19]. The incidence rates were higher in male compared to female patients [19]. Similar incidence rates were reported in another review of the published literature with incidence rates per 100,000 between 0.84 and 1.91 [20]. Guillain-Barré syndrome is believed to be an autoimmune reaction following certain bacterial and viral infections [19], and has for example been reported following influenza vaccination [21, 22]. It has also been reported in patients following COVID-19 [23]. A study from Italy showed a variation in annual incidence rates per 100,000 from 0.9 to 5.37 with a mean of 3 [22].

4.5. Incidence rates of Guillain-Barré syndrome from the ADVANCE study

Results from the ADVANCE study showed an overall incidence rate per 100,000 person-years of Guillain-Barré syndrome of 2.06 (95% confidence interval 2.00-2.12). The ADVANCE study, where based on ICD 10 codes, used the same definition of Guillain-Barré syndrome. Results by database showed the following incidence rates (95% confidence intervals) per 100,000 person-years:

- THIN UK: 1.8 (1.67–1.89)
- ARS Italy: 2.6 (2.49–2.80)
- BIFAP Spain: 1.1 (0.97–1.21)
- Denmark: 2.4 (2.27–2.49)

4.6. Incidence rates of Guillain-Barré syndrome from the ACCESS study

Incidence rates for Guillain-Barré syndrome are currently available between 2017 and 2020 from Italy. Reported yearly incidence rates per 100,000 person-years (95% confidence intervals) are the following:

- 2017: 3.8 (3.15-4.48)
- 2018: 3.8 (3.19-4.52)
- 2019: 4.0 (3.39-4.75)
- 2020: 3.7 (2.83-4.87)

4.7. Discussion of results of Guillain-Barré syndrome from IMS® Disease Analyzer France and Germany

Using the same definition of Guillain-Barré syndrome as in the ADVANCE/ACCESS study, overall estimates per 100,000 person-years (95% confidence intervals) were:

- IMS® Disease Analyzer France: 1.4 (0.9-2.0)
- IMS® Disease Analyzer Germany: 4.5 (4.0-5.0)

For Guillain-Barré syndrome the incidence rate was within the expected range in IMS® Disease Analyzer France. The results from IMS® Disease Analyzer Germany were in the higher range of expected incidence rates. The data from both France and Germany were also in line with published

data suggesting that the risk of Guillain-Barré syndrome increases with increasing age. Estimates were also numerically higher in males compared to females in Germany, but confidence intervals were overlapping.

The data on Guillain-Barré syndrome are also subject to risks of over- and underestimation similar to the data on Bell's palsy. However, the risk of misclassification of diagnosis, and the extent to which patients are diagnosed in primary care could be different for Bell's palsy and Guillain-Barré syndrome as Guillain-Barré syndrome is more likely to be diagnosed in secondary care whereas Bell's palsy is also likely to be diagnosed in primary care.

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