Disease-modifying drugs, multiple sclerosis and infection-related healthcare use in British Columbia, Canada: a population-based study

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Summary

Background Much remains unknown surrounding the disease-modifying drugs (DMDs) used to treat multiple sclerosis and infection-related healthcare use in the 'real-world' setting. We examined if DMD exposure was associated with altered infection-related healthcare use.

Methods We assessed if DMD (versus no) exposure was associated with altered infection-related hospitalizations, physician claims, and prescriptions filled in British Columbia, Canada (1996–2017). Healthcare use was assessed using negative binomial and proportional means regression models, reported as sex-/age-/comorbidity-/calendar year-/socioeconomic-adjusted rate and hazard ratios [aRR, aHR], with 95% confidence intervals [CIs]).

Findings We identified 19,360 multiple sclerosis cases (13,940/19,360; 72.0% women; mean age at study start = 44.5 standard deviation, SD = 13.3; mean follow-up = 11.7 [SD = 7.3] years). Relative to unexposed periods, exposure to any DMD was associated with a lower infection-related rate of physician claims (aRR = 0.88; 95% CI:0.85–0.92) and hazard of hospitalization (aHR = 0.64; 95% CI:0.56–0.73), and a higher rate of infection-related prescriptions (aRR = 1.14; 95% CI:1.08–1.20). Exposure to any injectable or oral DMD was associated with a lower infection-related rate of physician claims (injectable aRR = 0.88; 95% CI:0.84–0.92, oral aRR = 0.83; 95% CI:0.77–0.90) and hazard of hospitalization (injectable aHR = 0.65; 95% CI:0.56–0.75, oral aHR = 0.54; 95% CI:0.38–0.77), whereas intravenous DMD exposure was not (aRR = 0.99; 95% CI:0.86–1.14, aHR = 0.73; 95% CI:0.49–1.09). Exposure to any injectable or intravenous DMD was associated with a higher rate of infection-related prescriptions (injectable aRR = 1.15; 95% CI:1.08–1.22, intravenous = 1.34; 95% CI:1.15–1.56), whereas oral DMDs were not (aRR = 0.98; 95% CI:0.91–1.05).

Interpretation DMD exposure for the treatment of MS was associated with differences in infection-related healthcare use. While infection-related hospitalizations and physician visits were lower, prescription fills were higher. How these differences in infection-related healthcare use affect outcomes in persons with multiple sclerosis warrants consideration.

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Keywords: Multiple sclerosis; Disease-modifying drugs; Infections; Healthcare use

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Research in context

Evidence before this study

Much remains unknown surrounding the disease-modifying drugs (DMDs) used to treat multiple sclerosis (MS) and infection-related healthcare use in the 'real-world' setting. Using the search terms "multiple sclerosis" and "infection", we searched for articles published through until September 2022 within PubMed.

Similar to all immunosuppressive medications, DMDs used for the treatment of MS carry risk of infections. The burden of infections in the MS population over the life span can be considerable and surpasses that seen in the general population. However, relatively few studies published to date have evaluated the role of the MS DMDs on infection risk. Evidence before this study suggests that use of any monoclonal antibody (versus any DMD) was associated with a higher incident rate of infection-related hospitalizations among MS enrollees of the Department of Defense military healthcare system (n = 8695; 2004–2017). Further, a Swedish study examined the risk of the first infection-related hospitalization in MS DMD-exposed persons only, the majority of whom (>50% of the 6421 cases) had received rituximab. Study authors were unable to access primary care information, and neither the Swedish nor US study authors examined similar MS cases not undergoing a DMD treatment.

Added value of this study

We examined the relationship between DMD exposure and infection-related healthcare use in a population-based MS cohort and explored whether any such associations were modified by characteristics such as patient age, sex, or presence of specific comorbidities. Our study added value by providing an overview of the infection-related healthcare utilization in people with MS, can help guide patient-clinician expectations surrounding infections and the DMDs as well as informing healthcare planning. Exposure to a MS DMD (versus no exposure) was associated with altered infection-related healthcare use. Interestingly, while the use of any (versus no) DMD was associated with lower infection-related hospitalizations and physician visits, prescription fills were higher. The mode of administration affected findings; while any injectable or oral DMD (versus no DMD) was associated with lower infection-related physician and hospital visits, this was less evident for the intravenous DMDs. The reasons for these differences remain subject to speculation; further investigations are warranted.

Implications of all the available evidence

Prior evidence was challenging to interpret across studies given that some study designs lacked primary care data and/or did not include MS cases not undergoing DMD treatment. All available evidence suggested that DMD exposure was associated with altered infection-related healthcare use. Also, the mode of administration affected findings. How these differences in infection-related healthcare use affect other outcomes in people with MS warrants consideration.

Introduction

In the past 25 years, a range of injectable, oral and infusion-administered disease-modifying drugs (DMDs) have been approved to treat multiple sclerosis (MS). All DMDs were approved based on relatively short-term (typically lasting 2–3 years), explanatory clinical trials, conducted in select individuals.[1] However, in routine clinical practice, a much broader range of people with MS may be expected to take DMDs for many years. Similar to all immunosuppressive medications, disease-modifying drugs used for the treatment of MS carry risk of infections.[2] Anti-infectives are therefore used by physicians in clinical practice to treat and sometimes prevent different types of infections in people with MS. The burden of infections in the MS population over the life span can be considerable and surpasses that seen in the general population.[3] A UK study found that infections represented the most common comorbidity in MS, affecting 80% of 1713 incident cases on or after MS diagnosis[4] in the primary care setting. Among the most common are the urinary tract infections[5,6] which cause an estimated 30–50% of all hospitalizations amongst MS patients.[6] Infections can trigger MS relapses and disease activity and carry a significant economic burden.[7] A 2023 US study estimated that average annual in-hospital charges for all MS inpatient hospitalizations was $US3 billion (adjusted to 2010 dollars) with infections, such as urinary tract-related, skin and soft tissue and pneumonia being major contributors.[7]

Administrative data offer the opportunity to access health-related information generated as part of routine clinical care for entire populations, and have been used to assess the infection risk in persons with MS previously.[8–11] However, relatively few studies published to date have evaluated the role of the MS DMDs on infection risk.[12–14] Of those that have, two focused on hospitalizations only,[12,14] with a (US-based study) examining just the monoclonal antibodies,[14] and a Swedish study primarily rituximab (as >50% of patients were exposed to this DMD). Finally, the third study included Canadian data but in a smaller and less contemporaneous population.[13] Further, despite the International Advisory Committee on Clinical Trials in MS call for more comorbidity-related studies,[15,16] and given the paucity of sex- and age-focused trial analyses, examining the potential impact of these characteristics on DMD outcomes in everyday clinical practice represents an unmet need. The need for age and sex-focused analyses in relation to the MS DMDs in particular has been highlighted by others[17–19]; both age and sex can

affect risk of adverse events as well as response to treatment.

We examined the relationship between DMD exposure and infection-related healthcare use in a population-based MS cohort and explored whether any such associations were modified by characteristics such as patient age, sex, or presence of specific comorbidities. We hypothesized DMD exposure will be associated with an increased use of infection-related healthcare use relative to no exposure.

Methods

Study design and data sources

Study design: observational, cohort

Our observational cohort study accessed prospectively collected population-based health administrative data in British Columbia (BC), Canada. BC has a public healthcare plan, with mandatory enrollment for residents. Encounters with the healthcare system (i.e. healthcare utilization) are routinely collected by the BC Ministry of Health, including physician and hospital visits and prescription drugs dispensed (i.e. filled) in the community or outpatient setting. Data accessed (via Population Data BC[20]) included: the Medical Services Plan[21] and Discharge Abstract Databases,[22] providing physician claims and hospital admissions/discharges-related information; PharmaNet,[23] capturing prescriptions filled at outpatient/community pharmacies; Census Geodata, providing socioeconomic status (SES), based on residential postal code linked to median neighborhood household income[24]; Registration and Premium Billing files,[25] enabling confirmation of provincial residency (via registration days within the mandatory healthcare plan) and demographics (sex, date of birth); and Vital Statistics,[26] capturing death dates.

All aforementioned data sources were complete except for SES which was missing for <1% of individuals (98 of the 19,360 MS cases). This was likely due to administrative reasons, and, therefore, we anticipate that their values to be symmetrically distributed around the median (SES = 3). The impact of the imputed values would be negligible.

Cohort selection

We used a validated algorithm to identify MS cases, requiring ≥3 MS International Classification of Diseases (ICD) codes (ICD-9/10-CA: 340/G35) from the hospital or physician data, or ≥1 prescription filled for a MS DMD (Tables 1 and 2).[27] Of note, filling a DMD prescription was not required for fulfilling this validated algorithm. This validated algorithm has been used previously,[28,29] which facilitating comparisons between studies,[29–32] and enables a population-based approach, by including all possible eligible MS cases. The algorithm has a positive predictive value (PV) of 99.5%, and the negative PV of 97.5% and has been validated against medical records and successfully applied in multiple Canadian regions.[30,33,34] The date of the first MS-specific or demyelinating disease-related ICD code (Table 1) or DMD prescription filled determined the index date. Persons with MS aged ≥18 years and resident in BC for ≥1 year pre-index date were eligible for inclusion. Based on data availability, the earliest possible index date was 1-January-1996, and all persons were followed until the earliest of emigration from BC, death, or 31-December-2017 (study end date). Our study population therefore comprised incident and prevalent MS cases. The year 1996 also represents the first full calendar year that the MS DMDs became available through the provincial government's universal health insurance plan. The vast majority of persons would not have been exposed to a DMD before the index date, aside from a very small number of persons who may have been randomized to receive a DMD as part of a clinical trial.[35]

	ICD-9	ICD-10
Multiple sclerosis		
Multiple sclerosis	340	G35
Demyelinating disease		
Optic neuritis	377.3	H46
Acute transverse myelitis	323.82 341.2	G37.3
Acute disseminated encephalomyelitis	323	G36.9
Demyelinating disease of CNS unspecified	341.9	G37.8
Other acute disseminated demyelination	not applicable	G36
Neuromyelitis optica	341.0	G36.0

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CA = International Classification of Diseases, Tenth Revision, Canada.

Table 1: **Multiple sclerosis and demyelinating disease related codes.**

Outcomes

The three outcomes were infection-related healthcare utilization (i.e. 1. Physician claims, 2. Hospitalizations, 3. Prescriptions filled) occurring between the index date and study end date. Physician claims represented the primary outcome, and hospitalizations and prescriptions filled the secondary outcomes. Infection-related physician clams and hospitalizations were identified using ICD-9/10-CA codes (Supplementary Table S1). A wide range of infection-related codes were included as used in previous studies.[8–10] Thus, any physician visit or hospitalization resulting in an ICD code for an infection being generated as the reason for the healthcare use was considered infection-related. As anti-infectives are used to treat or prevent some types of infections, we also examined the healthcare utilization in the outpatient care settings which included prescriptions filled for antibiotics, antivirals or anti-mycotics. The prescriptions filled were classified using the Anatomical Therapeutic Chemical (ATC) System

Disease-modifying therapy	Drug identification number	Mode of administration	Health Canada approval date
Betaseron® (IFNB-1b)	02169649	injectable	July 1995
Extavia® (IFNB-1b)	02337819	injectable	November 2009
Avonex® (IFNB-1a)	02237770 02269201 02267594	injectable	April 1998
Rebif® (IFNB-1a)	02281708 02277492 02237317 02237319 02237320 02277492 02281708 02318253 02318261 02318288	injectable	February 1998
Plegridy® (Peg-IFNB-1a)	02444372 02444380 02444399 02444402	injectable	August 2015
Copaxone® (glatiramer acetate)	02233014 02245619 02456915 02441446 02481510	injectable	October 1997
Glatect® (glatiramer acetate)	02460661	injectable	August 2017
Tysabri® (natalizumab)	02286386	intravenous	September 2006
Gilenya® (fingolimod)	02365480 02482533	oral	March 2011
Tecfidera® (dimethyl fumarate)	02404508 02420201	oral	April 2013
Aubagio® (teriflunomide)	02416328	oral	November 2013
Lemtrada® (alemtuzumab)	02418320	intravenous	December 2013
Zinbryta® (daclizumab)	02459620 02459639	injectable	December 2016
Ocrevus® (ocrelizumab)	02467224	intravenous	August 2017

The DMDs listed represented all those available (approved) for use in MS by Health Canada at some point during the study. Daclizumab was withdrawn from the market in March 2018 due to safety concerns.

***Table 2*: The disease-modifying therapies approved by Health Canada to treat multiple sclerosis (1995/6–2017): drug name (brand/generic), drug identification number, mode of administration (injectable, oral, intravenous), Health Canada approval date.**

(Supplementary Table S2).[36] Thus, any prescription filled for one of these drugs was considered 'infection-related'. To avoid double counting, physician claims with the same ICD code on the same day were considered as one claim. Similarly, any overlapping hospital stays were considered as one hospitalization, and any prescriptions filled for the same drug (i.e. same Health Canada unique drug identification number) on the same day were counted once.[29]

Exposure

The following DMDs were available/approved by Health Canada to treat MS during our study period: beta-interferon, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, daclizumab, and ocrelizumab. We identified all prescriptions filled for a DMD and determined the time each individual was exposed to that drug based on the days' supplied (via PharmaNet), allowing for a 30-day grace period.[29] Alemtuzumab and ocrelizumab exposure were defined as 12-months (alemtuzumab) and 6-months (ocrelizumab) from the date of first and any subsequent supply; if no further prescription fills occurred, a 30-day grace period was also applied. We considered a DMD as discontinued if there were no further dispensations for >90 days, or if a prescription was filled for a different DMD. For the six individuals exposed to daclizumab (withdrawn from the market for safety reasons), their follow-up was censored at the first daclizumab prescription filled.

Periods during which an individual had no DMD supply were considered 'unexposed,' and this formed the reference category. A person's DMD exposure status was examined as time-varying to account for treatment change(s) over time. Both the time period before, and after, the initiation of DMD were included in the analysis for all individuals. DMDs were grouped and assessed as any DMD, then by mode of administration

(i.e. invasiveness; injectable [beta-interferon/glatiramer acetate], intravenous [natalizumab/alemtuzumab/ocrelizumab] or oral [dimethyl fumarate/fingolimod/teriflunomide]) and finally as each individual DMD (except for ocrelizumab, as <6 cases were exposed).

Statistical analyses

We used negative binomial regression models to examine the associations between DMD exposure and infection-related physician claims and prescriptions filled, with each assessed as counts–either yearly or by DMD exposure period. The negative binomial regression is more flexible than Poisson regression since it does not require the mean and the variance of the counts to be equal. Models were fitted by generalized estimating equations (GEE) with an exchangeable working correlation matrix and person-time included as an offset.[37] Findings were reported as adjusted rate ratios (aRRs) with the corresponding 95% confidence intervals (CIs). As infection-related hospitalizations are rare, we employed a repeated time-to-event approach. The sojourn time between infection-related hospitalizations was analysed using the proportional means model for recurrent events with robust sandwich variance estimates,[38] thus allowing for multiple infection-related hospitalizations while accounting for dependence of events within an individual. Similar to the Cox proportional hazards regression model, tests for the proportional rates and means assumption are not considered necessary.[39] The hazard ratios reported represent the weighted average of the true hazard ratio over our study period. Death was treated as a censoring event. In other words, follow-up time was censored at the earliest of emigration from BC, death, or 31-December-2017 (study end date). Findings were reported as adjusted hazard ratios (aHRs) with the corresponding 95% CIs.

For the physician claims and prescriptions filled, models were adjusted for: sex and SES quintiles at the index date, and, updated annually for: age (continuous), calendar year (continuous) and comorbidities (categorized as 0, 1, 2 or ≥3). Comorbidities were measured via the Charlson Comorbidity Index, using the hospital and physician data in the one-year pre-index date and updated annually thereafter (excluding hemiplegia/paraplegia to avoid misclassifying MS complications as comorbidity[35] and hepatitis from within the liver disease comorbidity category given that this infection is an outcome variable). For hospitalizations, the same model adjustments were applied, except for age and calendar year which were measured at the index date. Statistical analyses were performed using R V.4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS V.9.4 (SAS Institute, Cary, NC, USA). In a prior sample size calculation based on a time-to-event outcome,[40] we demonstrated that under a hospitalization rate of 5%, 1307 individuals with 50% DMD exposure rate would be sufficient to detect a hazard ratio of 2.0 with 80% power using a two-tailed test with a 5% probability of type I error. Our sample size has exceeded this estimation. As infection-related physician visits and prescriptions were much more common than hospitalizations, we anticipated that a smaller sample size is required to achieve the same level of power.

Complementary analyses

For physician claims only, the most common infections—those affecting the respiratory tract—were examined separately (Supplementary Table S1). For prescriptions filled, we removed the antivirals (as antivirals are commonly used prophylactically when initiating intravenous alemtuzumab) and examined this outcome using the same approach as in the main analyses. We also explored the impact of: sex, age (grouped as <45 or ≥45 years [mean age at index date]) and presence/absence of specific comorbidities on the prescription-related findings (with and without the antivirals), in relation to any DMD, and by route of DMD administration, using interaction terms. Comorbidities included two broad groups: any circulatory system disease and any mood/anxiety disorder or alcohol abuse, and then five more specific comorbidities: ischemic heart disease, hypertension, diabetes mellitus, eye/adnexa disease, and depression/anxiety (Supplementary Table S3). These were selected based on clinical relevance to MS and prevalence in the MS population, as well as potential associations with DMD use, and infection risk.[41–43] The overall burden of comorbidities was measured using Charlson Comorbidity Index that included several other comorbidities relevant to DMD use and infection risk, such as malignancy, cerebrovascular diseases, and liver and renal diseases.

Role of the funding sources

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This study was part of a wider pre-registered research program (ClinicalTrials.gov; NCT04472975). We obtained ethics approval from the University of British Columbia's Clinical Research Ethics Board (H18-00407).

Results

Cohort characteristics are summarized in Table 3 (further details are available elsewhere),[35] and cohort

Characteristics	DMD treated[a], n = 4732	Not treated[a], n = 14,628	p-value
Women, n (%)	3469/4732 (73.3)	10,471/14,628 (71.6)	0.02 (Pearson's Chi-squared test)
Age at index date in years, mean (SD)	37.1 (9.8)	46 9/14,628 (13.7)	<0.0001 (Wilcoxon rank sum test)
Socioeconomic status[b], n (%)			0.65 (Pearson's Chi-squared test)
1 (lowest income quintile)	914/4732 (19 3)	2849/14,628 (19.5)	
2	870/4732 (18 4)	2825/14,628 (19.3)	
3, or unavailable	1004/4732 (21.2)	3025/14,628 (20.7)	
4	1006/4732 (21.3)	3088/14,628 (21.1)	
5 (highest income quintile)	938/4732 (19 8)	2841/14,628 (19.4)	
Comorbidity score[c], n (%)			<0.0001 (Pearson's Chi-Squared test)
0	3974/4732 (84.0)	11,077/14,628 (75.7)	
1	588/4732 (12.4)	2391/14,628 (16.4)	
2	132/4732 (2.8)	723/14,628 (4.9)	
≥3	38/4732 (0.8)	437/14,628 (3.0)	
Presence of specific comorbidities[c], n (%[d])			–
Diseases of circulatory system	677/4732 (14.3)	3368/14,628 (23.0)	
Ischemic heart disease	90/4732 (1.9)	596/14,628 (4.1)	
Hypertension	238/4732 (5.0)	1572/14,628 (10.7)	
Eye and adnexa diseases	1967/4732 (41.6)	5626/14,628 (38.5)	
Diabetes mellitus	99/4732 (2.1)	661/14,628 (4.5)	
Any mood or anxiety disorder or alcohol abuse	1415/4732 (29.9)	4348/14,628 (29.7)	
Depression and anxiety disorders	1388/4732 (29.3)	4239/14,628 (29.0)	
Follow-up[a] time in years, mean (SD)	12.0 (7.0)	11.6 (7.3)	–
Death before study end, n (%)	267/4732 (5.6)	2943/14,628 (20.1)	–
Type of DMD exposure during follow-up, n (%)[a]		NA	–
Injectable DMDs—any[e]	4124/4732 (87.2)		
Beta-interferon	3140/4732 (66.4)		
Glatiramer acetate	1719/4732 (36.3)		
Oral DMDs—any[e]	1495/4732 (31.6)		
Fingolimod	421/4732 (8.9)		
Dimethyl fumarate	758/4732 (16.0)		
Teriflunomide	520/4732 (11.0)		
Intravenous DMDs—any[e]	436/4732 (9.2)		
Natalizumab	286 (6 0)		
Alemtuzumab	179 (3 8)		
Ocrelizumab	<6		
Daclizumab[f]	6 (0 1)		
Any infection-related health service use during study period, mean (SD)	12.0 (6.99)	11.54 (7.3)	0.0001 (Wilcoxon rank sum test)

Characteristics of the multiple sclerosis study population in British Columbia, Canada (1996–2017). Details have been published previously.[34] Key: DMD, disease-modifying drugs; MS, multiple sclerosis; NA, not applicable; SD, standard deviation. The date of the first MS-specific or demyelinating disease-related event was the index date. As per data privacy and access agreements, small cell size (<6 individuals within any group) are suppressed. [a]Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). [b]Socioeconomic status is represented by neighborhood income quintiles (based on closest available measurement to index date). There are n = 98 unavailable SES values, likely due to administrative reasons, and, therefore, we anticipate that their values to be symmetrically distributed around the median (SES = 3). The impact of the imputed values would be negligible. [c]Comorbidities were assessed using the physician and hospital data during the one-year period prior to the index date. The comorbidity score was measured using the Charlson Comorbidity Index (modified to exclude hemiplegia/paraplegia to avoid misclassifying MS complications as comorbidity and to exclude hepatitis given that this infection is an outcome variable). [d]Some individuals had none of these comorbidities and others could have more than one, thus, the percentages are not expected to add up to 100%. Alcohol abuse was combined with mood or anxiety disorder because they both belong to the 'Mental Disorder' chapter under the ICD classification system. [e]Some people were exposed to >1 DMD; hence the sum of the individual injectable, oral or intravenous DMDs exceeds the sum of any injectable, oral or intravenous DMD. [f]As this DMD was withdrawn from the market for safety reasons, each individual's follow-up was censored at the first daclizumab prescription filled.

Table 3: **Cohort characteristics.**

creation in the Supplementary Fig. S1. Briefly, we identified 19,360 persons with MS, of whom 13,940 (72.0%) were women. The mean age (standard deviation [SD]) at index date was 44.5 (13.3) years. Overall, 4732/19,360 (24.4%) persons filled at least one MS DMD prescription, and the mean (SD) follow-up time was similar between those who did, or did not, fill a DMD prescription, with the mean being 11.7 (7.3) years for the entire group. Persons never (versus ever) filling a DMD prescription were, on average, older at the index date (46.9 [13.7] versus 37.1 [9.8] years), and had a higher comorbidity burden, while the distribution of

socioeconomic status quintiles was similar between the two groups.

Infection-related physician claims

Relative to no DMD, any DMD exposure was associated with a 12% lower rate ratio of infection-related physician claims (aRR = 0.88; 95% CI: 0.85–0.92; p < 0.0001), with similar findings for the injectable and oral DMDs, but not intravenous (aRR = 0.99; 95% CI: 0.86–1.14; p = 0.95; Fig. 1). Rate ratios were also lower for each of the individual injectable and oral DMDs, ranging from 8% lower for glatiramer acetate (p = 0.038) to 24% for teriflunomide (p < 0.0001), with dimethyl fumarate, fingolimod and beta-interferon falling in between, being 13–16% lower (aRR range: 0.76–0.92). Rate ratios did not differ for either of the intravenous DMDs (alemtuzumab aRR = 1.03, natalizumab aRR = 0.98), although the 95% CIs were wide (Fig. 1).

Infection-related hospitalizations

Relative to no DMD, any DMD exposure was associated with a 36% lower hazard of infection-related hospitalizations (aHR = 0.64; 95% CI: 0.56–0.73; p < 0.0001; Fig. 2). Lower hazards were also observed for the DMDs when examined by mode of administration, ranging from 46% for the oral DMDs (p = 0.0006), to 35% for the injectables (p < 0.0001) and 27% for intravenous, although the 95% CIs for the latter did not reach significance (aHR = 0.73; 95% CI: 0.49–1.09; p = 0.13). Somewhat similar findings were observed for the individual DMDs examined: hazards of hospitalization were significantly lower for the two injectable DMDs, glatiramer acetate (aHR = 0.61; 95% CI 0.46–0.79; p = 0.0003) and beta-interferon (aHR: 0.66; 95% CI: 0.56–0.78; p < 0.0001), and lower for the three oral DMDs, and natalizumab (aHR range: 0.45–0.66). However, only dimethyl fumarate reached statistical significance (aHR = 0.45; 95% CI: 0.27–0.75; p = 0.0027). For alemtuzumab, the 95% CI was wide in this small group, limiting interpretation (Fig. 2).

Antibiotic, antimycotic, and antiviral prescriptions

Relative to no DMD, any DMD exposure was associated with a 14% higher rate ratio of infection-related prescription fills (aRR = 1.14; 95% CI: 1.08–1.20; p < 0.0001; Fig. 3). Significantly higher rate ratios were also observed for the injectable DMDs (aRR = 1.15; 95% CI: 1.08–1.22; p < 0.0001) as well as the intravenous DMDs (aRR = 1.34; 95% CI: 1.15–1.56; p = 0.0001). However, we did not observe a higher rate ratio of infection-related prescription fills for the oral DMDs (aRR = 0.98; 95% CI: 0.91–1.05; p = 0.62). By individual DMD, rate ratios were higher, by 12% for beta-interferon (p = 0.0017), 23% for glatiramer acetate (p < 0.0001), and 126% for alemtuzumab (p < 0.0001), but not natalizumab (p = 0.45) or the three oral DMDs.

Complementary analyses

The distributions of infection-related healthcare utilization are included within Supplementary Table S4.

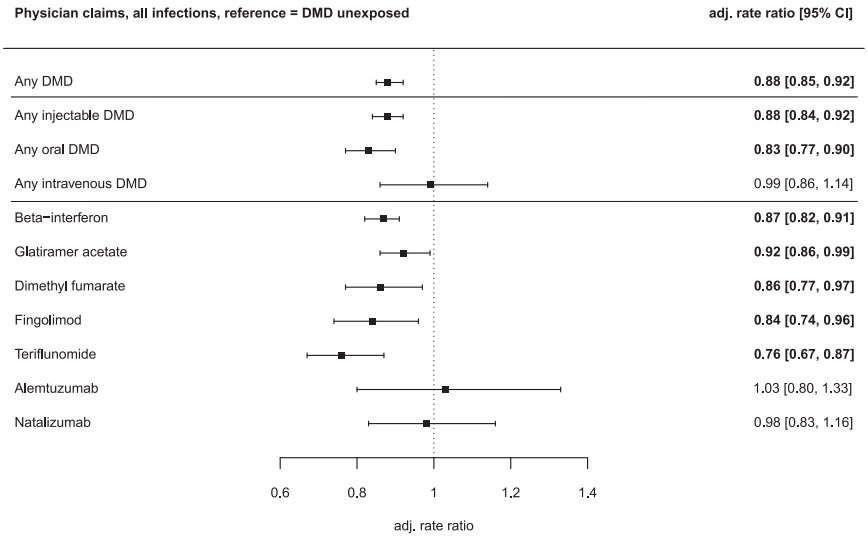

Fig. 1: Infection-related physician claims in the multiple sclerosis study population[a] in British Columbia, Canada (1996–2017) expressed as adjusted rate ratios. Key: DMD, disease-modifying drugs; adj., adjusted; CI, confidence interval; bold depicts statistical significance. a Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). Rate ratios were adjusted for the following covariates: sex, socioeconomic status (categorical; quintiles) at the index date, and, updated annually, age (continuous), calendar year (continuous) and comorbidities (categorized as 0, 1, 2 or ≥3 comorbidities) measured using the Charlson Comorbidity Index.

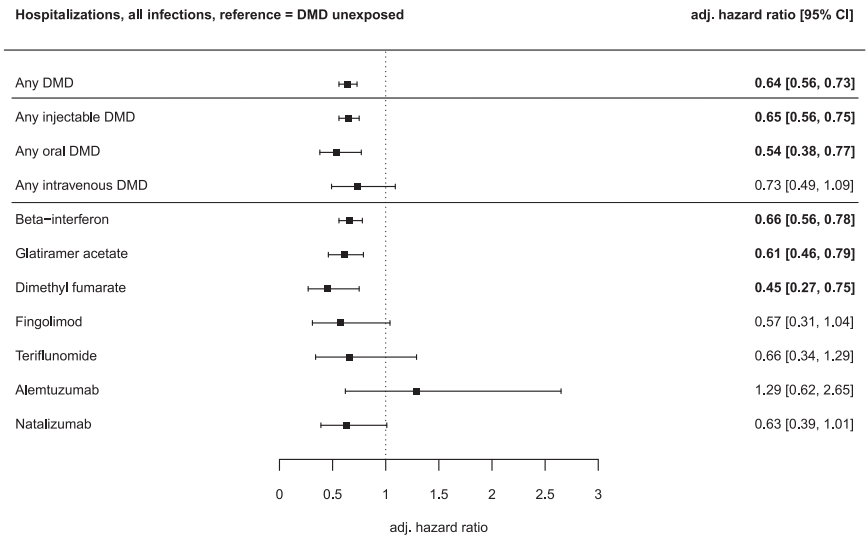

Fig. 2: Infection-related hospitalizations in the multiple sclerosis study population[a] in British Columbia, Canada (1996–2017) expressed as adjusted hazard ratios. Key: DMD, disease-modifying drugs; adj., adjusted; CI, confidence interval; bold depicts statistical significance. a Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). Hazard ratios were adjusted for the following covariates: sex, comorbidity score (0, 1, 2 or ≥3; updated annually) measured using the Charlson Comorbidity Index, and the following covariates at the index date: age (continuous), socioeconomic status (categorical; quintiles), and calendar year (continuous).

Any, versus no DMD exposure was associated with a 9% lower rate of respiratory tract infection-related physician claims (aRR = 0.91; 95% CI: 0.87–0.96; p = 0.0007), with similar findings for the injectable/oral DMDs (aRR = 0.90 [p = 0.0004]/0.87 [p = 0.029]), Fig. 4. In contrast, any intravenous DMD was associated with a 22% higher rate (aRR = 1.22; 95% CI: 1.01-1.48; p = 0.037). For the individual injectable and oral DMDs, only beta-interferon was associated with a significantly lower rate ratio (aRR = 0.89; 95% CI: 0.84–0.95; p = 0.0003). While rate ratios were higher for alemtuzumab (aRR = 1.42; 95% CI: 0.90–2.23; p = 0.12) and natalizumab (aRR = 1.16; 95% CI: 0.95–1.42; p = 0.14), the 95% CIs were wide and neither reached significance.

When the antivirals were removed from the prescriptions filled, the direction of findings remained largely the same, except for the intravenous DMDs, which no longer differed versus no DMD exposure (p = 0.90; Fig. 5). Further, while a higher rate ratio was still observed for alemtuzumab (aRR = 1.11; p = 0.34), this no longer reached significance. For the prescriptions filled for any anti-infective, sex, but not age affected findings (Supplementary Table S5). In detail, among women, any DMD exposure (versus none) was associated with a 18% higher rate of infection-related prescription fills (aRR = 1.18; p < 0.0001); this differed significantly from that found among men (aRR = 0.98; p = 0.82). A similarly higher rate ratio among women (aRR = 1.20; p < 0.0001) than among men (aRR = 0.99; p = 0.91) was observed for the injectable DMDs. For the comorbidities, rate ratios of anti-infective prescriptions filled were similar regardless of whether that comorbidity was present or not, except for the intravenous DMDs only, where it was lower when depression/anxiety was present (Supplementary Table S5). However, after removing the antivirals, this latter finding was no longer significant (data not shown).

Discussion

In this population-based study, we examined the relationship between DMD exposure and infection-related healthcare encounters in a large MS cohort by accessing more than 20-years of prospectively collected data, which comprised information on all hospital and physician visits, and prescriptions filled. Our study provided an overview of the infection-related healthcare utilization in people with MS to inform healthcare planning. Exposure to a MS DMD (versus no exposure) was associated with altered infection-related healthcare use. Interestingly, while the use of any (versus no) DMD was associated with lower infection-related hospitalizations and physician visits, prescription fills were higher. The mode of administration affected findings; while any injectable or oral DMD (versus no DMD) was associated with lower infection-related physician and hospital visits, this was less evident for the intravenous DMDs. Further, while the injectable and intravenous DMDs were associated with a 15–34% higher rate (aRR) of infection-related prescription fills, no measurable effect was observed for the latter when the antivirals were

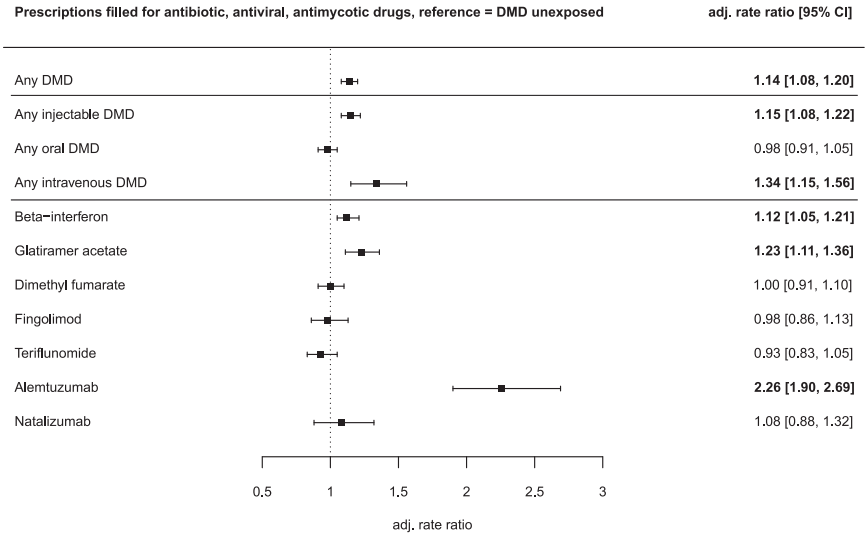

Fig. 3: Infection-related prescriptions filled by the multiple sclerosis study population[a] in British Columbia, Canada (1996–2017) expressed as adjusted rate ratios. Key: DMD, disease-modifying drugs; adj., adjusted; CI, confidence interval; bold depicts statistical significance. a Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). Rate ratios were adjusted for the following covariates: sex, socioeconomic status (categorical; quintiles) at the index date, and, updated annually, age (continuous), calendar year (continuous) and comorbidities (categorized as 0, 1, 2 or ≥3 comorbidities) measured using the Charlson Comorbidity Index.

removed. The reasons for these differences remain subject to speculation; further investigations are warranted. In contrast, the oral DMDs had no measurable effect on infection-related prescription fills, whether or not the antivirals were included. Also, if the mode of administration itself may alter the infection risk remains uncertain. How these differences in infection-related healthcare use affect other outcomes in people

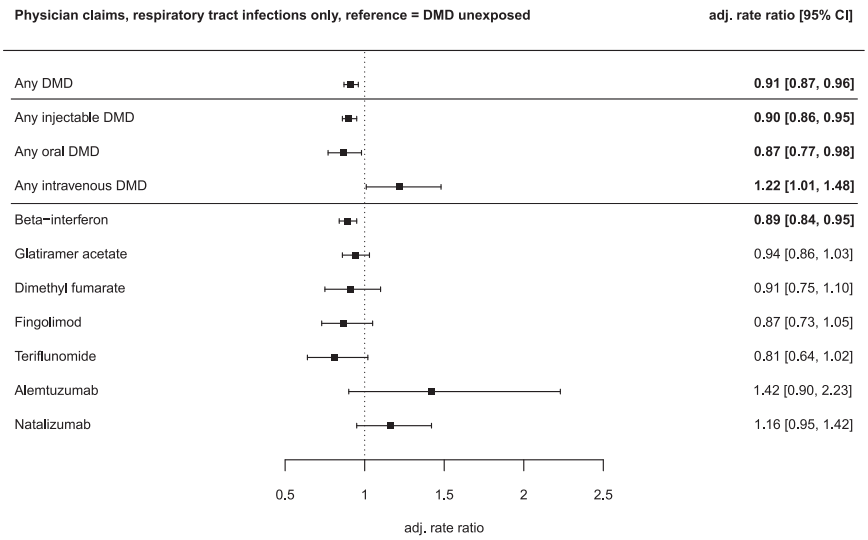

Fig. 4: Association between disease-modifying drug (DMD) exposure and respiratory tract infection-related physician claims in the multiple sclerosis study population[a] in British Columbia, Canada (1996–2017) expressed as rate ratios. Key: DMD, disease-modifying drugs; adj., adjusted; CI, confidence interval; bold, 95% CI did not include 1. ICD-9-codes used to identify respiratory tract infection physician claims: 460, 461, 462, 463, 464, 465, 466, 473, 474, 476, 480, 481, 482, 483, 484, 485, 486, 487, 490. a Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). Rate ratios were adjusted for the following covariates: sex, socioeconomic status (categorical; quintiles) at the index date, and, updated annually, age (continuous), calendar year and comorbidities (categorized as 0, 1, 2 or ≥3 comorbidities) measured using the Charlson Comorbidity Index.

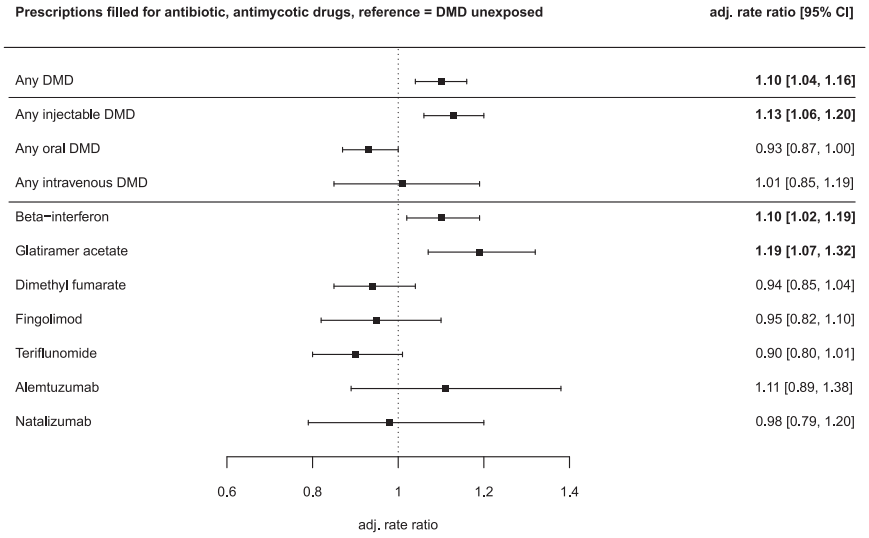

Fig. 5: Association between disease-modifying drug (DMD) exposure and antibiotic or antimycotic prescriptions filled only in the multiple sclerosis study population[a] in British Columbia, Canada (1996–2017) expressed as rate ratios. Key: DMD, disease-modifying drugs; adj., adjusted; CI, confidence interval; bold, 95% CI did not include 1. Prescriptions filled for antivirals (bold in Supplementary Table S2) were not considered as outcome. a Follow-up was from index date until the earliest of: death; emigration from the province; or study end (December 31st 2017). Rate ratios were adjusted for the following covariates: sex, socioeconomic status (categorical; quintiles) at the index date, and, updated annually, age (continuous), calendar year and comorbidities (categorized as 0, 1, 2 or ≥3 comorbidities) measured using the Charlson Comorbidity Index.

with MS warrants consideration. Future studies may also wish to consider the contribution of other medications a person with MS may be taking (with or without a DMD) and their possible contribution to infection risk.

Few other studies have assessed the relationship between DMD use and infections in the MS population. A prior study from our group, also using data from British Columbia (1996–2013, n = 6793), observed lower infection-related hospitalization risk in those exposed to the newer DMDs available at that time. However, findings did not reach statistical significance in this smaller cohort, and all the oral and intravenous DMDs were grouped together due to their lower uptake at that time.[13] Our current study advanced these findings considerably by accessing more contemporary data and a much larger MS population (n = 19,360) with a longer follow-up period.[13] A US study found that use of any monoclonal antibody (versus any DMD) was associated with a higher incident rate of infection-related hospitalizations among MS enrollees of the Department of Defense military healthcare system (n = 8695; 2004–2017).[14] However, the individual DMDs used were not specified. Finally, a Swedish study examined the risk of the first infection-related hospitalization in MS DMD-exposed persons only, the majority of whom (>50% of the 6421 cases) had received rituximab.[12] Study authors were unable to access primary care information, and neither the Swedish nor US study authors examined similar MS cases not undergoing a DMD treatment, making it challenging to compare across studies.[12,14] Our study further advances current understanding of infection risk in MS as we were also able to examine respiratory tract infection-related physician claims by route of DMD administration, and observed that the intravenous DMDs were associated with a higher rate (by 22%) versus no DMD. This increase in infections likely relates to drug-induced immune cell depletion or cell trafficking disruptions. Also consistent with our observation, the most commonly reported infections in MS persons enrolled in a clinical trial or drug company initiated observational study, and treated with an intravenous DMD (alemtuzumab or natalizumab), were respiratory-related.[44,45]

Ours is one of few studies to assess infection-related prescriptions filled in the MS population, comparing periods of DMD exposure versus no exposure. While a previous smaller study from British Columbia found that MS cases (n = 7179; 1996–2013) had a higher risk to fill an infection-related prescription relative to the general population (aRR = 1.57; 95% CI: 1.49–1.65), that study was not designed to examine associations with the MS DMDs.[8] Our current findings suggested that relative to no DMD use, injectable DMDs were associated with a 12–23% higher rate (aRR) of filling an infection-related prescription, while the oral DMDs, or the intravenously administrated natalizumab were not. Further, the direction of these findings persisted whether antivirals were included or not. These results warrant further investigation. It is possible that use of one of these DMDs increases the likelihood that a clinician would

recommend an anti-infective drug (relative to a patient not being treated with a DMD). This in turn could lower the risk of an infection-related hospitalization or physician visit. However, for the intravenously administered alemtuzumab, while we observed a 126% higher rate of infection-related prescription fills, this was attenuated after removal of the antivirals, resulting in only an 11% higher rate which no longer reached significance. Although the wide 95% CIs for this finding create uncertainty, the observed difference in rate ratios of infection-related prescription fills may reflect prophylactic use of antivirals when initiating alemtuzumab.

Our findings further underscore the importance of considering sex-based disparities in healthcare to reduce the sex differences in health outcomes. We found that sex, but not age affected findings; consistent with the absence of age-related increases in DMD-associated infections in pooled information from 45 clinical trials.[46] For sex, we specifically observed that DMD exposed (relative to unexposed) women with MS had a higher rate (aRR) of filling infection-related prescriptions and that such increase was not observed in men with MS. While a systematic review of sex-differences in primary care found that in the general population, women were more likely than men to be prescribed an antibiotic,[47] we were unable to find another study to directly compare our findings. This dearth of sex-specific studies in relation to the effects of the MS DMDs has been highlighted by others.[17] Our findings further underscore the importance of considering sex-based differences/disparities in healthcare.

We were also able to examine the influence of comorbidities on the relationship between DMD exposure and infections. Of the select comorbidities studied, absence (versus presence) of depression/anxiety disorders was associated with a higher rate of anti-infective prescription fill in relation to use of an intravenous DMD. However, this association was not present after removing the antivirals, which are recommended for prophylactic use when receiving alemtuzumab. Despite the International Advisory Committee on Clinical Trials in MS call for further work in this area,[15,16] we were unable to find other studies with which to compare our findings. Thus, our findings underscore the needs for further examinations of the potential impacts of comorbidities on outcomes related to the DMDs used in everyday clinical practice.

Strengths and limitations

Study strengths included access to comprehensive, prospectively collected population-based health administrative data, minimizing selection or recall bias. Our cohort also included over 4700 DMD treated MS cases, totaling 24,967 8 person-years of exposure. Nonetheless, our ability to examine infection-related healthcare associated with more recently approved DMDs, that only became available towards the end of our study, was rather limited. Moreover, as more DMDs with different mechanisms of action become available, future studies may benefit from using different approaches to grouping the DMDs when evaluating infection-risk as the mode of administration may not always reflect the underlying infection-related risk associated with that drug. We also did not have access to data related to ethnicity, and whilst we could examine the route of administration (delivery), for the injectables, we did not differentiate between the two main modes of delivery–subcutaneous and intramuscular, or consider the drug dose used and medication adherence. While access to population-based healthcare data was a study strength, we were unable to independently verify the accuracy of each diagnosis with an infectious disorder specialist. We acknowledge the general limitation of administrative data; they are captured for billing purposes and health system management–not clinical purposes–thus may be subject to misclassification. We did not have access to clinical data (other than that available in the health administrative and billing data), such as the MS disease course, severity or activity, or disability measures such as the Expanded Disability Status Scale (EDSS) score, or relevant demographic data such as education (e.g. highest degree) and lifestyle-related information (e.g. smoking or alcohol consumption). Still, we were able to adjust for sex, age, socioeconomic status, and comorbidity burden measured using the Charlson Comorbidity Index. It would be of value for future studies to consider other comorbidities (e.g. autoimmune disease) which were not captured by this study. We cannot exclude residual bias in our findings. Furthermore, we accounted for the changing DMD treatment status over time, thus avoiding immortal time bias, a major threat in pharmaco-epidemiological studies.[48–50] We aimed to compare the infection risk of DMD exposed versus unexposed MS cases; it would be of value for future, appropriately designed studies to consider comparing the infection risk between each individual DMD.

Conclusion

To the best of our knowledge, this is the largest, population-based study to examine the relationship between the MS DMDs and infection-related healthcare use. While use of any DMD was not associated with an increased risk of infection-related hospitalizations or rate of physician visits, prescription fills for an anti-infective agent were higher. However, both the route of DMD administration and sex of the person with MS affected these findings. How the differences in infection-related healthcare use identified affect other outcomes in persons with MS warrants further study.

Contributors

Jonas Graf, and Helen Tremlett interpreted the results and drafted the manuscript.

Jonas Graf, Huah Shin Ng, Feng Zhu, José M A Wijnands, Charity Evans, John D. Fisk, Ruth Ann Marrie, Yinshan Zhao, and Helen Tremlett conceptualized and designed the study.

Jonas Graf (Research Fellowship from the Deutsche Forschungsgemeinschaft), as well as Feng Zhu, Charity Evans, John D. Fisk, Ruth Ann Marrie, Yinshan Zhao, and Helen Tremlett facilitated obtaining funding (PI: Tremlett, CIHR Project and Foundation award).

Jonas Graf, Huah Shin Ng, and Feng Zhu accessed the data and performed data analysis.

All authors revised the manuscript critically for intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Data sharing statement

As we are not the data custodians, we are not authorized to make the data available. With the appropriate approvals, the data may be accessed through the Population Data British Columbia.

Declaration of interests

Jonas Graf has received in the last 3 years travel/meeting/accommodation reimbursements from Merck Serono, Sanofi-Genzyme, Grifols, and a Research Fellowship from the Deutsche Forschungsgemeinschaft (project number 438899010, GZ: GR 5665/1-1).

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Feng Zhu, Yinshan Zhao, José M A Wijnands, and Charity Evans declare no conflicts.

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Ruth Ann Marrie receives research funding from: CIHR, Research Manitoba, MS Canada, Multiple Sclerosis Scientific Foundation, Crohn's and Colitis Canada, National Multiple Sclerosis Society, CMSC, the US Department of Defense, the Arthritis Society, Biogen Idec (no funds to her/her institution) and Roche (no funds to her/her institution), and is supported by the Waugh Family Chair in Multiple Sclerosis.

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Disclaimer: Access to data provided by the Data Steward(s) is subject to approval, but can be requested for research projects through the Data Steward(s) or their designated service providers. All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100667.

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