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# **Incidence of infections associated with oral glucocorticoid dose in people diagnosed with polymyalgia rheumatica and giant cell arteritis: a cohort study in England**

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## **AUTHOR CONTRIBUTIONS**

Drs Wu and Pujades-Rodriguez had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept: MPR and AWM. Study design, ethics approval, and data acquisition: MPR. Creation and validation of lists of diagnostic codes and algorithms to define infections: MPR, CM and AWM. Creation of disease cohorts and covariates: MPR and AK. Management,

analysis, and interpretation of data: JW and MPR. Drafting of the manuscript: MPR. Critical revision of the manuscript for important intellectual content: JW, CM and AWM. All authors approved the submission.

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## **COMPETING INTERESTS**

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work except for CM and AWM who received salary support from National Institute of Health Research and the UK Medical Research Council. AWM has undertaken consultancy work in relation to giant cell arteritis for Roche, Chugai, GlaxoSmithKline, Sanofi and Regeneron, with all funding having been paid directly into a Research Account; there are no other relationships or activities that could appear to have influenced the submitted work.

## **ABSTRACT**

### **Background**

Dose-response risk estimates for infection associated with glucocorticoid use have yet to be quantified, particularly in primary care populations and in people with polymyalgia rheumatica and/or giant cell arteritis (PMR/GCA).

### **Methods**

Retrospective record-linkage cohort of 39 938 people with PMR/GCA registered in 389 family practices (1998-2017) across England. Time-variant current and cumulative dose estimates of first occurring infection were obtained using Kaplan-Meier methods and multilevel proportional-hazard Cox models.

### **Results**

Overall, 22 234 (55.7%) patients had at least one infection over a median follow-up of 4.8 years, with 5937 (26.7%) requiring hospitalisation and 1616 (7.3%) dying within 7 days of diagnosis. Cumulative risks of all-cause infection were 18.3% (95% confidence interval [CI] 17.9%-18.7%), 54.7% (54.1%-55.2%), and 76.9% (76.2%-77.5%) at 1, 5 and 10 years, respectively. Lower respiratory tract infections, conjunctivitis and herpes zoster were the most commonly diagnosed infections. The increases in hazard ratios for all-cause infection per 5 mg prednisolone-equivalent dose daily increase and per 1000 mg cumulative dose increase in last year from the patient's end date of follow-up were 1.13 (95%CI 1.12-1.14) and 1.50 (1.49-1.52) respectively. Hazard ratios associated with periods of current glucocorticoid versus non-glucocorticoid use ranged from 1.48 (1.39-1.57) for fungal to 1.70 (1.60-1.80) for bacterial infection. Stepwise dose-related associations were found for bacterial, viral, parasitic, and fungal infections, irrespective of age, duration of underlying chronic disease, and baseline vaccination status.

### **Interpretation**

We quantified the excess risk of all-cause, bacterial, viral, parasitic and fungal infection conferred by oral glucocorticoids in people with PMR/GCA and found strong dose-responses for all types even at daily doses of <5 mg prednisolone.

**Key words:** Adverse events; Dose-response assessment; Giant cell arteritis; Glucocorticoids; Treatment; Infection; Polymyalgia rheumatica

## **INTRODUCTION**

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are chronic inflammatory diseases requiring immunosuppressive therapy with glucocorticoids to induce remission and treat subsequent episodic flares. The majority of patients with PMR and/or GCA (PMR/GCA) are treated with medium to high doses prednisolone (up to 15mg for PMR and 60mg for GCA) for 6 months to several years.<sup>1,2</sup> Glucocorticoids are effective in reducing symptoms and inflammation associated with both diseases, but their immunosuppressive effects<sup>3-5</sup> are known to increase the risk of infection.

Dose-response estimates of absolute and relative risks of infections in people diagnosed with PMR/GCA are not available, despite these being the leading indications for long-term glucocorticoid prescription in primary care. It is uncertain whether the magnitude of dose-response risks varies for different types of infections.<sup>6</sup>

Previous studies have provided evidence of the increased risk of serious and opportunistic infection in patients with autoimmune diseases treated with high doses of glucocorticoids.<sup>7-9</sup> Most were observational studies that examined risks of specific infections, such as septicaemia and lower respiratory tract infections (LRTI). The majority were conducted amongst patients with rheumatoid arthritis (RA) aged 65 years and older only, and examined risks of severe infections requiring hospitalisation or accident and emergency services.<sup>7,8,10-12</sup> Findings from a recent cohort study suggest that the risk of infection in patients treated with oral glucocorticoids may vary for different types of autoimmune diseases.<sup>13</sup>

For patients with PMR/GCA, for whom current therapeutic options are limited, adequate characterisation of glucocorticoid dose-response relationships is required to conduct benefit-harm assessments and cost-effectiveness studies. These results will help guide the introduction of newly-licensed glucocorticoid-sparing drugs, such as tocilizumab, into clinical practice.

We aimed to assess the risk of all-cause, bacterial, viral, parasitic, and fungal infections associated with current daily and cumulative dose of oral glucocorticoids in a large cohort of people diagnosed with PMR/GCA in England.

## **METHODS**

### **Study design and follow-up**

This was a retrospective cohort study conducted amongst adults attending Clinical Practice Research Datalink (CPRD) family practices in England that consented to data linkage to hospital databases. All patients continuously registered in their family practice for 1 year or more between 1<sup>st</sup> Jan 1997 and 15<sup>th</sup> March 2017, aged  $\geq 18$  years, and had a diagnosis of PMR/GCA, were eligible for inclusion (see Supplemental Figure 1 in Appendix 1). Patients with prevalent and incident PMR/GCA were included. For each patient, follow-up started on the earliest date on which all the eligibility criteria were met and ended on the earliest of the following dates: first occurrence of the outcome analysed, death, date leaving the practice, or last date of data collection in the practice.

### **Data sources**

Three linked data sources were analysed (see supplementary methods in Appendix 2). Primary health care records from CPRD contained demographic and health behaviour data, diagnosed diseases (e.g. infections), prescribed medication, and results of laboratory and clinical examinations.<sup>14</sup> Patients are broadly representative of the population in England in terms of age, sex, and ethnicity.<sup>14,15</sup> Validation studies have provided evidence of the accuracy of diagnostic and prescribing information recorded.<sup>14</sup> Hospital records from the Hospital Episode Statistics (HES) contained diagnoses recorded during hospital admissions for National Health Service funded patients in England.<sup>16</sup> Data from the mortality registry were used to identify dates and causes of death. Patients with PMR/GCA were identified with codes previously used and validated (Read version 2: G755100, G755000, G755.00, Nyu4100, G755z00, G755200, N20..00, N20..11, N200.00; International Classification of Diseases version 10: M31.5, M31.6, M35.3).<sup>17,18</sup> The positive predictive value for GCA in CPRD is 91%.<sup>18</sup>

### **Oral glucocorticoid exposure**

For each prescription of oral glucocorticoids, the daily dose was derived from recorded information on the product strength (e.g. 1mg), directions given (e.g. one tablet a day) and quantity prescribed (e.g. 28 tablets). The duration of each prescription was then derived subtracting the daily dose from the prescribed total dose. The daily dosage was converted into milligrams of prednisolone-equivalent dose (see supplemental Table 1 in Appendix 3) to account for variation in the relative anti-inflammatory effects of different types of glucocorticoids.

Seven time-variant glucocorticoid exposure variables were predefined (see supplemental Figure 2 in Appendix 1): i) binary variable for ever use from one year prior to follow-up start; ii) binary variable for current use (e.g. whether the patient received glucocorticoids at a given

time point or not); iii) current daily dose per 5mg/day (zero when medication was not prescribed), considered as continuous and categorical (non-use, >0-4.9mg, 5.0-14.9mg, 15.0-24.9mg,  $\geq$  25.0mg/day) variables; iv) cumulative dose since one year prior to follow-up start per 1000mg, calculated by summing the total dose prescribed up to that point and dividing it by 1000. This was also considered as continuous and categorical variables (non-use, >0-959mg, 960-3054mg, 3055-7299mg, and  $\geq$ 7300mg, cutoffs as defined by Movahedi et al.<sup>19</sup>); and v) cumulative dose 1 year prior the end of follow-up, calculated by summing the total dose from 1 year before the end of follow-up or the whole study period if the duration of follow-up was less than 1 year. To create these variables, we determined the start and end of each medication exposure period and split patient follow-up on the dates on which the dose changed (see supplemental methods in Appendix 2).

### **Study outcomes**

The primary outcome was the first occurrence of all-cause infection (see supplemental Figure 3 in Appendix 1; supplemental Table 2 in Appendix 3). Secondary outcomes were first occurrence of cause specific types of infection: bacterial, viral, parasitic, and fungal. To capture incident cases of infection, episodes from patients with the same type of infection code recorded within 14 days (or 1 year for tuberculosis and hepatitis) before the start of follow-up were not considered.

### **Covariates**

Covariates considered were: baseline age, sex, smoking status, ethnicity, body mass index (BMI), socioeconomic status (index of multiple deprivation<sup>20</sup>, an area-based indicator based on the patient's residence), underlying disease (PMR, GCA, and both), comorbidities (cardiovascular disease [CVD], diabetes, cancer, asthma, chronic obstructive pulmonary disease [COPD], renal disease, human immunodeficiency virus [HIV]), vaccination status (within last year for influenza; at any time prior to follow-up start for varicella zoster/pneumococcus); the number of hospital visits, and prescribed non-oral glucocorticoids (inhaled, nasal, parenteral, topical, and rectal), H2 antagonists and proton pump inhibitors, in the last year; and time-variant prescribed disease-modifying antirheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs) during follow-up (see supplemental methods in Appendix 2).

### **Statistical analysis**

Standard descriptive statistics were reported for baseline characteristics. Cumulative probabilities of all-cause and type-specific infection were assessed using Kaplan-Meier

methods. Incident rates with 95% confidence intervals (CI) were estimated by dividing the number of infections by the total number of person-years of follow-up.

Dose-response associations were assessed using Cox proportional hazards models including the practice identifier as a random intercept to account for clustering effect. Adjusted hazard ratios (aHRs) with 95% CI were estimated for each type of infection regressed on each of the time-variant exposures. Every model was adjusted for the covariates listed and using time-variant prescribed DMARDs and NSAIDs during follow-up. The proportional hazards assumption was assessed using Schoenfeld residuals tests. Missing daily glucocorticoid dose and baseline covariates were replaced through generation of 25 datasets using multiple imputation with chained equations (see supplemental methods in Appendix 2). All models were conducted for each imputed dataset. Pooled estimates and accompanying 95% CIs were generated using Rubin's rules. Data management and analyses were performed in Stata version 15 (StataCorp LP, College Station, USA) and R version 3.3.1 (<http://cran.r-project.org/>).

In secondary analyses, estimates were obtained by sex, duration of time since PMR/GCA diagnosis, age group, baseline vaccination status, and non-oral glucocorticoid use in last year.

### **Ethical approval**

Approval for the study was obtained from the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (ISAC).

## **RESULTS**

### **Patient characteristics**

A total of 39 938 patients attending 389 family practices were included, 32 735 (82.0%) with PMR, 4505 (11.3%) with GCA, and 2698 (6.8%) with both (Table 1). The median time since diagnosis of PMR/GCA was 4.9 years (IQR 3.0-7.0). 12 346 (30.9%) were men and the median time at risk was 2.4 years (IQR 0.9-5.0). At follow-up start, mean age was 73.0 (SD=10.7), 16 966 (42.5%) were non-smokers, 19 515 (48.9%) vaccinated against pneumococcus, 25 640 (64.2%) vaccinated against influenza, and 7676 (19.2%) received inhaled or nasal glucocorticoids (see supplemental Tables 3&4 in Appendix 3). At baseline, the most common diagnosed comorbidities were CVD (32.7%), asthma (15.9%), and diabetes (12.6%).

The median glucocorticoid cumulative dose received during follow-up was 3451.5mg (IQR 1606.5-6465.0) and in the last year of follow-up 1598mg (IQR 780-2552). During follow-up, 3809 (9.5%) patients received a DMARD.

### **Incidence, type and severity of infection**

A total of 22 234 (55.7%) people had an infection during 138 412 person-years of follow-up. The incidence of all-cause infection was 160.7/1000 person-years (95% CI 159.3-162.2) (see supplemental Table 5 in Appendix 3). Types of infection most frequently diagnosed were LRTI (6064 [27.3%]), conjunctivitis (1905 [8.6%]), and herpes zoster (1642 [7.4%]) (see supplemental Table 6 in Appendix 3). Of 22 234 people, 5937 (26.7%) were hospitalised on the date of or within 7 days after infection diagnosis, 1930 (9%) patients with infection died within 30 days of diagnosis, and 1616 (7.3%) patients died within 7 days of diagnosis. The most common causes of death for infection were pneumonia (1015 [52.6%]), urinary tract infection (58 [3.0%]), and peritonitis (43 [2.2%]).

The cumulative probabilities of all types of infection increased with higher daily dose (Table 2). At one year, probabilities of all-cause infection increased from 12.9% (95% CI 12.4-13.4) for periods of non-use, through 18.0% (95% CI 17.1-18.8) for >0-4.9mg/day, to 35.8% (95% CI 32.9-38.6) for  $\geq$ 25.0mg/day.

### **Dose-response associations**

Compared to periods of non-oral glucocorticoid use, aHRs of all types of infections were higher in periods of current use (aHR=1.49, 95%CI 1.44-1.53 for all-cause; Table 3). The highest estimates were seen for bacterial infections (1.70, 95% CI 1.60-1.80) and the lowest for fungal infections (1.48, 95% CI 1.39-1.57). Compared to non-glucocorticoid use, the increase in aHR per 5mg/day dose was 1.13 (95%CI 1.12-1.14) for all-cause infection; with aHRs increasing from 1.39 (95% CI 1.34-1.45) for a dose > 0-4.9mg/day to 2.30 (95% CI 2.13-2.49) for  $\geq$  25mg/day. The increase in aHR per 1000 mg cumulative dose during the last year was 1.50 (95%CI 1.49-1.52).

Secondary analyses showed similar dose-response estimates regardless of sex and time since diagnosis of the underlying disease (Table 4, see supplemental Table 7-8 in Appendix 3). Higher cumulative probabilities of all-cause and bacterial infection were found in older patients (see supplemental Table 9 in Appendix 3). Patients vaccinated had higher risks of all types of infections than those not vaccinated. Patients prescribed non-oral glucocorticoids had higher risks of all types of infections than those not treated with non-oral glucocorticoids (see supplemental Tables 10-12 in Appendix 3)

## INTERPRETATION

In this population-based study including 39 938 patients diagnosed with PMR/GCA, we found high absolute risks of all types of infections and a marked stepwise increase in risk with higher oral glucocorticoid doses. In periods with prescribed medication, patients' risk was 50% higher than when it was not prescribed. Increases in risk ranged from 48% for fungal to 70% for bacterial infections. For every increase of 5mg daily dose and of 1000 mg cumulative dose in the last year, the increased risks of all-cause infection were 13% and 50%, respectively.

We found evidence of dose-response only for a total cumulative dose  $\geq 7300$  mg. This weaker association is expected given that the risk conferred by glucocorticoids would decrease with time since exposure discontinuation. Dose-response estimates were similar regardless of sex, disease subtype (ie – PMR, GCA, or both), and disease duration. However, higher dose-response risks of all infections were observed for patients prescribed than for those not prescribed non-oral glucocorticoids and higher risks of bacterial infections were found in older patients compared to younger patients. Higher dose-response risks were also found for patients vaccinated against pneumococcus, influenza, and varicella zoster than for those patients. This is consistent with patients with high morbidity burden (e.g. older) being more often vaccinated and having high risk for infections for which they are unprotected.

A previous study conducted amongst 1664 patients with GCA reported adjusted rate ratios of LRTIs, upper urinary tract infection and sepsis for oral glucocorticoid users, compared to matched controls.<sup>9</sup> Studies amongst patients with RA have reported increased risk of common serious infections (e.g. bacterial pneumonia, herpes zoster),<sup>8,10-12,21</sup> but not of non-serious infections.<sup>21</sup> In contrast, in a large case-control study of patients with RA, the risk of non-serious infections was higher in patients receiving oral glucocorticoids, with aHR increasing from 1.10 for patients receiving 5-10mg/day, to 1.85 for  $\geq 20$  mg/day, compared to controls.<sup>9</sup>

In our study, 26.7% of patients with infection required hospitalisation and 7.3% died within 7 days of diagnosis. Furthermore, by considering periods of drug use and changes in dosage over time (i.e. through time-variant exposure variables) marked dose-response effects for current and recent cumulative glucocorticoid use were found. This is consistent with results of a nested case-control study conducted in Canada amongst 1947 cases and 16 207 controls with RA aged  $\geq 60$  years,<sup>7</sup> in which the risk of infections requiring hospitalisation varied with dosage and treatment duration. In agreement with our findings, a study in the UK identified

older age but not sex as a risk factor for septicaemia, LRTIs and herpes zoster in patients treated with oral glucocorticoids, compared to non-users.<sup>13</sup>

The large sample size allowed the investigation of dose-responses for different infection types and relevant subgroups (e.g. by disease duration). The contemporary study period and data linkage across primary and secondary care databases allowed for a large unselected cohort of patients with uncommon diseases and assessment of risk for both serious and non-serious infections. To minimise length and time-dependent bias,<sup>22,23</sup> the start and end of follow-up were unrelated dates of prescribed glucocorticoids and medication variables identified periods with and without treatment (i.e. time-variant).

To define incident episodes of infection and its types we used an algorithm combining diagnostic codes for infection and antibiotic and antiviral drug use. Reporting bias related to a higher suspicion of infections during periods of glucocorticoid use cannot be excluded. However, in our cohort 93.7% of infections were diagnosed on dates on which oral glucocorticoids were not prescribed, suggesting the primary reason for consultation was new infection-related symptoms. It remains likely that self-treated minor infections were missed.

No information on adherence or on hospital prescribed medication was available. This might underestimate medication use when patients are treated by specialists (e.g. around diagnosis or serious disease flares). Nevertheless, median time since diagnosis was five years, a low proportion of patients had newly diagnosed PMR/GCA, and the bulk of prescribing in the UK happens in primary care.

The observed high excess infection risk and infection-related mortality in patients with PMR/GCA, even for daily doses of <5 mg; and the higher dose-response estimates in non-oral glucocorticoid users and immunised patients, highlights the need for regular review of glucocorticoid requirements, even at low doses. Patients and clinicians should be educated about the risk of infection, need for symptom identification, prompt treatment, timely immunisation, and history of chronic infection documentation (e.g. herpes zoster).

The estimates of dose-response can be used to conduct benefit-harm evaluations and cost-effectiveness studies of new glucocorticoid-sparing drugs required to guide policy and improve patient care outcomes in patients with PMR/GCA.

In this large contemporary population-based study we estimated absolute and relative risks of all-cause, bacterial, viral, parasitic and fungal infections and found strong glucocorticoid dose-responses for all types amongst people diagnosed with PMR/GCA.

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**Table 1. Patient baseline characteristics by disease type**

<b>Characteristic</b>	<b>All patients</b>	<b>GCA only</b>	<b>PMR only</b>	<b>PMR and GCA</b>
	<b>N= 39 938</b>	<b>N = 4505</b>	<b>N = 32 735</b>	<b>N = 2698</b>
<b>Sociodemographic information</b>				
<b>Men, n (%)</b>	12 346 (30.9)	1391 (31.0)	10 373 (31.7)	582 (21.6)
<b>Age (years), mean (SD)</b>	73.0 (10.7)	71.1 (12.6)	73.2 (10.5)	73.9 (8.7)
<b>Ethnicity, n (%)</b>				
White	35 692 (89.4)	4 001 (88.8)	29 205 (89.2)	2 486 (92.1)
Other	959 (2.5)	220 (4.9)	671 (2.0)	68 (2.5)
<b>Index of multiple deprivation (fifths), n (%)</b>				
1st (least deprived)	7583 (19.0)	709 (15.7)	6358 (19.4)	516 (19.1)
5th (most deprived)	5311 (13.3)	829 (18.4)	4104 (12.5)	378 (14.0)
<b>Biomarkers, mean (SD)</b>				
Body Mass Index (kg/m <sup>2</sup> )	27.5 (5.6)	27.3 (6.0)	27.5 (5.5)	26.9 (5.7)
C-reactive protein (mg/L)	33.1 (43.4)	36.7 (57.2)	32.2 (40.8)	40.0 (53.6)
Erythrocyte sedimentation rate (mm/h)	40.4 (29.0)	41.4 (32.5)	39.9 (28.2)	45.2 (32.1)
Total white blood cells (cells/L)	8.7 (2.7)	8.5 (3.0)	8.7 (2.7)	9.0 (2.9)
Neutrophils (cells/L)	5.8 (2.4)	5.7 (2.7)	5.8 (2.3)	6.2 (2.6)
Lymphocytes (cells/L)	2.0 (0.9)	2.0 (1.0)	2.0 (0.9)	1.9 (0.9)
Eosinophils (cells/L)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)
Haemoglobin (gr/dL)	12.8 (1.4)	12.9 (1.5)	12.8 (1.4)	12.6 (1.4)
Creatinine (µmol/L)	88.8 (33.6)	92.2 (49.7)	88.5 (31.2)	87.0 (29.8)
<b>Health behaviour</b>				
<b>Smoking status, n (%)</b>				
Non-smoker	16 966 (42.5)	1710 (38.0)	14 084 (43.0)	1172 (43.4)
Ex-smoker	8302 (20.8)	824 (18.3)	6982 (21.3)	496 (18.4)
Current smoker	8197 (20.5)	1221 (27.1)	6440 (19.7)	536 (19.9)
<b>Duration since first recorded diagnosed disease in years, median (IQR)</b>				
	4.9 [3.0, 7.0]	4.0 [2.0, 6.0]	4.9 [3.0, 7.0]	6.1 [2.0, 9.0]
<b>No. of hospitalisation in last year, mean (SD)</b>				
	0.6 (2.6)	0.9 (4.0)	0.5 (2.4)	0.6 (1.3)
<b>Comorbidities*, n (%)</b>				
Cardiovascular disease	13 044 (32.7)	1649 (36.6)	10 464 (32.0)	931 (34.5)
Diabetes	5020 (12.6)	647 (14.4)	4055 (12.4)	318 (11.8)
Asthma	6336 (15.9)	817 (18.1)	5057 (15.4)	462 (17.1)
COPD	2987 (7.5)	466 (10.3)	2328 (7.1)	193 (7.2)
Cancer	4050 (10.1)	466 (10.3)	3348 (10.2)	236 (8.7)
Chronic renal disease	1347 (3.4)	163 (3.6)	1095 (3.3)	89 (3.3)

Note: COPD, chronic obstructive pulmonary disease; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; SD, standard deviation. Data on ethnicity, body mass index and smoking status were missing for 8.1%, 29.8% and 16.2% of patients, respectively. \*2 people had HIV infection at baseline.

**Table 2. Kaplan Meier estimates of infection per level of time-variant current daily and cumulative oral glucocorticoid prednisolone-equivalent dose**

	Infection type				
	All-cause	Bacterial	Viral	Parasitic	Fungal
<b>Incident infections, n (%)</b>	22 234 (100)	5234 (23.5)	5344 (24.0)	1120 (5.0)	5416 (24.4)
<b>Cumulative probability (95% CI) at 1-yr</b>	18.3 (17.9-18.7)	3.2 (3.0-3.3)	3.8 (3.6-3.9)	0.9 (0.8-1.0)	3.9 (3.7-4.1)
<b>Current daily dose</b>					
No-use	12.9 (12.4-13.4)	2.1 (1.8-2.3)	2.5 (2.2-2.7)	0.6 (0.5-0.7)	2.4 ( 2.2- 2.7)
>0-4.9 mg	18.0 (17.1-18.8)	3.4 (3.0-3.8)	3.6 (3.2-4.0)	0.8 (0.6-1.0)	4.0 ( 3.6- 4.5)
5.0-14.9 mg	21.1 (20.4-21.8)	3.5 (3.1-3.8)	4.6 (4.2-5.0)	1.1 (0.9-1.3)	4.7 ( 4.3- 5.1)
15.0-24.9 mg	30.4 (28.5-32.2)	6.3 (5.3-7.4)	7.2 (6.1-8.3)	2.0 (1.4-2.5)	7.3 ( 6.3- 8.4)
≥25.0 mg	35.8 (32.9-38.6)	7.9 (6.2-9.7)	8.0 (6.2-9.7)	2.1 (1.1-3.0)	8.5 ( 6.7-10.3)
<b>Cumulative dose in last year</b>					
No-use	5.1 ( 4.8- 5.3)	0.7 ( 0.6- 0.8)	0.8 ( 0.7- 0.9)	0.2 (0.1-0.2)	0.9 ( 0.7- 1.0)
>0-959.9 mg	39.0 (37.4-40.5)	11.4 (10.0-12.7)	13.9 (12.5-15.3)	3.6 (2.8-4.4)	12.9 (11.6-14.3)
960.0-3054.9 mg	49.2 (47.9-50.4)	17.1 (15.7-18.5)	18.5 (17.1-19.9)	5.6 (4.7-6.5)	20.3 (18.9-21.7)
≥3055.0 mg	60.2 (57.9-62.4)	23.3 (20.2-26.3)	25.8 (22.7-28.7)	7.9 (5.9-9.9)	24.4 (21.3-27.3)
<b>Total cumulative dose</b>					
No-use	20.6 (19.6-21.6)	3.5 (3.0-4.0)	4.0 (3.5-4.5)	1.0 (0.8-1.3)	4.3 (3.8-4.9)
>0-959.9 mg	29.0 (27.8-30.3)	5.4 (4.7-6.0)	6.9 (6.2-7.6)	1.6 (1.2-1.9)	6.6 (5.9-7.3)
960.0-3054.9 mg	21.9 (21.2-22.6)	4.0 (3.7-4.4)	4.5 (4.2-4.9)	1.1 (1.0-1.3)	5.2 (4.8-5.6)
3055.0-7299.9 mg	10.2 ( 9.7-10.7)	1.8 (1.5-2.0)	2.1 (1.9-2.4)	0.5 (0.4-0.6)	1.8 (1.6-2.1)
≥7300.0 mg	7.4 ( 6.0- 8.9)	0.6 (0.2-1.0)	1.2 (0.7-1.8)	0.4 (0.1-0.8)	1.4 (0.8-2.0)
<b>Cumulative probability (95% CI) at 5-yr</b>	54.7 (54.1-55.2)	11.6 (11.2-12.0)	13.1 (12.7-13.5)	2.8 (2.6-3.0)	13.7 (13.3-14.1)
<b>Current daily dose</b>					
No-use	42.1 (41.3-42.9)	7.6 ( 7.2- 7.9)	8.8 ( 8.4- 9.2)	1.9 (1.7-2.1)	9.4 ( 8.9- 9.8)
>0-4.9 mg	65.0 (63.6-66.4)	17.0 (15.8-18.1)	17.7 (16.4-18.8)	3.3 (2.7-3.8)	18.5 (17.3-19.7)
5.0-14.9 mg	69.8 (68.7-71.0)	17.6 (16.6-18.6)	20.3 (19.2-21.4)	4.5 (4.0-5.1)	20.5 (19.4-21.6)
15.0-24.9 mg	77.9 (75.4-80.1)	23.7 (20.8-26.5)	24.6 (21.8-27.4)	6.4 (4.8-8.0)	27.7 (24.6-30.7)
≥25.0 mg	81.5 (78.2-84.3)	28.4 (24.0-32.5)	27.5 (23.1-31.6)	7.2 (4.6-9.7)	26.7 (22.6-30.5)
<b>Cumulative doe in last year</b>					

No-use	32.6 (31.8-33.3)	4.9 ( 4.6- 5.2)	5.9 ( 5.6- 6.2)	1.1 ( 1.0- 1.3)	6.3 ( 5.9- 6.6)
>0-959.9 mg	74.9 (73.3-76.3)	24.0 (22.1-25.8)	26.1 (24.2-27.9)	5.4 ( 4.5- 6.4)	26.7 (24.9-28.5)
960.0-3054.9 mg	84.5 (83.4-85.4)	33.1 (31.2-35.0)	35.0 (33.1-36.9)	9.2 ( 7.9-10.4)	36.9 (35.0-38.8)
≥3055.0 mg	92.7 (91.0-94.0)	50.3 (45.5-54.8)	47.7 (43.0-52.1)	13.4 (9.9-16.7)	45.2 (40.6-49.5)
<b>Total cumulative dose</b>					
No-use	58.7 (57.1-60.2)	12.3 (11.2-13.4)	14.3 (13.2-15.5)	3.4 (2.8-4.0)	15.6 (14.3-16.8)
>0-959.9 mg	62.4 (60.8-64.0)	14.2 (13.0-15.4)	17.2 (15.9-18.5)	3.9 (3.2-4.5)	17.3 (16.0-18.6)
960.0-3054.9 mg	61.7 (60.5-62.8)	14.5 (13.7-15.4)	16.1 (15.1-17.0)	3.6 (3.1-4.1)	18.0 (17.1-19.0)
3055.0-7299.9 mg	55.2 (54.1-56.2)	11.9 (11.2-12.6)	13.7 (13.0-14.4)	2.8 (2.4-3.1)	13.8 (13.0-14.5)
≥7300.0 mg	36.1 (34.8-37.3)	7.2 ( 6.6- 7.8)	7.4 ( 6.8- 8.0)	1.4 (1.2-1.7)	7.5 ( 6.9- 8.1)
<b>Cumulative probability (95% CI) at 10-yr</b>	<b>76.9 (76.2-77.5)</b>	<b>21.0 (20.4-21.7)</b>	<b>21.2 (20.6-21.8)</b>	<b>4.2 (4.0-4.5)</b>	<b>21.2 (20.6-21.8)</b>
<b>Current daily dose</b>					
No-use	68.0 (67.1-68.9)	15.6 (15.0-16.3)	15.9 (15.2-16.6)	3.0 ( 2.7- 3.3)	16.2 (15.6-16.9)
>0-4.9 mg	84.4 (82.9-85.8)	29.2 (27.2-31.1)	27.9 (26.0-29.8)	5.3 ( 4.4- 6.2)	28.6 (26.6-30.4)
5.0-14.9 mg	88.7 (87.6-89.7)	30.6 (28.8-32.4)	30.9 (29.2-32.6)	6.8 ( 5.8- 7.8)	29.4 (27.8-31.1)
15.0-24.9 mg	92.3 (89.9-94.2)	35.9 (31.2-40.2)	38.2 (33.2-42.8)	9.6 ( 6.7-12.5)	36.1 (31.8-40.1)
≥25.0 mg	93.1 (90.1-95.2)	45.5 (37.9-52.2)	39.4 (32.5-45.5)	11.6 (7.0-15.9)	36.9 (30.6-42.6)
<b>Cumulative dose in last year</b>					
No-use	62.5 (61.5-63.5)	12.8 (12.1-13.4)	13.1 (12.5-13.7)	2.3 (2.0- 2.5)	13.3 (12.7-13.9)
>0-959.9 mg	88.7 (87.1-90.1)	33.1 (30.4-35.7)	33.1 (30.4-35.7)	6.7 (5.4- 7.9)	32.9 (30.4-35.4)
960.0-3054.9 mg	93.1 (92.0-94.0)	41.8 (39.0-44.4)	40.5 (37.8-43.1)	10.4 (8.6-2.2)	37.8 (35.5-40.1)
≥3055.0 mg	97.2 (95.7-98.2)	54.4 (48.4-59.7)	50.7 (43.9-56.7)	10.7 (6.5-14.6)	47.0 (40.6-52.7)
<b>Total cumulative dose</b>					
No-use	79.3 (77.5-80.9)	22.3 (20.3-24.2)	23.4 (21.5-25.2)	5.2 (4.2-6.2)	23.2 (21.4-25.0)
>0-959.9 mg	82.2 (80.4-83.8)	22.6 (20.7-24.5)	25.8 (23.8-27.8)	5.8 (4.7-6.8)	26.2 (24.2-28.1)
960.0-3054.9 mg	81.3 (80.0-82.5)	24.2 (22.7-25.6)	23.7 (22.3-25.1)	5.2 (4.5-5.9)	26.0 (24.6-27.4)
3055.0-7299.9 mg	76.0 (74.8-77.2)	21.0 (19.8-22.1)	21.6 (20.4-22.7)	4.0 (3.5-4.6)	21.5 (20.4-22.7)
≥7300.0 mg	67.4 (65.9-68.8)	17.4 (16.3-18.4)	16.1 (15.1-17.1)	2.9 (2.5-3.3)	14.8 (13.8-15.8)

Note: CI, confidence interval

**Table 3. Association between time-variant prescribed oral glucocorticoids and incident infections**

	Hazard ratio with 95% CI				
	All infections	Bacterial infections	Viral infections	Parasitic infections	Fungal infections
<b>Current use</b> (ref = non-use)	1.49 (1.44-1.53)	1.70 (1.60-1.80)	1.53 (1.44-1.62)	1.50 (1.32-1.71)	1.48 (1.39-1.57)
<b>Current daily dose per 5 mg/day</b>	1.13 (1.12-1.14)	1.16 (1.14-1.19)	1.13 (1.11-1.15)	1.14 (1.09-1.18)	1.11 (1.09-1.14)
<b>Current daily dose category</b>					
Non-use	1.00	1.00	1.00	1.00	1.00
>0-4.9 mg	1.39 (1.34-1.45)	1.58 (1.43-1.75)	1.47 (1.34-1.62)	1.41 (1.14-1.74)	1.46 (1.34-1.59)
5.0-14.9 mg	1.46 (1.41-1.52)	1.64 (1.51-1.78)	1.46 (1.34-1.59)	1.42 (1.21-1.68)	1.41 (1.31-1.53)
15.0-24.9 mg	1.66 (1.55-1.77)	1.95 (1.71-2.23)	1.78 (1.54-2.06)	1.87 (1.43-2.43)	1.62 (1.42-1.85)
≥25 mg	2.30 (2.13-2.49)	3.02 (2.51-3.63)	2.28 (1.89-2.74)	2.40 (1.70-3.40)	2.10 (1.74-2.52)
<b>Cumulative dose in last year (per 1000 mg)</b>	1.50 (1.49-1.52)	1.53 (1.51-1.55)	1.51 (1.50-1.53)	1.52 (1.49-1.55)	1.59 (1.57-1.61)
<b>Cumulative dose in last year category</b>					
Non-use	1.00	1.00	1.00	1.00	1.00
>0-959.9 mg	1.88 (1.84-1.92)	2.17 (2.09-2.25)	2.3 (2.22-2.37)	2.43 (2.25-2.60)	2.31 (2.23-2.39)
960-3054.9 mg	2.50 (2.47-2.54)	2.85 (2.78-2.92)	2.95 (2.88-3.02)	3.12 (2.97-3.26)	2.98 (2.91-3.04)
≥3055	3.23 (3.19-3.28)	3.69 (3.60-3.79)	3.72 (3.63-3.81)	3.90 (3.70-4.10)	3.66 (3.56-3.75)
<b>Total cumulative dose (per 1000 mg)</b>	1.01 (1.00-1.01)	1.02 (1.01-1.02)	1.01 (1.00-1.01)	1.01 (1.00-1.02)	1.00 (1.00-1.01)
<b>Total cumulative dose category</b>					
Non-use	1.00	1.00	1.00	1.00	1.00
>0-959.9 mg	1.08 (1.03-1.14)	1.10 (0.98-1.23)	1.08 (0.97-1.21)	1.08 (0.86-1.36)	1.07 (0.96-1.18)
960-3054.9 mg	1.01 (0.97-1.06)	1.08 (0.98-1.20)	0.96 (0.87-1.05)	1.00 (0.81-1.23)	1.07 (0.97-1.17)
3055-7299.9 mg	1.05 (1.00-1.09)	1.10 (1.00-1.21)	1.06 (0.97-1.16)	1.08 (0.88-1.32)	1.02 (0.93-1.13)
≥7300 mg	1.11 (1.06-1.17)	1.36 (1.23-1.51)	1.13 (1.02-1.25)	1.17 (0.94-1.47)	1.07 (0.96-1.19)

Note: CI, confidence interval; IQR, interquartile range. Hazard ratios from Cox proportional models adjusted for baseline age, sex, index of multiple deprivation, smoking status, ethnicity, BMI, chronic inflammatory disease type, comorbidities (CVD, diabetes, HIV, cancer, asthma, COPD, and renal disease), vaccination status (varicella zoster, pneumococcus and influenza), number of hospital admissions in last year, prescribed non-oral glucocorticoids, proton pump inhibitors and H2 antagonists; and time-variant use of DMARDs and NSAIDs; the practice identifier was included as a random intercept to account for clustering effect.

**Table 4. Kaplan-Meier estimates of infections per level of current daily and cumulative oral glucocorticoid prednisolone-equivalent dose by time since PMR/GCA diagnosis**

All-cause infection	Duration since PMR/GCA diagnosis				
	Within 1 year	1st year	2nd year	3 <sup>rd</sup> year	After 3 <sup>rd</sup> year
Incident infections, n (%)	15 187	1703	1015	807	3522
<b>Cumulative probability (95% CI) at 1 year</b>	18.2 (17.8-18.7)	18.0 (16.6-19.5)	18.8 (16.8-20.7)	18.0 (15.8-20.1)	18.7 (17.7-19.7)
<b>Current daily dose</b>					
no-use	11.0 (10.4-11.7)	13.0 (11.0-15.0)	13.5 (11.0-15.9)	14.1 (11.4-16.7)	16.8 (15.6-18.0)
>0-4.9 mg	17.3 (16.4-18.3)	19.2 (15.8-22.5)	20.2 (15.2-25.0)	22.2 (16.6-27.5)	19.8 (17.0-22.4)
5.0-14.9 mg	20.8 (20.0-21.6)	22.2 (19.2-25.1)	24.6 (20.5-28.5)	20.2 (15.4-24.7)	21.6 (19.1-24.0)
15.0-24.9 mg	31.2 (29.1-33.2)	27.5 (19.6-34.6)	28.2 (16.8-38.0)	26.5 ( 9.9-40.0)	24.4 (17.3-30.9)
≥25.0 mg	35.7 (32.5-38.8)	26.1 (12.7-37.4)	28.6 ( 9.5-43.6)	47.9 (24.1-64.2)	42.0 (29.3-52.4)
<b>Cumulative dose in last year</b>					
no-use	3.4 ( 3.1- 3.6)	4.1 ( 3.2- 5.0)	5.7 ( 4.3- 7.0)	8.2 ( 6.4-10.0)	11.2 (10.3-12.1)
>0-959.9 mg	40.4 (38.6-42.2)	33.9 (27.3-40.0)	33.3 (24.8-40.9)	30.8 (22.0-38.6)	36.2 (31.7-40.3)
960.0-3054.9 mg	49.2 (47.7-50.7)	48.5 (43.1-53.4)	53.4 (46.4-59.6)	49.6 (40.9-57.0)	47.7 (43.6-51.5)
≥3055.0 mg	56.3 (53.6-58.8)	76.4 (68.7-82.2)	68.5 (56.6-77.1)	67.6 (50.8-78.7)	72.6 (63.1-79.7)
<b>Total cumulative dose</b>					
no-use	25.9 (24.1-27.7)	17.5 (13.1-21.7)	16.0 (11.8-20.0)	17.2 (13.3-20.9)	17.6 (16.1-19.0)
>0-959.9 mg	32.6 (31.0-34.1)	21.7 (17.0-26.1)	15.3 (10.0-20.3)	14.6 ( 9.3-19.7)	21.4 (18.3-24.3)
960.0-3054.9 mg	21.4 (20.7-22.2)	22.9 (19.7-25.9)	25.2 (20.7-29.4)	25.4 (20.2-30.3)	23.8 (21.3-26.3)
3055.0-7299.9 mg	8.1 ( 7.6- 8.7)	16.0 (13.8-18.2)	18.3 (15.0-21.6)	15.2 (11.2-19.0)	16.7 (14.5-18.9)
≥7300.0 mg	6.0 ( 4.2- 7.7)	7.4 ( 3.7-10.9)	13.1 ( 7.3-18.5)	12.8 ( 4.1-20.7)	7.1 ( 3.4-10.6)
<b>Cumulative probability (95% CI) at 5 years</b>	54.0 (53.3-54.7)	54.9 (52.8-57.0)	55.9 (53.0-58.5)	55.6 (52.5-58.6)	57.2 (55.7-58.7)
<b>Current daily dose</b>					
no-use	39.0 (38.1-39.9)	43.8 (40.9-46.6)	45.3 (41.5-48.9)	47.6 (43.4-51.5)	51.3 (49.4-53.2)
>0-4.9 mg	65.0 (63.3-66.6)	64.3 (58.7-69.1)	65.0 (57.2-71.3)	70.1 (61.8-76.5)	63.9 (60.0-67.5)
5.0-14.9 mg	71.0 (69.7-72.3)	69.4 (64.9-73.3)	67.9 (62.1-72.9)	61.5 (54.4-67.5)	65.8 (62.5-68.8)
15.0-24.9 mg	78.0 (75.1-80.5)	80.3 (68.9-87.5)	81.5 (66.6-89.7)	79.3 (58.5-89.6)	71.2 (62.3-78.0)
≥25.0 mg	82.3 (78.5-85.4)	73.9 (57.3-84.0)	85.9 (61.9-94.8)	80.3 (44.3-93.1)	77.5 (66.9-84.7)
<b>Cumulative dose in last year</b>					
no-use	29.0 (28.1-29.9)	33.1 (30.3-35.7)	35.4 (31.8-38.8)	37.5 (33.6-41.3)	43.4 (41.5-45.2)
>0-959.9 mg	74.0 (72.2-75.7)	74.9 (68.3-80.1)	78.3 (69.9-84.3)	80.5 (71.3-86.8)	77.3 (73.1-80.8)

960.0-3054.9 mg	84.6 (83.3-85.8)	87.2 (83.3-90.2)	83.2 (77.7-87.4)	84.0 (77.3-88.8)	82.1 (79.1-84.7)
≥3055.0 mg	92.3 (90.3-93.9)	93.1 (85.8-96.7)	92.3 (81.2-96.8)	91.9 (79.6-96.8)	93.3 (88.1-96.2)
<b>Total cumulative dose</b>					
no-use	61.0 (58.6-63.3)	59.5 (52.2-65.7)	55.8 (48.4-62.1)	56.9 (50.6-62.3)	57.4 (54.8-59.8)
>0-959.9 mg	63.8 (61.9-65.6)	61.3 (54.5-67.0)	51.9 (42.8-59.6)	50.1 (40.6-58.1)	61.5 (57.2-65.5)
960.0-3054.9 mg	61.6 (60.4-62.9)	60.2 (55.4-64.5)	61.3 (55.0-66.7)	62.4 (54.9-68.7)	62.5 (58.8-65.9)
3055.0-7299.9 mg	53.0 (51.8-54.2)	59.1 (55.3-62.6)	65.4 (59.8-70.2)	64.4 (57.4-70.2)	62.9 (59.5-66.0)
≥7300.0 mg	34.5 (33.0-36.0)	39.5 (35.2-43.6)	42.4 (36.6-47.6)	40.1 (32.8-46.6)	38.7 (34.9-42.3)
<b>Cumulative probability (95% CI) at 10 years</b>	<b>75.9 (75.1-76.7)</b>	<b>77.6 (75.4-79.6)</b>	<b>78.0 (75.2-80.6)</b>	<b>77.2 (74.0-80.0)</b>	<b>79.9 (78.4-81.4)</b>
<b>Current daily dose</b>					
no-use	65.6 (64.4-66.7)	69.0 (65.9-71.9)	69.9 (65.7-73.6)	69.7 (65.2-73.7)	76.2 (74.1-78.2)
>0-4.9 mg	84.4 (82.5-86.2)	86.5 (81.1-90.4)	85.6 (77.3-90.8)	88.0 (80.6-92.6)	81.3 (77.3-84.5)
5.0-14.9 mg	88.9 (87.5-90.2)	89.4 (85.4-92.4)	88.6 (83.2-92.2)	87.4 (80.1-92.0)	86.7 (83.6-89.3)
15.0-24.9 mg	92.9 (89.8-95.1)	93.4 (83.5-97.4)	94.0 (79.1-98.3)	90.0 (66.8-97.0)	87.0 (77.9-92.4)
≥25.0 mg	93.9 (90.0-96.3)	90.1 (72.6-96.4)	-	82.6 (53.8-93.4)	91.6 (82.0-96.0)
<b>Cumulative dose in last year</b>					
no-use	60.0 (58.7-61.3)	62.3 (58.9-65.5)	64.8 (60.2-68.8)	63.4 (58.5-67.7)	71.1 (68.9-73.2)
>0-959.9 mg	87.4 (85.3-89.3)	92.9 (87.5-96.0)	93.9 (85.6-97.4)	88.6 (79.8-93.6)	88.4 (84.6-91.3)
960.0-3054.9 mg	92.7 (91.3-93.8)	95.0 (91.4-97.1)	93.0 (88.2-95.9)	97.0 (90.5-99.1)	92.3 (89.5-94.4)
≥3055.0 mg	96.6 (94.6-97.9)	98.7 (91.4-99.8)	91.4 (76.0-96.9)	-	98.6 (91.3-99.8)
<b>Total cumulative dose</b>					
no-use	79.2 (76.5-81.5)	79.4 (71.9-84.9)	79.0 (71.0-84.9)	75.6 (68.5-81.1)	80.9 (77.8-83.7)
>0-959.9 mg	82.3 (80.1-84.2)	85.6 (77.7-90.7)	79.3 (68.7-86.3)	78.8 (68.2-85.9)	81.2 (76.6-84.9)
960.0-3054.9 mg	80.7 (79.1-82.1)	79.4 (74.5-83.4)	81.7 (75.2-86.5)	84.3 (77.0-89.3)	84.0 (80.5-86.9)
3055.0-7299.9 mg	74.5 (73.0-75.9)	79.6 (75.8-82.8)	79.2 (73.7-83.6)	80.3 (72.8-85.8)	82.2 (78.8-85.0)
≥7300.0 mg	66.3 (64.3-68.1)	69.5 (64.9-73.6)	72.6 (66.3-77.6)	67.3 (59.4-73.7)	69.3 (65.1-72.9)
<b>Bacterial infections</b>	<b>Within 1 year</b>	<b>1st year</b>	<b>2nd year</b>	<b>3rd year</b>	<b>After 3rd year</b>
Incident infections, n (%)	3421	422	254	227	910
<b>Cumulative probability (95% CI) at 1 year</b>	<b>2.9 (2.7-3.1)</b>	<b>3.1 (2.5-3.8)</b>	<b>3.0 (2.1-3.8)</b>	<b>3.6 (2.5-4.6)</b>	<b>4.3 (3.8-4.9)</b>
<b>Current daily dose</b>					
no-use	1.4 (1.2-1.7)	2.0 ( 1.2- 2.8)	1.8 ( 0.9- 2.7)	3.0 ( 1.7- 4.3)	3.6 ( 3.0- 4.2)
>0-4.9 mg	3.0 (2.6-3.5)	3.6 ( 1.9- 5.2)	3.8 ( 1.5- 6.1)	5.7 ( 2.5- 8.7)	5.7 ( 4.1- 7.2)
5.0-14.9 mg	3.3 (2.9-3.6)	4.0 ( 2.6- 5.4)	3.1 ( 1.4- 4.8)	3.0 ( 1.1- 5.0)	4.9 ( 3.6- 6.2)
15.0-24.9 mg	6.3 (5.1-7.4)	6.3 ( 2.0-10.5)	9.7 ( 2.6-16.4)	2.7 ( 0.0- 7.8)	6.2 ( 2.4- 9.9)
≥25.0 mg	7.5 (5.7-9.4)	4.2 ( 0.0- 9.8)	8.4 ( 0.0-18.8)	10.0 ( 0.0-22.2)	15.0 ( 5.4-23.6)

<b>Cumulative dose in last year</b>					
no-use	0.4 (0.3-0.4)	0.5 (0.2-0.8)	0.6 (0.2-1.1)	1.4 (0.7-2.1)	2.1 (1.7-2.5)
>0-959.9 mg	11.3 (9.8-12.9)	11.9 (6.0-17.5)	8.4 (2.6-13.9)	11.9 (3.7-19.4)	12.1 (8.4-15.5)
960.0-3054.9 mg	16.2 (14.7-17.8)	17.8 (12.0-23.3)	15.1 (8.3-21.4)	18.6 (9.7-26.6)	22.7 (18.0-27.1)
≥3055.0 mg	20.5 (17.1-23.7)	37.7 (21.4-50.5)	30.2 (12.8-44.1)	17.6 (1.9-30.8)	36.5 (22.6-48.0)
<b>Total cumulative dose</b>					
no-use	3.7 (2.9-4.5)	1.7 (0.2-3.2)	1.7 (0.2-3.1)	3.8 (1.8-5.7)	3.7 (3.0-4.5)
>0-959.9 mg	5.7 (4.9-6.5)	4.5 (2.2-6.8)	3.3 (0.7-5.8)	1.8 (0.0-3.7)	5.6 (3.8-7.3)
960.0-3054.9 mg	3.8 (3.4-4.1)	4.5 (2.9-6.1)	4.2 (2.1-6.2)	6.0 (3.1-8.8)	5.8 (4.4-7.2)
3055.0-7299.9 mg	1.2 (1.0-1.4)	2.8 (1.8-3.8)	3.1 (1.6-4.5)	3.1 (1.3-5.0)	4.4 (3.2-5.6)
≥7300.0 mg	0.4 (0.0-0.8)	0.9 (0.0-2.1)	1.9 (0.0-4.1)	0.0 (0.0-0.0)	0.8 (0.0-1.9)
<b>Cumulative probability (95% CI) at 5 years</b>	10.9 (10.5-11.4)	11.9 (10.5-13.2)	12.0 (10.1-13.8)	14.4 (12.2-16.6)	13.9 (12.9-14.9)
<b>Current daily dose</b>					
no-use	6.6 (6.2-7.0)	7.3 (5.9-8.7)	7.8 (5.8-9.7)	10.5 (8.1-12.9)	11.3 (10.1-12.5)
>0-4.9 mg	16.4 (15.0-17.7)	19.1 (14.4-23.6)	18.2 (12.0-23.9)	22.5 (15.2-29.2)	17.2 (14.2-20.1)
5.0-14.9 mg	17.6 (16.3-18.8)	18.2 (14.3-22.0)	16.1 (11.3-20.6)	19.4 (13.6-24.8)	17.3 (14.6-19.9)
15.0-24.9 mg	22.3 (19.0-25.4)	35.6 (19.6-48.4)	25.9 (12.0-37.5)	20.8 (2.3-35.8)	24.5 (16.2-32.0)
≥25.0 mg	27.9 (22.9-32.6)	19.4 (3.5-32.7)	38.5 (10.9-57.5)	26.0 (0.1-45.1)	31.5 (18.0-42.8)
<b>Cumulative dose in last year</b>					
no-use	4.2 (3.8-4.5)	4.4 (3.4-5.4)	5.2 (3.8-6.6)	7.0 (5.1-8.8)	7.9 (7.0-8.8)
>0-959.9 mg	21.8 (19.8-23.9)	29.9 (21.3-37.5)	28.5 (16.4-38.9)	38.6 (24.6-50.1)	28.2 (22.7-33.4)
960.0-3054.9 mg	31.8 (29.5-34.0)	42.3 (32.9-50.4)	30.9 (21.3-39.3)	39.8 (27.8-49.9)	34.7 (29.9-39.2)
≥3055.0 mg	46.7 (40.8-51.9)	55.5 (37.6-68.3)	67.0 (39.8-81.9)	64.2 (35.7-80.1)	57.8 (43.0-68.7)
<b>Total cumulative dose</b>					
no-use	11.4 (9.7-13.0)	9.1 (4.8-13.3)	11.4 (6.6-16.0)	14.7 (10.1-19.1)	13.3 (11.5-15.0)
>0-959.9 mg	14.2 (12.7-15.7)	12.6 (8.3-16.8)	12.7 (6.7-18.3)	10.2 (4.4-15.6)	16.1 (12.8-19.3)
960.0-3054.9 mg	14.3 (13.2-15.2)	14.3 (10.8-17.7)	11.9 (7.8-15.9)	19.5 (13.4-25.1)	16.6 (13.6-19.4)
3055.0-7299.9 mg	10.8 (10.1-11.6)	13.2 (10.5-15.9)	16.3 (11.8-20.5)	18.3 (12.7-23.6)	16.5 (13.9-19.0)
≥7300.0 mg	6.5 (5.9-7.2)	9.3 (7.1-11.5)	8.8 (5.9-11.6)	9.4 (5.7-13.0)	8.8 (6.9-10.6)
<b>Cumulative probability (95% CI) at 10 years</b>	20.4 (19.6-21.1)	21.2 (19.1-23.3)	22.4 (19.5-25.1)	23.5 (20.4-26.5)	23.0 (21.4-24.6)
<b>Current daily dose</b>					
no-use	14.7 (13.8-15.5)	16.2 (13.9-18.6)	16.8 (13.5-19.9)	18.1 (14.5-21.5)	18.7 (16.8-20.5)
>0-4.9 mg	29.8 (27.2-32.2)	32.6 (25.3-39.2)	27.8 (19.2-35.4)	33.0 (23.3-41.5)	26.1 (21.7-30.2)
5.0-14.9 mg	31.2 (28.9-33.5)	27.6 (21.8-33.0)	27.7 (20.3-34.5)	29.6 (21.4-36.9)	30.8 (26.5-34.9)
15.0-24.9 mg	34.7 (29.0-40.0)	30.5 (17.1-41.7)	46.0 (22.6-62.3)	61.9 (5.2-84.7)	33.1 (21.3-43.1)

≥25.0 mg	41.1 (31.7-49.3)	49.6 (11.8-71.2)	83.2 (14.5-96.7)	47.8 ( 3.4-71.8)	46.9 (29.9-59.7)
<b>Cumulative dose in last year</b>					
no-use	12.0 (11.3-12.8)	12.4 (10.3-14.4)	13.6 (10.7-16.3)	14.4 (11.3-17.4)	15.1 (13.5-16.7)
>0-959.9 mg	31.4 (28.2-34.6)	38.4 (28.4-47.0)	41.9 (17.7-59.0)	38.3 (24.4-49.7)	35.4 (28.6-41.6)
960.0-3054.9 mg	40.8 (37.4-44.0)	42.0 (33.3-49.6)	42.4 (30.4-52.3)	46.2 (33.7-56.3)	43.4 (36.3-49.8)
≥3055.0 mg	48.9 (42.5-54.5)	56.2 (32.6-71.5)	69.8 (39.5-85.0)	49.1 (30.6-62.7)	67.1 (47.3-79.5)
<b>Total cumulative dose</b>					
no-use	20.5 (17.7-23.3)	17.7 (10.1-24.7)	27.0 (17.6-35.3)	23.3 (16.1-29.9)	23.8 (20.1-27.2)
>0-959.9 mg	22.3 (20.0-24.5)	19.8 (13.2-25.9)	21.2 (12.5-29.1)	21.3 (11.6-29.9)	25.3 (20.2-30.1)
960.0-3054.9 mg	24.0 (22.2-25.7)	23.4 (18.0-28.4)	22.4 (15.6-28.7)	31.7 (22.9-39.4)	24.9 (20.7-28.9)
3055.0-7299.9 mg	19.4 (18.0-20.7)	26.9 (22.3-31.3)	25.7 (19.5-31.5)	25.5 (18.2-32.1)	25.5 (21.8-29.1)
≥7300.0 mg	17.3 (16.1-18.6)	16.7 (13.6-19.7)	18.8 (14.2-23.2)	18.1 (13.0-23.0)	17.7 (14.9-20.3)
<b>Viral infections</b>	<b>Within 1 year</b>	<b>1st year</b>	<b>2nd year</b>	<b>3<sup>rd</sup> year</b>	<b>After 3<sup>rd</sup> year</b>
Incident infections, n (%)	3731	361	240	193	819
<b>Cumulative probability (95% CI) at 1 year</b>	3.9 (3.6-4.1)	3.3 (2.6-4.0)	4.1 (3.1-5.1)	3.8 (2.7-4.9)	3.3 (2.8-3.8)
<b>Current daily dose</b>					
no-use	2.2 ( 1.9- 2.5)	2.1 (1.2-2.9)	3.2 ( 2.0- 4.4)	3.2 ( 1.9- 4.5)	2.8 ( 2.3- 3.4)
>0-4.9 mg	3.6 ( 3.1- 4.1)	4.0 (2.3-5.8)	5.7 ( 2.9- 8.5)	3.9 ( 1.2- 6.6)	2.4 ( 1.3- 3.4)
5.0-14.9 mg	4.6 ( 4.2- 5.1)	4.5 (3.0-6.0)	4.3 ( 2.3- 6.3)	4.1 ( 1.8- 6.4)	4.7 ( 3.5- 6.0)
15.0-24.9 mg	7.3 ( 6.1- 8.5)	5.6 (1.5-9.6)	5.9 ( 0.1-11.4)	2.7 ( 0.0- 7.8)	9.1 ( 4.4-13.5)
≥25.0 mg	8.4 ( 6.4-10.3)	2.2 (0.0-6.3)	4.2 ( 0.0-11.8)	20.0 ( 0.4-35.7)	3.5 ( 0.0- 8.3)
<b>Cumulative dose in last year</b>					
no-use	0.6 ( 0.5- 0.7)	0.6 ( 0.3- 0.9)	0.8 ( 0.3- 1.3)	1.6 ( 0.9- 2.4)	1.6 ( 1.3- 2.0)
>0-959.9 mg	15.4 (13.6-17.1)	9.6 ( 4.2-14.6)	13.8 ( 6.8-20.4)	12.6 ( 3.9-20.5)	8.3 ( 5.2-11.3)
960.0-3054.9 mg	18.2 (16.6-19.7)	20.6 (14.6-26.1)	24.6 (16.6-31.8)	18.3 ( 9.5-26.2)	17.2 (13.2-21.0)
≥3055.0 mg	25.8 (22.4-29.1)	27.2 (15.3-37.4)	18.6 ( 4.2-30.9)	19.1 ( 3.8-32.0)	24.8 (12.9-35.0)
<b>Total cumulative dose</b>					
no-use	6.0 (5.0-7.0)	3.4 (1.3-5.4)	2.6 (0.8-4.4)	3.7 (1.8-5.6)	2.6 (2.0-3.2)
>0-959.9 mg	8.2 (7.2-9.1)	3.3 (1.3-5.4)	3.4 (0.7-6.0)	4.0 (1.0-6.8)	4.2 (2.6-5.7)
960.0-3054.9 mg	4.4 (4.0-4.8)	4.7 (3.1-6.3)	5.9 (3.5-8.3)	6.3 (3.2-9.2)	4.8 (3.5-6.1)
3055.0-7299.9 mg	1.8 (1.5-2.0)	2.9 (1.9-3.9)	4.4 (2.7-6.1)	2.9 (1.1-4.6)	3.3 (2.2-4.3)
≥7300.0 mg	1.0 (0.3-1.6)	1.3 (0.0-2.7)	2.0 (0.0-4.2)	0.0 (0.0-0.0)	2.0 (0.2-3.6)
<b>Cumulative probability (95% CI) at 5 years</b>	13.2 (12.8-13.7)	11.3 (10.0-12.7)	13.2 (11.3-15.1)	13.7 (11.6-15.9)	13.1 (12.0-14.1)
<b>Current daily dose</b>					
no-use	8.4 ( 7.9- 8.9)	7.5 ( 6.0- 8.9)	10.6 ( 8.4-12.8)	10.7 ( 8.2-13.1)	10.5 ( 9.3-11.7)

>0-4.9 mg	18.1 (16.7-19.5)	15.6 (11.3-19.7)	19.0 (12.8-24.8)	17.1 (10.0-23.6)	16.1 (13.0-19.1)
5.0-14.9 mg	21.5 (20.2-22.8)	19.1 (15.0-22.9)	13.4 ( 9.2-17.3)	16.8 (11.4-21.8)	17.9 (15.1-20.6)
15.0-24.9 mg	25.0 (21.6-28.2)	21.9 ( 8.3-33.4)	28.3 (11.3-42.1)	36.1 (13.2-52.9)	19.0 (11.7-25.7)
≥25.0 mg	28.7 (23.5-33.5)	19.8 ( 5.3-32.1)	34.0 ( 0.0-57.0)	43.4 ( 3.3-66.9)	19.4 ( 7.8-29.5)
<b>Cumulative dose in last year</b>					
no-use	5.5 ( 5.1- 5.9)	4.6 ( 3.5- 5.6)	6.7 ( 5.0- 8.3)	7.4 ( 5.6- 9.3)	7.5 ( 6.6- 8.5)
>0-959.9 mg	25.7 (23.6-27.8)	22.9 (15.3-29.7)	26.4 (15.5-35.9)	23.3 (10.2-34.5)	30.2 (24.3-35.6)
960.0-3054.9 mg	35.0 (32.7-37.2)	40.7 (32.3-48.1)	32.5 (24.3-39.7)	46.0 (33.4-56.2)	31.6 (26.9-35.9)
≥3055.0 mg	48.3 (42.8-53.2)	37.6 (22.4-49.7)	46.3 (11.1-67.5)	59.5 ( 5.2-82.7)	47.3 (31.6-59.4)
<b>Total cumulative dose</b>					
no-use	17.5 (15.5-19.4)	11.3 ( 6.6-15.7)	12.9 ( 7.9-17.6)	14.8 (10.3-19.0)	12.1 (10.4-13.9)
>0-959.9 mg	19.1 (17.5-20.8)	12.2 ( 7.7-16.6)	10.2 ( 4.9-15.2)	11.2 ( 5.6-16.5)	14.2 (11.0-17.3)
960.0-3054.9 mg	16.1 (15.0-17.1)	14.2 (10.7-17.5)	16.3 (11.5-20.9)	15.2 ( 9.6-20.5)	17.3 (14.3-20.3)
3055.0-7299.9 mg	13.2 (12.4-14.0)	13.2 (10.5-15.9)	18.4 (13.8-22.8)	16.1 (10.8-21.2)	16.3 (13.5-18.9)
≥7300.0 mg	7.2 ( 6.5- 7.8)	7.4 ( 5.4- 9.4)	8.2 ( 5.3-10.9)	10.4 ( 6.5-14.1)	7.9 ( 6.1- 9.6)
<b>Cumulative probability (95% CI) at 10 years</b>	21.2 (20.5-22.0)	18.9 (16.9-20.9)	21.5 (18.8-24.2)	20.3 (17.3-23.1)	22.5 (20.9-24.1)
<b>Current daily dose</b>					
no-use	15.5 (14.7-16.3)	13.5 (11.3-15.6)	17.2 (14.1-20.2)	15.3 (12.1-18.4)	19.3 (17.3-21.2)
>0-4.9 mg	28.2 (25.8-30.6)	24.4 (18.0-30.4)	28.4 (18.9-36.8)	28.6 (18.3-37.6)	26.9 (22.3-31.3)
5.0-14.9 mg	31.8 (29.5-34.0)	31.9 (25.5-37.8)	28.1 (20.4-35.0)	28.3 (19.5-36.1)	27.7 (23.6-31.6)
15.0-24.9 mg	42.0 (35.2-48.0)	29.9 (15.0-42.2)	35.5 (15.5-50.8)	38.0 (15.4-54.5)	27.0 (15.3-37.0)
≥25.0 mg	39.0 (30.3-46.6)	42.4 (13.4-61.7)	-	36.7 ( 5.1-57.8)	36.1 (18.7-49.7)
<b>Cumulative dose in last year</b>					
no-use	12.8 (12.0-13.5)	10.6 ( 8.7-12.5)	13.3 (10.6-16.0)	12.5 ( 9.7-15.3)	15.9 (14.2-17.5)
>0-959.9 mg	32.6 (29.4-35.8)	29.8 (20.8-37.8)	43.8 (25.2-57.8)	25.5 (12.6-36.5)	35.0 (28.1-41.2)
960.0-3054.9 mg	40.5 (37.0-43.8)	42.8 (33.8-50.6)	42.1 (31.6-50.9)	46.6 (32.2-58.0)	37.4 (31.0-43.1)
≥3055.0 mg	49.9 (41.5-57.0)	49.4 (27.8-64.6)	27.7 (14.2-39.0)		58.3 (32.5-74.2)
<b>Total cumulative dose</b>					
no-use	25.8 (22.9-28.5)	17.2 (10.4-23.5)	25.4 (16.7-33.1)	21.4 (15.3-27.1)	22.9 (19.5-26.1)
>0-959.9 mg	28.1 (25.5-30.7)	17.6 (11.5-23.3)	16.7 ( 8.6-24.0)	20.9 (11.5-29.2)	23.9 (18.6-28.8)
960.0-3054.9 mg	23.9 (22.2-25.5)	20.8 (15.9-25.4)	21.4 (15.2-27.2)	18.0 (11.6-23.9)	26.8 (22.3-30.9)
3055.0-7299.9 mg	20.7 (19.4-22.0)	22.2 (18.1-26.1)	26.5 (20.4-32.2)	24.1 (16.3-31.1)	25.0 (21.2-28.7)
≥7300.0 mg	15.8 (14.6-17.0)	15.7 (12.5-18.7)	17.8 (13.3-22.1)	16.8 (11.7-21.5)	17.0 (14.2-19.8)
<b>Parasitic infections</b>	<b>Within 1 year</b>	<b>1st year</b>	<b>2nd year</b>	<b>3<sup>rd</sup> year</b>	<b>After 3<sup>rd</sup> year</b>
Incident infections, n (%)	771	73	40	54	182

<b>Cumulative probability (95% CI) at 1 year</b>	1.0 (0.8-1.1)	0.7 (0.4-1.0)	1.0 (0.5-1.4)	1.1 (0.5-1.7)	0.8 (0.6-1.0)
<b>Current daily dose</b>					
no-use	0.6 (0.4-0.8)	0.3 (0.0-0.5)	0.6 (0.1-1.2)	1.0 (0.3- 1.8)	0.7 (0.4-0.9)
>0-4.9 mg	0.8 (0.6-1.0)	0.4 (0.0-1.0)	1.5 (0.0-3.0)	1.0 (0.0- 2.3)	0.9 (0.2-1.5)
5.0-14.9 mg	1.1 (0.9-1.4)	1.2 (0.4-1.9)	1.0 (0.0-1.9)	1.1 (0.0- 2.3)	1.2 (0.5-1.8)
15.0-24.9 mg	1.9 (1.3-2.6)	3.0 (0.1-5.9)	2.6 (0.0-6.0)	5.3 (0.0-12.1)	0.6 (0.0-1.7)
≥25.0 mg	2.3 (1.2-3.4)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0- 0.0)	1.7 (0.0-5.0)
<b>Cumulative dose in last year</b>					
no-use	0.2 (0.1-0.2)	0.0 (0.0- 0.0)	0.1 (0.0- 0.2)	0.5 (0.1- 0.9)	0.3 (0.2-0.5)
>0-959.9 mg	3.9 (2.9-4.9)	1.7 (0.0- 4.0)	3.1 (0.0- 6.5)	1.7 (0.0- 4.9)	3.2 (1.2-5.1)
960.0-3054.9 mg	5.6 (4.5-6.6)	4.3 (1.1- 7.5)	8.0 (2.7-13.0)	7.3 (0.8-13.4)	5.4 (2.8-7.8)
≥3055.0 mg	7.6 (5.3-9.8)	10.0 (3.6-16.0)	5.6 (0.0-12.9)	15.3 (0.0-31.5)	4.0 (0.0-8.3)
<b>Total cumulative dose</b>					
no-use	1.8 (1.2-2.4)	0.0 (0.0-0.0)	0.3 (0.0-1.0)	1.0 (0.0-2.0)	0.6 (0.3-0.9)
>0-959.9 mg	1.8 (1.4-2.3)	0.7 (0.0-1.5)	1.1 (0.0-2.5)	1.2 (0.0-2.8)	1.0 (0.3-1.8)
960.0-3054.9 mg	1.1 (0.9-1.3)	0.8 (0.1-1.4)	1.9 (0.5-3.2)	1.6 (0.0-3.1)	1.2 (0.5-1.8)
3055.0-7299.9 mg	0.4 (0.3-0.5)	1.0 (0.4-1.5)	0.7 (0.0-1.5)	1.1 (0.0-2.3)	0.9 (0.3-1.4)
≥7300.0 mg	0.6 (0.1-1.1)	0.0 (0.0-0.0)	0.6 (0.0-1.9)	0.0 (0.0-0.0)	0.4 (0.0-1.1)
<b>Cumulative probability (95% CI) at 5 years</b>	2.8 (2.6-3.0)	2.4 (1.7-3.0)	2.6 (1.7-3.5)	3.5 (2.3-4.6)	2.9 (2.4-3.4)
<b>Current daily dose</b>					
no-use	1.7 (1.5-1.9)	1.7 (1.0- 2.4)	1.6 (0.7- 2.5)	2.7 (1.5- 4.0)	2.5 (1.9- 3.1)
>0-4.9 mg	3.3 (2.7-4.0)	1.8 (0.2- 3.3)	4.9 (1.4- 8.3)	4.8 (0.9- 8.6)	3.1 (1.7- 4.5)
5.0-14.9 mg	4.9 (4.2-5.5)	3.9 (1.9- 5.8)	2.6 (0.6- 4.6)	3.2 (0.8- 5.5)	4.0 (2.6- 5.4)
15.0-24.9 mg	6.3 (4.4-8.1)	12.0 (2.9-20.3)	9.0 (0.0-17.7)	12.2 (0.0-23.1)	2.5 (0.0- 5.4)
≥25.0 mg	7.0 (4.2-9.8)	3.2 (0.0- 9.2)	16.1 (0.0-34.3)	16.7 (0.0-41.7)	5.5 (0.0-11.6)
<b>Cumulative dose in last year</b>					
no-use	1.0 (0.9- 1.2)	1.1 (0.6- 1.6)	0.7 (0.2- 1.3)	1.7 (0.8- 2.6)	1.7 (1.3- 2.2)
>0-959.9 mg	5.5 (4.4- 6.6)	3.9 (0.5- 7.2)	11.5 (3.4-18.9)	0.8 (0.0- 2.5)	5.1 (2.8- 7.4)
960.0-3054.9 mg	8.8 (7.4-10.2)	10.8 (3.7-17.4)	8.3 (2.7-13.5)	14.2 (6.2-21.5)	9.4 (5.9-12.6)
≥3055.0 mg	13.3 (9.5-17.0)	5.3 (1.9- 8.6)	20.6 (0.0-41.9)	38.6 (0.0-66.2)	8.2 (1.4-14.5)
<b>Total cumulative dose</b>					
no-use	3.9 (2.9-4.9)	3.6 (0.7-6.5)	2.6 (0.3-4.8)	2.5 (0.6-4.3)	3.3 (2.3-4.2)
>0-959.9 mg	4.4 (3.6-5.3)	2.7 (0.5-4.9)	2.9 (0.0-5.8)	4.9 (0.9-8.7)	2.0 (0.8-3.2)
960.0-3054.9 mg	3.6 (3.1-4.1)	3.8 (1.9-5.7)	2.7 (0.8-4.6)	4.1 (1.0-7.1)	3.9 (2.3-5.4)
3055.0-7299.9 mg	2.7 (2.3-3.1)	2.2 (1.1-3.3)	3.2 (1.1-5.3)	4.2 (1.4-6.9)	3.4 (2.1-4.7)

≥7300.0 mg	1.3 (1.0-1.6)	1.3 (0.4-2.1)	2.0 (0.6-3.4)	2.6 (0.7-4.5)	1.7 (0.8-2.5)
<b>Cumulative probability (95% CI) at 10 years</b>	4.2 (3.8-4.5)	3.4 (2.6-4.3)	3.0 (2.0-4.0)	6.0 (4.2-7.7)	5.1 (4.3-6.0)
<b>Current daily dose</b>					
no-use	2.9 (2.5- 3.2)	2.4 ( 1.6- 3.3)	1.8 ( 0.8- 2.7)	4.1 ( 2.4- 5.9)	4.1 ( 3.2- 5.0)
>0-4.9 mg	5.2 ( 4.1- 6.2)	4.0 ( 1.1- 6.8)	6.0 ( 1.9- 9.9)	7.7 ( 2.0-13.0)	5.3 ( 3.0- 7.5)
5.0-14.9 mg	7.0 ( 5.8- 8.3)	5.3 ( 2.5- 8.0)	2.7 ( 0.6- 4.7)	8.4 ( 2.8-13.7)	7.0 ( 4.6- 9.4)
15.0-24.9 mg	8.2 ( 5.1-11.2)	12.0 ( 3.1-20.1)	9.0 ( 0.0-17.7)	33.1 ( 1.3-54.6)	8.0 ( 0.0-16.1)
≥25.0 mg	8.6 ( 5.1-12.1)	3.0 ( 0.0- 8.7)	26.8 ( 0.0-51.0)	11.1 ( 0.0-29.4)	18.8 ( 2.7-32.3)
<b>Cumulative dose in last year</b>					
no-use	2.2 ( 1.9- 2.5)	1.5 ( 0.9- 2.2)	1.0 ( 0.3- 1.7)	3.3 ( 1.8- 4.8)	3.3 ( 2.5- 4.1)
>0-959.9 mg	6.4 ( 4.9- 7.9)	6.5 ( 2.4-10.5)	9.2 ( 3.0-15.1)	6.2 ( 0.0-13.6)	7.2 ( 3.6-10.7)
960.0-3054.9 mg	9.3 ( 7.2-11.3)	10.1 ( 4.4-15.4)	5.9 ( 2.3- 9.4)	17.5 ( 7.8-26.2)	13.8 ( 8.3-19.0)
≥3055.0 mg	8.4 ( 6.5-10.1)	8.9 ( 0.0-17.6)	7.5 ( 0.2-14.3)	17.7 ( 2.6-30.5)	18.4 ( 0.0-37.6)
<b>Total cumulative dose</b>					
no-use	6.5 (4.8-8.1)	4.2 (0.8-7.5)	3.0 (0.4-5.6)	3.9 ( 0.9- 6.9)	4.6 ( 3.1- 6.0)
>0-959.9 mg	5.9 (4.6-7.2)	3.7 (0.9-6.4)	3.0 (0.0-5.9)	5.3 ( 1.0- 9.4)	7.1 ( 3.8-10.3)
960.0-3054.9 mg	5.3 (4.4-6.1)	4.0 (1.9-6.0)	2.9 (0.9-4.8)	8.1 ( 2.7-13.1)	5.6 ( 3.6- 7.7)
3055.0-7299.9 mg	3.8 (3.2-4.4)	3.3 (1.7-4.9)	3.8 (1.4-6.2)	6.1 ( 2.3- 9.8)	5.8 ( 3.7- 8.0)
≥7300.0 mg	2.6 (2.1-3.1)	2.8 (1.5-4.1)	2.5 (0.9-4.0)	5.8 ( 2.7- 8.8)	3.7 ( 2.3- 5.1)
<b>Fungal infections</b>	<b>Within 1 year</b>	<b>1st year</b>	<b>2nd year</b>	<b>3<sup>rd</sup> year</b>	<b>After 3<sup>rd</sup> year</b>
Incident infections, n (%)	3890	351	226	177	772
<b>Cumulative probability (95% CI) at 1 year</b>	4.2 (4.0-4.4)	3.0 (2.3-3.6)	4.0 (3.0-5.0)	2.6 (1.7-3.5)	3.2 (2.8-3.7)
<b>Current daily dose</b>					
no-use	2.3 ( 2.0- 2.6)	1.7 (1.0-2.5)	3.2 ( 2.0- 4.5)	2.2 ( 1.1- 3.3)	3.0 ( 2.4- 3.5)
>0-4.9 mg	4.1 ( 3.6- 4.7)	4.0 (2.3-5.7)	4.2 ( 1.7- 6.6)	4.2 ( 1.5- 6.9)	3.1 ( 1.9- 4.3)
5.0-14.9 mg	5.0 ( 4.6- 5.5)	3.8 (2.4-5.2)	4.8 ( 2.7- 6.8)	2.1 ( 0.4- 3.7)	3.7 ( 2.6- 4.8)
15.0-24.9 mg	7.8 ( 6.5- 9.0)	5.4 (1.4-9.3)	7.1 ( 0.9-12.9)	2.7 ( 0.0- 7.8)	5.0 ( 1.5- 8.3)
≥25.0 mg	9.4 ( 7.3-11.4)	2.0 (0.0-5.9)	4.3 ( 0.0-12.3)	5.3 ( 0.0-14.8)	5.1 ( 0.0-10.6)
<b>Cumulative dose in last year</b>					
no-use	0.7 ( 0.6- 0.8)	0.7 ( 0.3- 1.0)	0.9 ( 0.4- 1.4)	1.0 ( 0.4- 1.7)	1.7 ( 1.3- 2.0)
>0-959.9 mg	14.4 (12.8-16.1)	6.8 ( 2.1-11.3)	10.5 ( 4.1-16.5)	7.2 ( 0.8-13.1)	9.2 ( 6.0-12.3)
960.0-3054.9 mg	21.1 (19.5-22.7)	16.9 (11.4-22.1)	22.6 (14.7-29.7)	13.6 ( 6.0-20.6)	17.0 (13.0-20.9)
≥3055.0 mg	24.1 (20.7-27.4)	26.6 (15.4-36.3)	33.0 (14.8-47.3)	16.0 ( 0.0-29.5)	14.3 ( 4.6-23.0)
<b>Total cumulative dose</b>					
no-use	6.6 (5.5-7.6)	4.8 (2.3-7.2)	3.7 (1.5-5.8)	2.6 (1.0-4.2)	2.8 (2.2-3.5)

>0-959.9 mg	8.0 (7.0-8.9)	2.7 (0.8-4.5)	1.7 (0.0-3.5)	2.3 (0.0-4.5)	4.2 (2.7-5.7)
960.0-3054.9 mg	5.3 (4.9-5.8)	3.9 (2.4-5.4)	6.0 (3.5-8.4)	4.2 (1.7-6.6)	4.4 (3.1-5.7)
3055.0-7299.9 mg	1.5 (1.3-1.8)	2.6 (1.7-3.6)	3.3 (1.8-4.8)	1.7 (0.3-3.1)	3.0 (2.0-4.0)
≥7300.0 mg	1.3 (0.5-2.1)	0.0 (0.0-0.0)	5.2 (1.6-8.6)	1.3 (0.0-3.7)	0.8 (0.0-1.8)
<b>Cumulative probability (95% CI) at 5 years</b>	14.2 (13.7-14.7)	10.9 ( 9.5-12.2)	12.4 (10.5-14.2)	13.0 (10.9-15.2)	13.2 (12.2-14.3)
<b>Current daily dose</b>					
no-use	8.9 ( 8.4- 9.4)	7.5 ( 6.1- 8.9)	9.8 ( 7.6-11.9)	11.0 ( 8.5-13.5)	11.9 (10.6-13.1)
>0-4.9 mg	20.1 (18.6-21.6)	14.2 (10.1-18.0)	15.6 ( 9.9-21.0)	16.4 ( 9.4-22.8)	14.1 (11.3-16.9)
5.0-14.9 mg	22.3 (20.9-23.6)	17.6 (13.7-21.5)	15.1 (10.6-19.4)	15.4 (10.1-20.3)	15.8 (13.1-18.3)
15.0-24.9 mg	28.9 (25.2-32.4)	20.5 ( 7.9-31.4)	30.0 (13.8-43.2)	29.4 ( 9.5-44.9)	21.8 (13.5-29.3)
≥25.0 mg	29.8 (24.9-34.3)	22.8 ( 3.3-38.3)	6.7 ( 0.0-18.5)	7.1 ( 0.0-19.7)	14.6 ( 5.0-23.3)
<b>Cumulative dose in last year</b>					
no-use	5.8 ( 5.4- 6.2)	5.3 ( 4.2- 6.4)	6.1 ( 4.5- 7.6)	7.4 ( 5.5- 9.2)	8.5 ( 7.5- 9.4)
>0-959.9 mg	27.2 (25.0-29.3)	21.5 (14.2-28.2)	31.8 (19.2-42.4)	22.4 ( 9.8-33.1)	25.7 (20.6-30.6)
960.0-3054.9 mg	38.2 (35.8-40.4)	37.1 (27.6-45.4)	32.0 (22.9-40.1)	42.8 (31.2-52.5)	30.6 (26.0-35.0)
≥3055.0 mg	47.1 (41.7-52.0)	39.8 (19.8-54.9)	46.5 ( 3.4-70.3)	29.1 (10.6-43.8)	37.7 (24.6-48.5)
<b>Total cumulative dose</b>					
no-use	17.7 (15.7-19.6)	12.7 ( 7.9-17.3)	15.3 ( 9.8-20.5)	13.7 ( 9.3-17.9)	14.7 (12.7-16.6)
>0-959.9 mg	18.8 (17.1-20.4)	14.3 ( 9.4-18.9)	11.1 ( 5.6-16.4)	11.4 ( 5.5-17.0)	15.1 (11.9-18.2)
960.0-3054.9 mg	19.0 (17.8-20.1)	12.2 ( 9.0-15.3)	16.6 (11.7-21.3)	16.6 (10.4-22.3)	15.2 (12.3-18.0)
3055.0-7299.9 mg	13.8 (13.0-14.7)	12.2 ( 9.6-14.8)	13.3 ( 9.3-17.2)	15.4 (10.0-20.4)	14.6 (12.1-17.0)
≥7300.0 mg	7.4 ( 6.7- 8.1)	6.9 ( 4.9- 8.9)	8.2 ( 5.5-10.9)	9.0 ( 5.4-12.4)	7.2 ( 5.5- 8.9)
<b>Cumulative probability (95% CI) at 10 years</b>	21.8 (21.1-22.6)	18.5 (16.5-20.5)	19.5 (16.8-22.0)	20.2 (17.1-23.2)	20.6 (19.1-22.1)
<b>Current daily dose</b>					
no-use	15.9 (15.1-16.8)	15.0 (12.7-17.2)	15.4 (12.4-18.2)	16.3 (12.9-19.6)	18.4 (16.6-20.2)
>0-4.9 mg	29.8 (27.4-32.1)	24.3 (17.3-30.8)	28.7 (19.7-36.7)	31.3 (19.8-41.1)	23.2 (18.9-27.3)
5.0-14.9 mg	31.7 (29.5-33.8)	24.6 (19.4-29.5)	24.8 (17.5-31.4)	22.6 (15.2-29.4)	25.0 (21.0-28.9)
15.0-24.9 mg	39.3 (33.7-44.4)	30.7 (14.2-44.0)	31.7 (14.5-45.4)	52.3 (19.7-71.6)	21.3 (13.4-28.5)
≥25.0 mg	41.8 (33.3-49.2)	25.4 ( 5.7-41.0)	20.8 ( 0.0-45.4)	5.9 ( 0.0-16.4)	27.6 (13.3-39.5)
<b>Cumulative dose in last year</b>					
no-use	13.1 (12.3-13.8)	12.5 (10.5-14.5)	12.3 ( 9.6-14.8)	13.4 (10.3-16.3)	15.1 (13.5-16.6)
>0-959.9 mg	32.9 (29.8-35.9)	34.3 (22.8-44.1)	39.3 (25.4-50.7)	33.5 (16.4-47.1)	29.9 (23.9-35.5)
960.0-3054.9 mg	39.0 (36.0-41.8)	30.3 (23.8-36.3)	33.4 (23.6-42.0)	45.6 (30.8-57.2)	34.6 (28.6-40.1)
≥3055.0 mg	50.8 (42.2-58.1)	34.1 (19.5-46.1)	31.1 (10.5-47.0)		46.8 (24.8-62.4)
<b>Total cumulative dose</b>					

no-use	24.0 (21.3-26.6)	20.7 (13.3-27.4)	22.1 (14.5-29.0)	24.8 (17.0-31.8)	23.4 (20.3-26.4)
>0-959.9 mg	28.0 (25.4-30.4)	25.8 (18.1-32.8)	18.4 (10.2-25.8)	19.3 (10.4-27.3)	22.6 (17.7-27.2)
960.0-3054.9 mg	27.1 (25.4-28.8)	21.8 (16.5-26.8)	22.7 (16.2-28.7)	24.5 (16.2-32.1)	22.7 (18.7-26.6)
3055.0-7299.9 mg	21.8 (20.4-23.1)	20.5 (16.5-24.3)	18.6 (13.4-23.5)	20.9 (13.8-27.5)	22.1 (18.4-25.6)
≥7300.0 mg	15.1 (13.9-16.2)	13.0 (10.1-15.8)	17.4 (12.9-21.7)	14.6 ( 9.7-19.2)	14.0 (11.5-16.5)

Note: CI, confidence interval; IQR, interquartile range. Estimates are shown for time-variant prednisolone-equivalent dosage.

