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A nationwide population-based cohort study of the incidence of severe and rare infections among adults with psoriasis in Denmark*

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Abstract

Background Patients with psoriasis have a high risk for multiple comorbid conditions. However, few studies have examined the association between psoriasis and severe and rare infections. This study reports the incidence of severe and rare infections (considered as rare in Denmark) among Danish patients with psoriasis, compared with the general population.

Objectives The objectives of this study were to assess the incidence and risk of severe and rare infections in Danish patients with psoriasis and the matched general population, and to compare this risk for patients with severe or mild psoriasis with that of the general population.

Methods Data for individuals aged ≥18 years who were alive and resident in the source population were collected from the Danish National Patient Register between 1 January 1997 and 31 December 2018. Individuals with any of the investigated chronic infections prior to inclusion were excluded. Patients with psoriasis were matched (1 : 6) for age and sex with general population controls. Severe infections were defined as infections requiring treatment in a hospital setting and rare infections included HIV, hepatitis B and C, and tuberculosis infections. Incidence rates (IRs) were reported per 100 000 person-years of exposure. Severe psoriasis was defined according to previous or active use of systemic or biological treatment. Patients who never received biological and/or systemic treatment were categorized as having mild psoriasis.

Results A total of 94 450 patients with psoriasis were matched with 566 700 controls. The respective IRs were higher for patients with any psoriasis compared with controls; IR 3104·9 [95% confidence interval (CI) 3066·6 to 3143·7] and IR 2381·1 (95% CI 2367·6 to 2394·6) for any infection, IR 3080·6 (95% CI 3042·5 to 3119·3) and IR 2364·4 (95% CI 2350·9 to 2377·9) for severe infections, and IR 42·9 (95% CI 38·89 to 47·4) and IR 31·8 (95% CI 30·34 to 33·3) for rare infections, respectively. Patients with severe psoriasis had higher IRs of severe or rare infections (IR 3847·7, 95% CI 3754·3 to 3943·4) compared with patients with mild psoriasis and controls.

Conclusions As the severity of psoriasis increases, so does the risk of severe and rare infections. Therefore, clinicians should be aware of the increased risk of severe and rare infections in patients with severe psoriasis so that early investigation and treatment can be initiated.

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Conflicts of interest
N.L. has been a paid speaker for Eli Lilly and Janssen Cilag. L.S. has received honoraria as consultant and/or speaker from AbbVie, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma, UCB, Almirall, Bristol Myers Squibb and Sanofi. She has served as an investigator for AbbVie, Sanofi, Janssen Cilag, Boehringer Ingelheim, AstraZeneca, Eli Lilly, Novartis, Regeneron and LEO Pharma, and has received research grants from Novartis, Sanofi, Bristol Myers Squibb, Janssen Cilag and LEO Pharma. A.E. has received research funding from Pfizer, Eli Lilly, Novartis, Bristol Myers Squibb, AbbVie, Janssen Pharmaceuticals, the Danish National Psoriasis Foundation, the Simon Spies Foundation and the Kongelig Hofbundtmager Aage Bang Foundation, in addition to honoraria as a consultant and/or speaker from AbbVie, Almirall, LEO Pharma, Zuellig Pharma Ltd., Galápagos NV, Sun Pharmaceuticals, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, UCB, Mylan, Bristol Myers Squibb and Janssen Pharmaceuticals. V.T. is an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA and C.R. and I.A. are employees of Novartis Pharma AG, Basel, Switzerland.

Data availability

Novartis is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the study, in accordance with applicable laws and regulations.

Ethics statement

Approval from an ethics committee is not required for register studies in Denmark.

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What is already known about this topic?

- Few studies have looked at the incidence and prevalence of serious infections (associated with hospitalization) and rare infections including tuberculosis, hepatitis B and C, and HIV among patients with different severities of psoriasis.

What does this study add?

- Patients with psoriasis have an increased risk of severe and rare infections.
- Clinicians should be aware of the increased risk of severe and rare infections in patients with severe psoriasis so that early investigation and treatment can be initiated.

Psoriasis is a common chronic, immune-mediated inflammatory disease that affects 2 to 4% of the population in Western countries.[1,2] Psoriasis is characterized by lesional skin exhibiting red plaques with silver or white scales and disease pathogenesis is driven by a network of leucocytes and cytokines.[3] The global burden of psoriasis is large, both in terms of impact on quality of life for patients[4] and healthcare costs.[5–7]

Patients with psoriasis are known to be at higher risk for multiple comorbid conditions, including psoriatic arthritis, nonalcoholic steatohepatitis, cardiovascular disease and certain types of cancer.[8–17] Previous studies have also found that patients with psoriasis have an increased risk of serious infections (associated with hospitalization, pneumonia and herpes zoster).[18–20] A UK population-based cohort study from 2020 describes the risk of hospitalization and death resulting from infection in people with psoriasis and found associations with small increases in risk for any infection, respiratory infections and soft tissue and skin infections.[21] Additionally, patients with psoriasis are often treated with immunosuppressive therapies, which may lead to or aggravate infections. Thus, the potential association between psoriasis and risk of incidence of infections is important. However, few studies have assessed the incidence and risk of severe infections and rare infections, the latter of which, in Denmark, includes tuberculosis (TB), hepatitis B (HBV) and hepatitis C (HCV) and HIV, among patients with psoriasis with different disease severities.[17–20]

There is currently limited real-world evidence regarding the occurrence and risk of severe and rare infections among patients with psoriasis. Furthermore, certain treatments for psoriasis may aggravate infections. Therefore, the current nationwide population-based cohort study aimed to investigate Danish nationwide administrative longitudinal registries for descriptive data on the incidence of severe infections and infections considered rare in Denmark among individuals with different psoriasis disease severities and matched individuals from the general population. Additionally, the risk for all patients with mild or severe psoriasis was compared with that of the general population.

Materials and methods

Study design and setting

In this population-based cohort study, descriptive data were obtained from Danish administrative registries for residents in Denmark and were linked using the Civil Registration System.[22] Collected data were linked using a unique numerical identification assigned to all Danish residents since 1968.[22] National data on drug use in Denmark were extracted from the Danish National Prescription Database.[23] This registry contains complete information, from 1 January 1995 onwards, on all prescriptions dispensed to Danish residents at community pharmacies. Registered drugs are categorized according to the Anatomical Therapeutic Chemical Classification System, a hierarchical classification developed by the World Health Organization for purposes of drug-use statistics. The Danish National Prescription Database is reported to have a high level of completeness and validity.[24] Medical data from inpatient and outpatient hospital clinics, including medication and treatment procedures (e.g. medication given during hospitalization or given directly from the outpatient clinics, or phototherapy treatments) were extracted from the Danish National Patient Register,[25] which contains nationwide data on hospital admissions since 1977 and outpatient contacts since 1995. In this registry, discharge and contact diagnoses are coded according to the International Classification of Diseases (ICD) 8th revision (ICD-8) from 1977 to 1993, and according to the ICD 10th revision (ICD-10) since 1994, noting that ICD-9 was never utilized.

Participants

All individuals in the entire Danish population aged ≥18 years between 1 January 1997 and 31 December 2018 were identified. To be eligible for inclusion in the study, individuals had to be alive and resident in the source population and have at least 1 day of follow-up. Individuals with any of the investigated chronic infections prior to inclusion were excluded. As

study cases, we identified all individuals with at least one diagnosis of psoriasis (ICD-10 diagnosis code L40·0 or L40·9) in the Danish National Patient Register during the study period or those who had filled a minimum of two prescriptions of calcipotriol (Anatomical Therapeutic Chemical code D05AX02 or D05AX52). Patients were followed from the date of first recorded psoriasis diagnosis or second calcipotriol prescription during the study period until the first of either death, migration, the occurrence of an endpoint, or 31 December 2018. Each patient with psoriasis was matched for sex and exact date of birth with six individuals from the general population in Denmark, using incidence density sampling. Furthermore, patients were stratified by psoriasis severity according to treatment with systemics, including biologics, for psoriasis (Table S1; see Supporting Information). The category of patients with 'any' type of psoriasis included all cases irrespective of severity. Patients with severe psoriasis were patients treated with systemic agents for psoriasis, and patients with mild psoriasis were those who were not treated with any of these agents. Psoriasis severity was included as a time-dependent variable and patients with severe psoriasis were considered as having severe psoriasis from the prescription date of the first prescribed systemic agent. This was in accordance with the newly proposed categorization of psoriasis severity from the International Psoriasis Council (IPC).[26] The diagnosis of psoriasis has been validated in the Danish National Patient Register, with an overall positive predictive value (PPV) of 97·1% (98·0% in adults and 94·6% in children) based on medical chart reviews.[27] The diagnosis of psoriasis based on prescription of calcipotriol has been validated with a PPV of 83·3% in adults.[28]

Study outcomes

The outcomes of the current study were occurrences of severe and/or rare infections. Rare infections included HIV, TB, HBV and HCV. Severe infections were defined as infections requiring assessment at a hospital department (both inpatients and outpatients); the full list of infections is provided in Table S2 (see Supporting Information). The list of infections was based on previous studies in atopic dermatitis and inflammatory bowel diseases (IBDs).[29,30] In a subanalysis, infections were limited to infections leading to hospitalization (inpatients only).

Statistical analysis

Population statistics were obtained and linked by Statistics Denmark, a governmental institution that collects and maintains data. Descriptive data were tabulated for patients with psoriasis and the matched general population. Incidence rates (IRs) are reported per 100 000 person-years and presented with 95% confidence intervals (CIs). Summary statistics were generated and expressed as mean for normally distributed variables, median and interquartile range (IQR) for nonnormally distributed continuous variables, and frequency for categorical variables. For age, both mean (SD) and median (IQRs) were presented, to give a more detailed impression of the subgroup distribution. Analyses were carried out for all patients with psoriasis, stratified by severity (mild and severe), and in the general population. Cox proportional hazards regression models with calendar time as the underlying timescale were used to estimate hazard ratios (HRs) for the association between psoriasis and the infections. In the adjusted model, the adjusted HRs (aHRs) were adjusted for sex, age, ethnicity, socioeconomic status, alcohol-related conditions and Charlson Comorbidity Index. Cox proportional hazard regressions were used to compare all severities of psoriasis with the matched general population. Subanalyses were conducted according to psoriasis severity, comparing those with mild or severe psoriasis with the matched general population.

Results

Participants

A total of 94 450 patients with psoriasis and 566 700 general population reference individuals matched for age and sex were included in this study. General study cohort characteristics are shown in Table 1. The median age was 52·3 years (IQR 38·3

Table 1 Characteristics of study cohort

	Reference (N = 566 700)	Psoriasis (N = 94 450)
Female sex	284 340 (50·2)	47 390 (50·2)
Age, years, median (IQR)	52·3 (38·3–64·1)	52·3 (38·3–64·1)
Mean (SD)	51·5 (17·0)	51·5 (17·0)
Mild psoriasis	–	85 389 (90·4%)
Severe infections	118 059 (20·8)	24 742 (26·2)
Rare infections	1761 (0·3)	396 (0·4)
Socioeconomic status		
Lowest	114 515 (20·2)	17 716 (18·8)
Below average	113 138 (20·0)	19 091 (20·2)
Average	113 164 (20·0)	19067 (20·2)
Above average	113 321 (20·0)	18 908 (20·0)
Highest	112 562 (19·9)	19 668 (20·8)
Alcohol-related conditions	24 676 (4·4)	5468 (5·8)
Charlson Comorbidity Index		
None	532 049 (93·9)	86 120 (91·2)
One comorbidity	24 014 (4·2)	5482 (5·8)
Two comorbidities	5116 (0·9)	1317 (1·4)
Three or more comorbidities	5521 (1·0)	1531 (1·6)
Specific comorbidities		
COPD	12 731 (2·3)	3111 (3·3)
Hypertension	69 951 (12·3)	14 622 (15·5)
Hyperlipidaemia	66 008 (11·7)	13 313 (14·1)
Ischaemic heart disease	30 731 (5·4)	6603 (7·0)
DM2	24 655 (4·4)	5855 (6·2)

COPD, chronic obstructive pulmonary disease; DM2, type 2 diabetes mellitus; IQR, interquartile range. Data are presented as n (%) unless otherwise stated.

Table 2 Infections among the general population and patients with any psoriasis

IR per 100 000 person-years among the general population (95% CI)		IR per 100 000 person-years among patients with any psoriasis (95% CI)	IR differences per 100 000 person-years (95% CI)
Any infections (rare or severe)	2381·1 (2367·6–2394·6)	3104·9 (3066·6–3143·7)	723·8 (699·0–749·1)
Severe infections			
Any severe infections	2364·4 (2350·9–2377·9)	3080·6 (3042·5–3119·3)	716·2 (691·6–741·4)
CNS infections	21·29 (20·12–22·55)	29·65 (26·34–33·38)	8·36 (6·23–10·84)
URTI	127·20 (124·26–130·21)	173·68 (165·36–182·42)	46·48 (41·10–52·21)
Pulmonary infections	772·53 (765·16–779·98)	984·21 (963·90–1005·01)	211·7 (198·7–227·0)
Heart infections	34·72 (32·00–36·30)	45·05 (40·92–49·59)	10·33 (8·92–13·29)
GI infections	565·04 (558·73–571·42)	718·21 (700·84–736·01)	153·2 (142·1–164·6)
UTI	456·33 (450·69–462·03)	564·98 (549·70–580·67)	108·7 (99·0–118·6)
Gynaecological infections	44·01 (41·59–46·57)	53·97 (47·63–61·16)	9·96 (6·04–14·58)
Musculoskeletal infections	55·94 (53·99–57·94)	82·96 (77·28–89·05)	27·02 (23·28–31·11)
Skin and subcutaneous tissue infections	337·18 (332·33–342·09)	502·94 (488·48–517·82)	165·8 (156·2–175·7)
Opportunistic infections	86·91 (84·48–89·39)	115·33 (108·59–122·48)	28·42 (24·11–33·08)
Other infections	280·60 (276·20–285·06)	381·85 (369·38–394·74)	101·3 (93·2–109·7)
Sepsis	240·74 (236·68–244·87)	335·40 (323·75–347·46)	94·7 (87·1–102·6)
Rare			
Any rare infections	31·79 (30·34–33·31)	42·91 (38·89–47·35)	11·13 (8·55–14·05)
HIV	3·86 (3·37–4·41)	5·95 (4·57–7·74)	2·09 (1·19–3·34)
Hepatitis (B and C)	21·23 (20·05–22·48)	29·89 (26·56–33·63)	8·65 (6·51–11·15)
Tuberculosis	7·05 (6·38–7·78)	7·46 (5·89–9·44)	0·41 (−0·49–1·66)

CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; IR, incidence rate; URTI, upper respiratory tract infections; UTI, urinary tract infections.

to 64·1), and 50·2% of the study cohort were female. Several comorbidities were more prevalent in patients with psoriasis compared with the general population (Table 1).

Incidence rates of any infections (severe and rare)

Patients with any type of psoriasis

Among patients with any type of psoriasis, the IR of any infection (severe and rare) per 100 000 person-years was higher at 3104·9 (95% CI 3066·6 to 3143·7), compared with 2381·1 (95% CI 2367·6 to 2394·6) for the control group (Table 2). The crude HR for patients with psoriasis and the age- and sex-matched general population (control group) was 1·31 (95% CI 1·29 to 1·33) and the HR adjusted for sex, age, ethnicity, socioeconomic status, alcohol-related conditions and Charlson Comorbidity Index (aHR) was 1·29 (95% CI 1·27 to1·31) (Table 3 and Figure 1). When infections were limited to only those infections leading to hospitalization (inpatients only), it resulted in a higher IR of 2005·1 (95% CI 1973·0 to 2037·7) among patients with any psoriasis, compared with 1531·8 (95% CI 1520·6 to 1543·0) among the control group (Table 4), and demonstrated similar HRs (Figure 2 and Table S3; see Supporting Information).

Patients with mild psoriasis

The IR of any infections among patients with mild psoriasis (IR 3003·5, 95% CI 2964·1 to 3043·4) was higher than in the control group (Table S4), and the aHR for patients with mild psoriasis compared with the matched general population was 1·26 (95% CI 1·25 to 1·28) (Figure 1 and Table S5; see Supporting Information). When infections were limited to only those infections leading to hospitalization, it resulted in an IR of 1925·7 (95% CI 1892·8 to 1959·1) among patients with mild psoriasis, with similar HRs for infections overall (Table S6; see Supporting Information).

Patients with severe psoriasis

The IR among patients with severe psoriasis (IR 3847·7, 95% CI 3754·3 to 3943·4) was higher than that found in the control group (Table 5); and the aHR for patients with severe psoriasis compared with the matched general population was 1·58 (95% CI 1·54–1·62) (Figure 1 and Table S7; see Supporting Information). When infections were limited to only those infections leading to hospitalization, it resulted in an IR of 2535·2 (95% CI 2456·2 to 2616·8) among patients with severe psoriasis (Table S8; see Supporting Information), with similar HRs for infections overall (Figure 2 and Table S9; see Supporting Information).

Incidence rates of any severe infections

Patients with any psoriasis

Among patients with any psoriasis, the IR of any severe infections was higher at 3080·6 (95% CI 3042·5 to 3119·3), compared with 2364·4 (95% CI 2350·9 to 2377·9) for the control group (Table 2). Pulmonary, gastrointestinal and urinary tract

Table 3 Infections among the general population and patients with any psoriasis

	Patient-years at risk	Number of events	HR (95% CI) crude	P-values	HR (95% CI) adjusted[a]	P-values
Any infections (rare or severe)						
Reference	4 987 540	118 756	–	–	–	–
Psoriasis	801 860	24 897	1·31 (1·29–1·33)	< 0·0001	1·29 (1·27–1·31)	< 0·0001
Severe infections						
Any severe infections						
Reference	4 993 240	118 059	–	–	–	–
Psoriasis	803 150	24 742	1·31 (1·29–1·32)	< 0·0001	1·29 (1·27–1·31)	< 0·0001
CNS infections						
Reference	5 545 840	1181	–	–	–	–
Psoriasis	924 040	274	1·39 (1·22–1·59)	< 0·0001	1·37 (1·20–1·56)	< 0·0001
URTI						
Reference	5 518 200	7019	–	–	–	–
Psoriasis	917 770	1594	1·37 (1·30–1·45)	< 0·0001	1·36 (1·29–1·43)	< 0·0001
Pulmonary infections						
Reference	5 404 440	41 751	–	–	–	–
Psoriasis	892 900	8788	1·28 (1·25–1·31)	< 0·0001	1·25 (1·22–1·28)	< 0·0001
Heart infections						
Reference	5 542 010	1924	–	–	–	–
Psoriasis	923 450	416	1·30 (1·17–1·44)	< 0·0001	1·26 (1·13–1·40)	< 0·0001
GI infections						
Reference	5 393 260	30 474	–	–	–	–
Psoriasis	892 640	6411	1·27 (1·24–1·31)	< 0·0001	1·25 (1·22–1·29)	< 0·0001
UTI						
Reference	5 452 470	24 881	–	–	–	–
Psoriasis	905 170	5114	1·24 (1·20–1·28)	< 0·0001	1·23 (1·19–1·26)	< 0·0001
Gynaecological infections						
Reference	2 730 940	1202	–	–	–	–
Psoriasis	455 790	246	1·23 (1·07–1·41)	0·004	1·20 (1·04–1·37)	0·01
Musculoskeletal infections						
Reference	5 533 190	3095	–	–	–	–
Psoriasis	920 980	764	1·48 (1·37–1·61)	< 0·0001	1·42 (1·31–1·54)	< 0·0001
Skin and subcutaneous infections						
Reference	5 442 850	18 352	–	–	–	–
Psoriasis	897 730	4515	1·49 (1·44–1·54)	< 0·0001	1·45 (1·41–1·50)	< 0·0001
Opportunistic infections						
Reference	5 531 270	4807	–	–	–	–
Psoriasis	920 870	1062	1·33 (1·24–1·42)	< 0·0001	1·30 (1·21–1·38)	< 0·0001
Other infections						
Reference	5 498 270	15 428	–	–	–	–
Psoriasis	912 930	3486	1·37 (1·32–1·42)	< 0·0001	1·34 (1·29–1·39)	< 0·0001
Sepsis						
Reference	5 519 210	13 287	–	–	–	–
Psoriasis	917 420	3077	1·39 (1·34–1·45)	< 0·0001	1·35 (1·29–1·40)	< 0·0001
Rare						
Any rare infections						
Reference	5 540 140	1761	–	–	–	–
Psoriasis	922 800	396	1·35 (1·21–1·51)	< 0·0001	1·34 (1·20–1·50)	< 0·0001
HIV						
Reference	5 549 580	214	–	–	–	–
Psoriasis	924 980	55	1·54 (1·14–2·07)	0·0044	1·58 (1·17–2·13)	0·0025
Hepatitis						
Reference	5 543 860	1177	–	–	–	–
Psoriasis	923 550	276	1·41 (1·23–1·60)	< 0·0001	1·39 (1·22–1·59)	< 0·0001
Tuberculosis						
Reference	5 549 360	391	–	–	–	–
Psoriasis	925 030	69	1·06 (0·82–1·37)	0·66	1·05 (0·81–1·36)	0·72

CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; HR, hazard ratio; URTI, upper respiratory tract infections; UTI, urinary tract infections. [a]Adjusted for sex, age, ethnicity, socioeconomic status, alcohol-related conditions and Charlson Comorbidity Index.

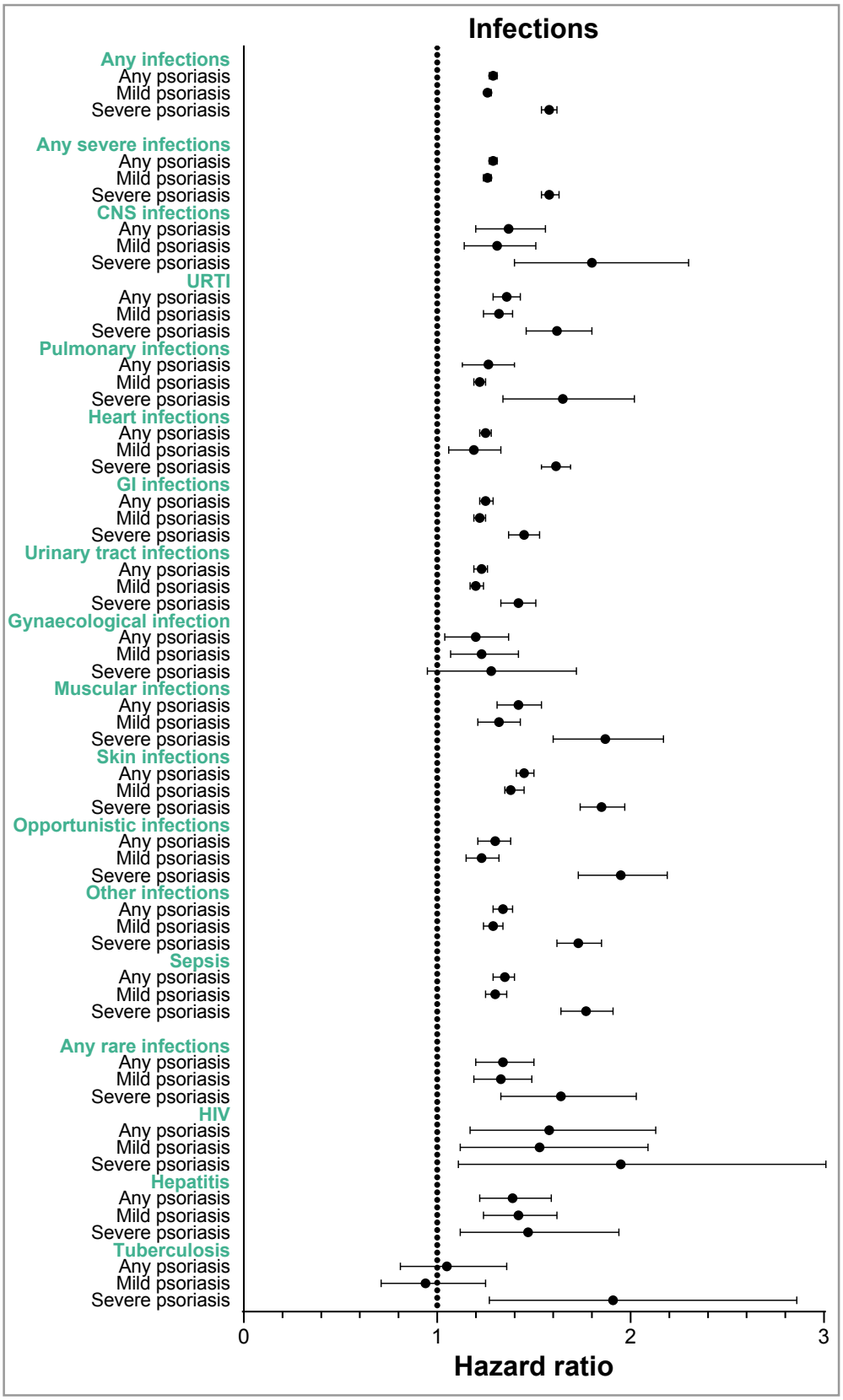

Figure 1 Hazard ratios (adjusted for sex, age, ethnicity, socioeconomic status, alcohol-related conditions and Charlson Comorbidity Index) for infections in patients with any psoriasis, patients with mild psoriasis and patients with severe psoriasis compared with the general population. CNS, central nervous system; GI, gastrointestinal; URTI, upper respiratory tract infections.

Table 4 Infections leading to hospitalization (inpatients only) among the general population and patients with any psoriasis

IR per 100 000 person-years among the general population (95% CI)		IR per 100 000 person-years among patients with any psoriasis (95% CI)	IR differences per 100 000 person-years (95% CI)
Any infections (rare or severe)	1531·8 (1520·6–1543·0)	2005·1 (1973·0–2037·7)	473·3 (452·4–494·7)
Serious infections			
Any severe infections	1529·7 (1518·5–1540·9)	2001·8 (1969·7–2034·3)	472·1 (451·2–493·4)
CNS infections	17·32 (16·25–18·45)	22·95 (20·06–26·26)	5·64 (3·81–7·81)
URTI	27·01 (25·67–28·42)	35·99 (32·29–40·11)	8·98 (6·63–11·69)
Pulmonary infections	620·59 (613·94–627·31)	780·45 (762·20–799·15)	159·9 (148·3–171·8)
Heart infections	29·04 (27·66–30·50)	36·62 (32·92–40·74)	7·58 (5·26–10·24)
GI infections	354·08 (349·05–359·18)	450·42 (436·57–464·72)	96·34 (87·52–105·5)
UTI	297·49 (292·91–302·13)	379·82 (367·25–392·83)	82·33 (74·34–90·70)
Gynaecological infections	23·13 (21·39–25·01)	27·03 (22·65–32·26)	3·90 (1·26–7·25)
Musculoskeletal infections	27·58 (26·23–29·00)	43·11 (39·06–47·57)	15·53 (12·84–18·57)
Skin and subcutaneous tissue infections	107·76 (105·01–110·57)	170·76 (162·34–179·63)	63·00 (57·33–69·06)
Opportunistic infections	46·34 (44·58–48·17)	63·25 (58·30–68·61)	16·91 (13·73–20·44)
Other infections	140·97 (137·85–144·16)	193·81 (184·92–203·13)	52·84 (47·07–58·97)
Sepsis	218·98 (215·11–222·93)	302·6 (291·53–314·08)	83·62 (76·42–91·15)
Rare			
Any rare infections	6·47 (5·83–7·18)	8·47 (6·78–10·57)	2·00 (0·95–3·39)
HIV	0·85 (0·64–1·13)	0·97 (0·51–1·87)	0·13 (−0·13–0·74)
Hepatitis	2·74 (2·34–3·22)	4·34 (3·18–5·91)	1·59 (0·84–2·69)
Tuberculosis	3·01 (2·59–3·50)	3·35 (2·36–4·77)	0·34 (−0·23–1·26)

CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; IR, incidence rate; URTI, upper respiratory tract infections; UTI, urinary tract infections.

infections showed the highest IRs (Table 2). The HR for any severe infections for patients with psoriasis compared with the control group was 1·31 (95% CI 1·29 to 1·32) and the aHR was 1·29 (95% CI 1·27 to 1·31) (Table 3). Psoriasis was associated with the development of all the assessed infections, compared with the control group (Figure 1). The highest observed HR was seen for musculoskeletal, skin and subcutaneous tissue infections (aHR 1·42, 95% CI 1·31 to 1·54 and aHR 1·45, 95% CI 1·41 to 1·50, respectively). The HR for central nervous system infections was 1·39 (95% CI 1·22 to 1·59) and the HR for opportunistic infections was 1·33 (95% CI 1·24 to 1·42). When infections were limited to only those infections leading to hospitalization, it resulted in an IR of 2001·8 (95% CI 1969·7 to 2034·3) among patients with psoriasis, compared with 1529·7 (95% CI 1518·5 to 1540·9) among the control group (Table 4), with similar HRs for all severe infections (Figure 2 and Table S3; see Supporting Information).

Patients with mild psoriasis

The IR among patients with mild psoriasis (IR 2979·1, 95% CI 2939·0 to 3018·8) was higher than the IR in the control group (Table S4), and the HR for patients with mild psoriasis compared with the matched general population was 1·26 (95% CI 1·24 to 1·28) (Table S5). When infections were limited to only those infections leading to hospitalization, it resulted in an IR of 1922·3 (95% CI 1899·5 to 1955·6) among patients with mild psoriasis, with similar HRs for infections overall (Table S6).

Patients with severe psoriasis

The IR of any severe infections among patients with severe psoriasis (IR 3824·6, 95% CI 3731·6 to 3919·9) was higher than that of the control group (Table 5) and the aHR for patients with severe psoriasis compared with the matched general population was 1·58 (95% CI 1·54 to 1·63) (Figure 1 and Table S7). For any severe infections leading to hospitalization (inpatients only) the IR was higher at 2537·7 (95% CI 2458·8 to 2619·2) among patients with severe psoriasis compared with 1460·9 (95% CI 1437·4 to 1484·7) among the control group (Table S8).

Incidence rates of any rare infections

Patients with any psoriasis

Among patients with any psoriasis, the IR of any rare infections was higher at 42·91 (95% CI 38·89 to 47·35), compared with 31·79 (95% CI 30·34 to 33·31) for the control group (Table 2). The IR was 5·95 (95% CI 4·57 to 7·74) for HIV, 7·46 (95% CI 5·89 to 9·44) for TB, and 29·89 (95% CI 26·56 to 33·63) for hepatitis (Table 2). Psoriasis was associated with an increased risk of any rare infections (aHR 1·34, 95% CI 1·20 to 1·50), which was attributed to higher incidences of HIV and hepatitis but not TB (Table 3). For any rare infections leading to hospitalization (inpatients only), the IR was higher at 8·47 (95% CI 6·78 to 10·57) among patients with psoriasis compared with 6·47 (95% CI 5·83 to 7·18)

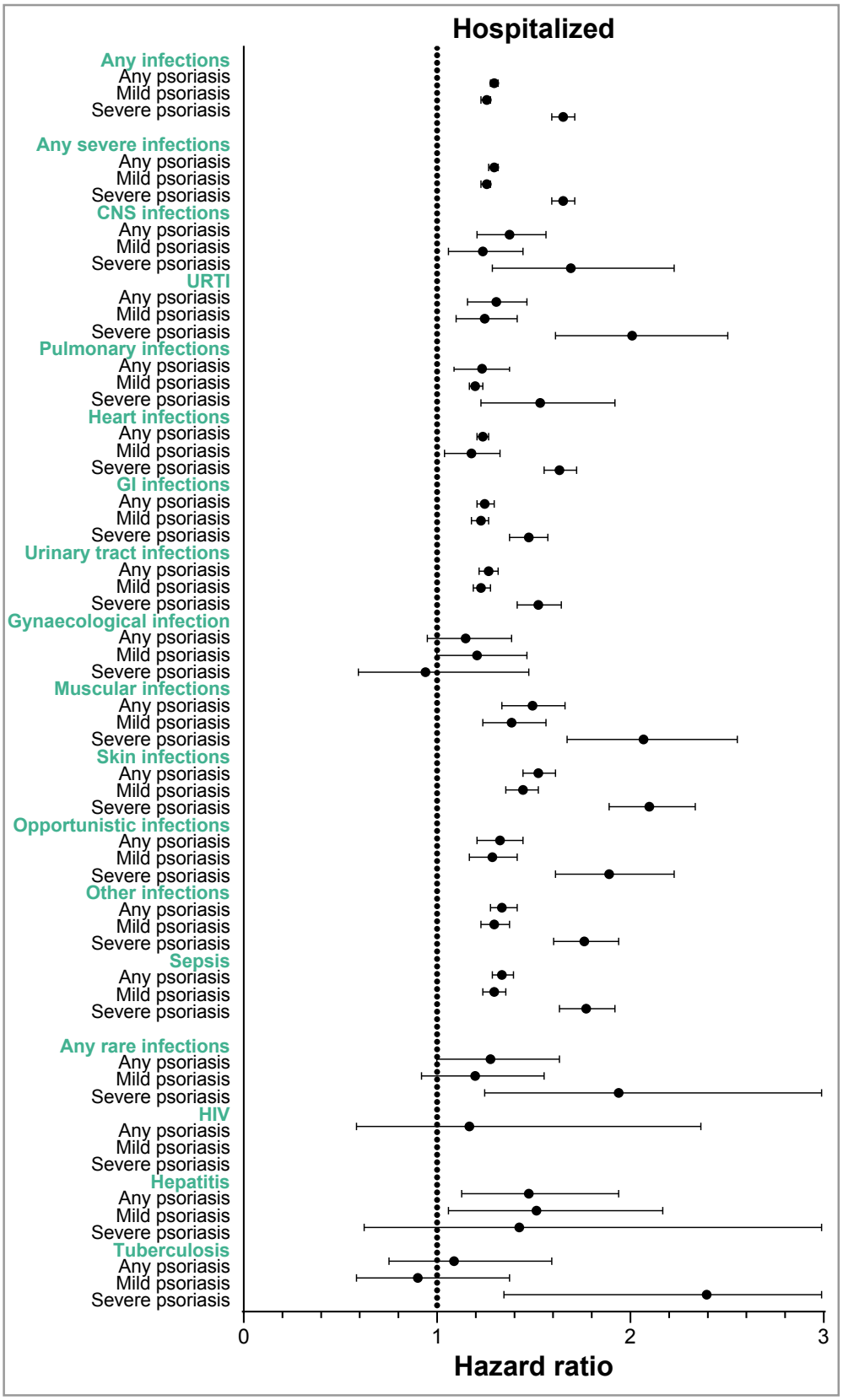

Figure 2 Hazard ratios (adjusted for sex, age, ethnicity, socioeconomic status, alcohol-related conditions and Charlson Comorbidity Index) for infections leading to hospitalization (inpatients only) in patients with any psoriasis, patients with mild psoriasis and patients with severe psoriasis compared with the general population. CNS, central nervous system; GI, gastrointestinal; URTI, upper respiratory tract infections.

Table 5 Infections among the general population and patients with severe psoriasis

IR per 100 000 person-years among the general population (95% CI)		IR per 100 000 person-years among patients with severe psoriasis (95% CI)	IR differences per 100 000 person-years (95% CI)
Any infections (rare or severe)	2351·9 (2322·9–2381·2)	3847·7 (3754·3–3943·4)	1495·8 (1431·4–1562·2)
Severe infections			
Any severe infections	2335·0 (2306·1–2364·1)	3824·6 (3731·6–3919·9)	1489·6 (1425·5–1555·8)
CNS infections	22·03 (19·53–24·84)	40·32 (32·47–50·06)	18·29 (12·94–25·22)
URTI	137·40 (130·92–144·21)	226·99 (207·11–248·79)	89·59 (76·19–104·6)
Pulmonary infections	732·82 (717·46–748·50)	1248·2 (1199·32–1299·0)	515·3 (481·9–550·5)
Heart infections	34·44 (31·28–37·92)	59·56 (49·84–71·18)	25·12 (18·56–33·26)
GI infections	581·99 (568·30–569·01)	872·69 (832·10–915·25)	290·7 (263·8–346·24)
UTI	445·53 (433·65–457·73)	663·59 (628·63–700·48)	218·1 (194·9–242·8)
Gynaecological infections	40·33 (35·52–45·79)	54·174 (41·49–70·73)	13·84 (5·98–24·94)
Musculoskeletal infections	55·23 (51·19–59·60)	110·88 (97·27–126·39)	55·64 (46·08–66·78)
Skin and subcutaneous tissue infections	342·69 (332·28–353·44)	671·88 (636·41–709·32)	329·19 (304·13–355·88)
Opportunistic infections	88·37 (83·20–93·85)	181·09 (163·46–200·63)	92·72 (80·25–106·8)
Other infections	298·21 (288·56–308·18)	542·26 (510·90–575·56)	244·1 (222·3–267·4)
Sepsis	235·25 (226·72–244·1)	450·33 (421·94–480·63)	215·1 (195·2–236·5)
Rare			
Any rare infections	31·45 (28·44–34·79)	55·69 (46·31–66·97)	24·24 (17·87–32·18)
HIV	4·15 (3·15–5·48)	7·86 (4·81–12·82)	3·70 (1·67–7·34)
Hepatitis	20·04 (17·66–22·73)	32·48 (25·52–41·34)	12·44 (7·86–18·61)
Tuberculosis	7·56 (6·15–9·28)	15·72 (11·11–22·22)	8·16 (4·96–12·94)

CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; IR, incidence rate; URTI, upper respiratory tract infections; UTI, urinary tract infections.

among the control group (Table 4). Only the association for hepatitis remained significant when infections were limited to those leading to hospitalization (Figure 2 and Table S3).

Patients with mild psoriasis

The IR among patients with mild psoriasis (IR 42·30, 95% CI 38·13 to 46·93) was higher than that found in the control group (Table S4); the HR was also higher than that found in the control group (Table S5). Restricting the definition of infections to only those leading to hospitalization resulted in an IR of 7·86 (95% CI 6·17 to 10·00) among patients with mild psoriasis.

Patients with severe psoriasis

The IR of any rare infections among patients with severe psoriasis (IR 55·69, 95% CI 46·31to 66·97) was higher than that of the control group (Table 5) and the aHR for patients with severe psoriasis compared with the matched general population was 1·64 (95% CI 1·33 to 2·03) (Figure 1 and Table S7). In particular, the IR of TB was higher among patients with severe psoriasis (Table S8) and an association between TB and severe psoriasis was observed (Figure 1 and Table S9; see Supporting Information). For any severe infections leading to hospitalization (inpatients only), the IR was 12·84 (95% CI 8·74–18·86) among patients with severe psoriasis (Table S8). The association for TB remained significant for patients with severe psoriasis when the definition of infections was restricted to only those leading to hospitalization (Figure 2 and Table S9).

Discussion

This Danish nationwide population-based cohort study revealed an increased incidence of severe and rare infections among patients with severe and mild psoriasis compared with the general population. The risk was higher for patients with severe psoriasis compared with those with mild psoriasis. To date, this is the first study to report the IRs of severe infections, rare infections and infections leading to hospitalization for patients with psoriasis in Denmark.

In Denmark, patients with psoriasis initiating biological medications are screened for TB and rare viral infections including HBV, HCV and HIV prior to starting such therapies.[17–20] The resulting data suggest that among patients with psoriasis overall, there were significantly higher rates of any infection (severe or rare). Patients with severe psoriasis had an increased risk of any rare infections, which was attributed to higher incidences of HIV and hepatitis, but not TB, indicating that susceptibility to infection rates may differ depending on psoriasis disease severity. In this patient group, there were higher rates of infections leading to hospitalization. For any rare infections, the association for hepatitis remained significant when infections were limited to only those leading to hospitalization, which supports a recent systematic review showing that patients with psoriasis have an increased

prevalence of HVC.[31] The current subanalysis showed a variability of infection risk based on severity of disease; however, this might be a result of the methodology used to screen patients. Similar to the previous findings, the current subanalysis also reported significantly higher rates of any, severe, and rare infections among patients with severe psoriasis. The IR of TB was higher among patients with severe psoriasis and an association between TB and severe psoriasis was observed, most likely owing to screening of TB prior to initiation of biologics. Also, there were higher rates of infections leading to hospitalization in this patient group. For any rare infections, the association for TB remained significant when infections were limited to only those leading to hospitalization.

Factors that may explain the increased risk of infection include the altered immune environment in patients with psoriasis, which involves a network of leucocytes and proinflammatory cytokines in disease pathogenesis.[2,3] Patients with severe psoriasis are defined by their eligibility for systemics, either conventional or biological. Therefore, the increased risk may be a consequence of treatment and not the severity of psoriasis. In a nationwide cohort study of 190 694 patients with IBD in France, the risks of serious and opportunistic infections were higher with immunosuppressive regimens.[29]

In contrast, a Dutch study revealed a greater risk for serious infection, independent of treatment, in patients with severe psoriasis.[17] Furthermore, a recently published investigation on 44 239 new users of biologics in France found that the risk of serious infections was higher for new users of adalimumab or infliximab vs. etanercept, whereas the risk of serious infections was not increased for users of secukinumab.[32] Certain treatments for psoriasis may aggravate existing infections and, as population-based studies are limited and the evidence is conflicting, the risk of rare infections in patients with psoriasis needs to be continually explored.[33,34]

Major limitations of the study include the absence of data describing confounding factors, such as weight, body mass index and smoking status. This study could potentially have been affected by surveillance bias, as the increased risk of TB in those with severe psoriasis may be due to screening for TB in this population rather than due to psoriasis or psoriasis treatments. Also, psoriasis severity indexes such as the Psoriasis Area and Severity Index, were not used in this study; however, the disease severity was based on prescription information. This is in agreement with the recent proposed severity categorization from the IPC.[26]

If clinicians are aware of the increased risk of severe infection in patients with severe psoriasis who are being treated with a systemic agent, the surveillance of these patients could be increased for signs of infection.

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Data availability statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymised to respect the privacy of patients who have participated in the study in line with applicable laws and regulations.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Treatments used to identify patients with severe psoriasis.
Table S2 List of severe infections and their corresponding International Classification of Diseases 10th revision codes.
Table S3 Infections leading to hospitalization (inpatients only) among the general population and patients with any type of psoriasis.
Table S4 Infections among the general population and patients with mild psoriasis.
Table S5 Infections among the general population and patients with mild psoriasis.
Table S6 Infections leading to hospitalization (inpatients only) among the general population and patients with mild psoriasis.
Table S7 Infections among the general population and patients with severe psoriasis.
Table S8 Infections leading to hospitalization (inpatients only) among the general population and patients with severe psoriasis.
Table S9 Infections leading to hospitalization (inpatients only) among the general population and patients with severe psoriasis.