Received: 31 May 2019 | Revised: 18 October 2019 | Accepted: 16 December 2019

DOI: 10.1002/pds.4957

ORIGINAL REPORT

WILEY

A rapid monitoring plan following a shift in coverage from brand name to biosimilar drugs for rheumatoid arthritis in British Columbia

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Abstract

Purpose: To describe a rapid monitoring plan to assess the impacts of a shift in drug coverage for biosimilar drugs in British Columbia following the introduction of a new policy on 27 May 2019. The Biosimilars Initiative requires users of originator infliximab or etanercept to switch to biosimilar versions of those drugs to maintain coverage. We propose a signal-detection method to provide near-real-time information to policymakers on the impacts of the policy change.

Methods: The exposure will be the Biosimilars Initiative, a policy affecting patients using originator infliximab (Remicade) and etanercept (Enbrel) for approved rheumatologic or dermatologic indications. Two policy cohorts and six historical control cohorts of patients using originator infliximab or etanercept will be assembled using linked and de-identified data from the British Columbia Ministry of Health. Patients will be identified during the 6-month period before the policy anniversary. Outcomes will include medication refills and switching, hospital admissions, emergency department visits, and physician visits. Summary outcome measures, such as cumulative incidence or average quantity as applicable, will be examined daily and reported monthly for 1 year. Outcomes in the policy cohorts will be compared with historical controls using likelihood ratios.

Results: The results of this rapid monitoring plan will be based on analyses involving approximately 9000 patients: four infliximab cohorts of approximately 430 patients and four etanercept cohorts of approximately 1800 patients.

Conclusions: Rapid monitoring results will inform ongoing policy decisions related to the Biosimilars Initiative, in terms of impacts on both patient health and health services utilization.

KEYWORDS

biological DMARDs, biosimilars, drug coverage, pharmacoepidemiology, rheumatoid arthritis

1 | INTRODUCTION

The Province of British Columbia, Canada, introduced a new drug coverage policy, the Biosimilars Initiative, on 27 May 2019. The first phase of the policy is aimed at patients who use originator versions of infliximab (Remicade) and etanercept (Enbrel) for rheumatologic or dermatologic indications. Infliximab and etanercept are members of the biological disease modifying antirheumatic drug class (bDMARD). Drugs in the bDMARD class are used to treat multiple autoimmune diseases. In the first phase of British Columbia's Biosimilars

Initiative, patients who use the originator infliximab (Remicade) or etanercept (Enbrel), and who rely on the provincial drug plan (PharmaCare), must switch to either the Inflectra or Renflexis brands of infliximab, and either the Brenzys or Erelzi brands of etanercept. In order to provide time for patients to discuss switching with their physicians, there is a 6-month transition period between 27 May 2019 and 25 November 2019, during which originator versions will continue to be covered. Further details on the policy are available online.[1]

Concurrent with the introduction of the new Biosimilars Initiative, PharmaCare officials have requested the implementation of a rapid monitoring plan to assess the early impacts of the policy. Policymakers want to know if policy changes have unintended adverse consequences on patient health or on utilization of health services. Rapid monitoring promises to meet the need for early feedback on the impacts of a policy change before more time-intensive rigorous policy evaluations. For example, in 1997, British Columbia was the first jurisdiction in North America to implement reference-based drug pricing (Reference Drug Program, RDP) for antihypertensive and nonsteroidal anti-inflammatory drugs.[2] The first rigorous evaluations of the RDP policy were published 5 years after the policy was introduced.[3-5] During that time, policymakers were unable to offer any postpolicy results to critics of the policy.[6-8] In retrospect, rapid monitoring analysis could have provided early feedback on basic measures such as drug switching, physician visits, and hospital admissions.

The goal of a rapid monitoring analysis for the Biosimilars Initiative is to provide feedback to policymakers on basic measures of health system utilization within months instead of years. The results of rapid monitoring are not intended as a substitute for rigorous policy evaluations but rather to provide interim results and early warning of unintended consequences while more comprehensive studies are planned. The remainder of this plan outlines the rapid monitoring protocol to analyze the impacts of the Biosimilars Initiative in patients with rheumatologic and dermatologic diseases.

KEY POINTS

- British Columbia is the first Canadian province to require patients to switch to biosimilar medications in order to maintain public drug coverage.
- This project outlines a rapid monitoring plan that will provide early feedback on the impacts of the British Columbia Biosimilars Initiative on health services utilization.
- Results from this project will inform policy and clinical decision making related to the Biosimilars Initiative.

2 | METHODS

2.1 | Study design and data sources

Rapid monitoring analyses will be conducted using the administrative health care databases of the British Columbia Ministry of Health. The British Columbia Medical Services Plan is a public health insurance plan that is available to eligible residents. Residents enrolled in the Medical Services Plan are eligible for outpatient services, including physicians and other providers, and hospital services (emergency department, outpatient, and inpatient). Residents enrolled in British Columbia's PharmaCare plan qualify for help with the cost of eligible prescription drugs, some medical supplies, and pharmacy services. PharmaCare includes several drug plans; the largest is the income-based Fair PharmaCare plan.[9] The available administrative data include all prescriptions filled at every community pharmacy (PharmaNet), records of patient enrollment in the provincial Medical Services Plan, and records for inpatient and outpatient encounters with physicians, hospitals, and emergency departments. Data on individuals are linkable using de-identified indicators, and many data dimensions are updated regularly. This facilitates near-real-time assessment of the new policy. Pharmacy refill data include patient-level prescriptions that specify the drug dispensed, the date of dispensing, and the quantity and days' supply of medication dispensed. Databases for inpatient and outpatient medical encounters include the date of the service encounter, up to 25 International Classification of Disease (ICD)-9 or ICD-10 diagnosis codes, and procedure and billing codes.

The rapid monitoring analyses will include policy cohorts and historical control cohorts. Cohorts will be followed for 1 year during which time patterns of health services utilization and proxies for health status will be measured and compared between the policy cohorts and historical control cohorts. We will examine medication refilling, medication switching, emergency hospital admissions, emergency department visits, and physician fee for service visits. Utilization and health status outcomes will be summaries of either cumulative incidences or average quantities, and these daily measures will be plotted using historical control cohorts drawn from the 3 years before the Biosimilars Initiative policy was announced.

Follow-up will begin on May 27 in each year and terminate 1 year later, on May 26. The outcome pattern observed in the historical control cohorts will serve as the expected pattern for the policy cohort in absence of a policy effect. Follow-up in the policy cohort will begin on 27 May 2019 and terminate 1 year later on 25 May 2020 (1 day shorter because 2020 is a leap year) (Figure 1). Utilization outcomes will be updated at 1-month intervals during the first year of the policy. The statistical significance of differences between each policy cohort and the mean of the historical control cohorts will be assessed at each follow-up interval using a likelihood ratio. Each analysis will be accompanied by descriptions of adoption patterns over time, percentages of patients refilling prescriptions with biosimilars, and the proportion of physicians who are prescribing biosimilars on a monthly basis. We will report results to policymakers at British Columbia PharmaCare on a monthly basis and will submit articles to peer-reviewed journals after 3 months and again after 1 year.

2.2 | Rapid monitoring cohorts

The source population for rapid monitoring cohorts will consist of British Columbia residents who were covered under the provincial Medical Service Plan at any time between 27 November 2015 and 26 May 2019. We will define an index day for each eligible patient as the anniversary of the announcement of the Biosimilars Initiative (May 27 of each year). A total of eight cohorts will be constructed for the years 2016 to 2019: four etanercept cohorts and four infliximab cohorts. Three of the four cohorts for each drug will be historical control cohorts against which outcome patterns will be compared with a fourth, policy cohort. Cohort identification will occur in the 6 months preceding the index day (between November 27 and May 26 in each year). To create each of the eight cohorts, we will identify prescriptions for the originator infliximab (Remicade) or etanercept (Enbrel) during each identification period. Patients may be included in more than one cohort depending on their medication use, but they will not be permitted to be in both an infliximab and etanercept cohort in the same year. Patients receiving both infliximab and etanercept in the same 6-month identification period will be assigned to the last drug category prescribed.

Phase 1 of the Biosimilars Initiative policy applies to patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis (for the latter, infliximab only). The policy does not apply to patients treated with infliximab for ulcerative colitis or Crohn's disease. Infliximab users will therefore be excluded from rapid monitoring cohorts if previously diagnosed with ulcerative colitis (ICD-9 code 556, ICD-10 code K51) or Crohn's disease (ICD-9 code 555, ICD-10 code K50). Etanercept patients will be excluded if they were diagnosed with psoriasis (ICD-9 code 696, ICD-10 code L40) but not if they were also diagnosed with psoriatic arthritis (ICD-9 code 696.0, ICD-10 code M07, L40.5). The detailed algorithms that will be used to exclude ineligible diseases are presented in Table 1. Patients will also be excluded if they potentially discontinue their treatment (last refill 84 days before index for infliximab and 56 days before index for etanercept) or if they had an insufficient supply of the last prescription in their identification period to cover the index day. The 84-day and 56-day refill windows are equal to twice the median number of refill days recorded in recent years in British Columbia. Finally, we will exclude patients who switched from their medication to a different bDMARD or any biosimilar during their identification period or if PharmaCare did not cover the cost of the last bDMARD prescription dispensed during the identification period. We estimate that the four infliximab cohorts will include between 370 and 490 patients each, and the etanercept cohorts will include between 1500 and 1750 patients each.

2.3 | Rapid monitoring of outcomes

The exposure will be the British Columbia Biosimilars Initiative introduced on 27 May 2019. Rapid monitoring algorithms are being developed for each outcome, which, if different between the policy cohort and historical control cohorts, may provide an early warning that the policy is having unintended consequences. During the follow-up period for each cohort, refilling analyses will include separate measurements for the cumulative incidence of first refill of any bDMARD; the first, second, and third refill of the index bDMARD; and first refill of a non-index bDMARD (switching). Cumulative dose will be defined as the mean quantity of bDMARD dispensed in milligrams per patient. Utilization of conventional synthetic DMARDs, steroids, and nonsteroidal anti-inflammatory medications will be measured as the mean cumulative number of prescriptions refilled per patient. We will compute cumulative incidence of the first, second, and third postindex visit to a physician. Separate analyses will be conducted for visits to rheumatologists and dermatologists. Hospital admissions and emergency department visits will be measured in the same way. Outcomes in policy and historical cohorts will be measured daily for the entire follow-up year. Outcomes in policy cohort will be updated monthly after 27 May 2019. We will update the measurements of hospital admissions and emergency department visits less frequently depending on lags in the availability of data.

Figure 2 depicts the format for presenting rapid monitoring analyses each time the data are refreshed. The lines that span the entire 1-year follow-up period denote the cumulative incidence of first visits to a physician in the historical control cohorts after the index date. The historical control cohorts provide the expected pattern against which patients in the policy cohort are compared and the pattern

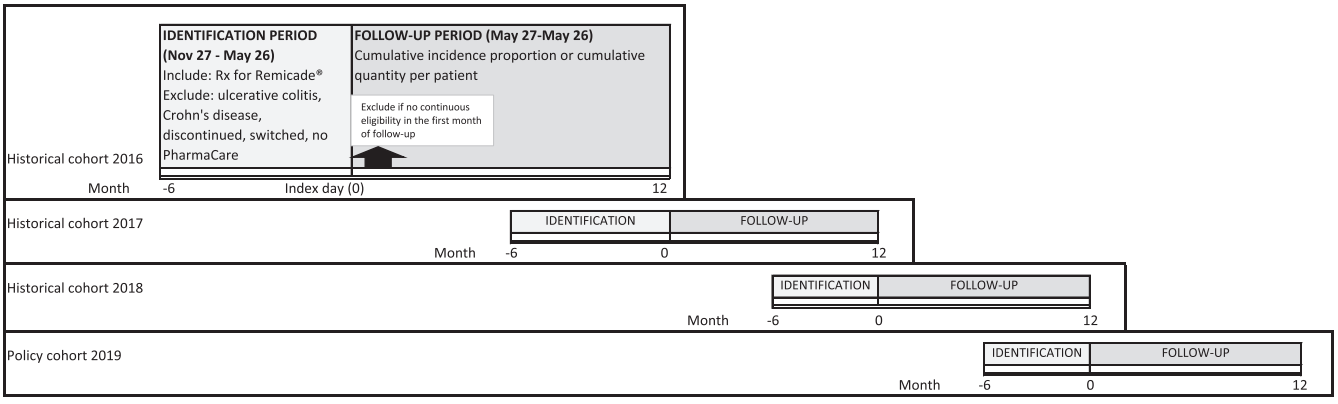

FIGURE 1 Rapid monitoring cohort identification and follow-up for infliximab originator (Remicade). Rx—prescription refill

TABLE 1 Exclusion indications for cohort identification

Infliximab: Excluding Patients with Ulcerative Colitis or Crohn's Disease	Etanercept: Excluding Patients with Psoriasis Unless They Also Have Psoriatic Arthritis
Step 1: Identifying patients with proxies for ulcerative colitis or Crohn's disease in the 5 y before the last refill in the identification period, based on at least one of the following: 1. Patients with a discharge from hospital or an emergency room with a diagnosis of ulcerative colitis or Crohn's disease; 2. Patients with at least two visits with a diagnosis of ulcerative colitis or Crohn's disease within 1 y; 3. Patients with at least five visits to a gastroenterologist.	Step 1: Identifying patients with proxies for psoriasis in the 5 y before the last refill in the identification period, based on at least one of the following: 1. Patients with a discharge from hospital or an emergency room with a diagnosis of psoriasis; 2. Patients with at least two visits with a diagnosis of psoriasis within 1 y; 3. Patients with at least five visits to a dermatologist.
Step 2: Excluding patients if the last refill in the identification period was prescribed by a gastroenterologist.	Step 2: Identifying patients with proxies for psoriatic arthritis in the 5 y before the last refill in the identification period, based on at least one of the following: 1. Patients with a discharge from hospital or an emergency room with diagnosis psoriatic arthritis; 2. Patients with at least two visits with diagnosis of psoriatic arthritis within 1 y apart; 3. Patients with at least two visits to a rheumatologist.
Step 3: Excluding patients if they had proxies for ulcerative colitis or Crohn's disease (Step 1), UNLESS the last refill in the identification period was prescribed by a rheumatologist.	Step 3: Excluding patients if (a) their last refill in the identification period was prescribed by a dermatologist or (b) they had proxies for psoriasis UNLESS (a) the last refill in the identification period was prescribed by a rheumatologist or (b) they had proxies for psoriatic arthritis.

that would be anticipated if the Biosimilars Initiative had no impact. The thicker line in red represents the cumulative incidence of first visits to a physician in the policy cohort. The policy cohort line extends each time the data are refreshed at monthly intervals. The plot for the policy cohort in Figure 2 is based on hypothetical data and is shown solely for the purpose of demonstration. Plots for the historical control cohorts are based on data from the system and physician billing data.

2.4 | Statistical analysis

The following patient characteristics will be described for each cohort on the anniversary of the announcement of the Biosimilars Initiative: sex, age, most likely diagnosis (based on prescriber, outpatient, and inpatient diagnoses), and time since first refill of the medication (infliximab or etanercept). We will also present the number of different generic medications, number of physician visits, and numbers of days in hospital in the previous year. Statistical significance will be assessed using likelihood ratios each time an analysis is updated. Likelihood ratios will be used for statistical inference instead of *P* values or confidence intervals because the interpretation of a likelihood ratio remains the same regardless of how many times the data are updated.[10] The likelihood ratio will denote the likelihood of the observed difference between the policy cohort and the average of the historical control cohorts relative to no difference. The likelihood ratio will be computed as

$$LR = exp\left(\frac{CID_{MLE}{}^2}{2s^2}\right) \quad (1)$$

where LR denotes the likelihood ratio, CID denotes the difference between the policy cohort and the historical cohorts in quantity of the outcome (eg, cumulative incidence difference in first visits to a physician), and *s* is the standard error (SE) of the cumulative incidence difference. Equation (1) is a simplified form of:

$$LR = exp\left[\frac{(CID_{MLE}-0)^2}{2s_0^2} - \frac{(CID_{MLE}-CID_{HA})^2}{2s_{HA}^2} + ln\left(\frac{s_{HA}^2}{s_0^2}\right)\right]. \quad (2)$$

[Correction added on 22 January 2020, after first online publication: The Equations 1 and 2 and its discussion have been corrected in this version.]

Equation (2) defines a likelihood ratio from a normal distribution when a null association is compared to another possible alternative association (HA). Equation (2) simplifies to Equation (1) when the alternative association of interest is the maximum likelihood estimate.

The third term in Equation (2) is equal to zero when $s_0 = s_{MLE} = s$ for all values of CID, as is typically assumed under a normal distribution. The importance of the third term in Equation (2) is that the cumulative incidence difference is derived from cumulative incidences in the policy cohorts and historical controls, and the variance of a binomial variable is $np(1-p)$, which is not constant but varies according to *p*. However, our rapid monitoring analyses will assume $s_0 = s_{MLE} = s$, as is done when using the binomial approximation to a normal distribution.

The threshold that will be used to identify statistically significant differences between a policy cohort and its historical controls will correspond to a likelihood ratio of $e^{1.96} = 7.1$. At a value of 7.1, the observed difference would be approximately 7.1 times as likely as no difference, given the observed data. Detailed explanations of the use

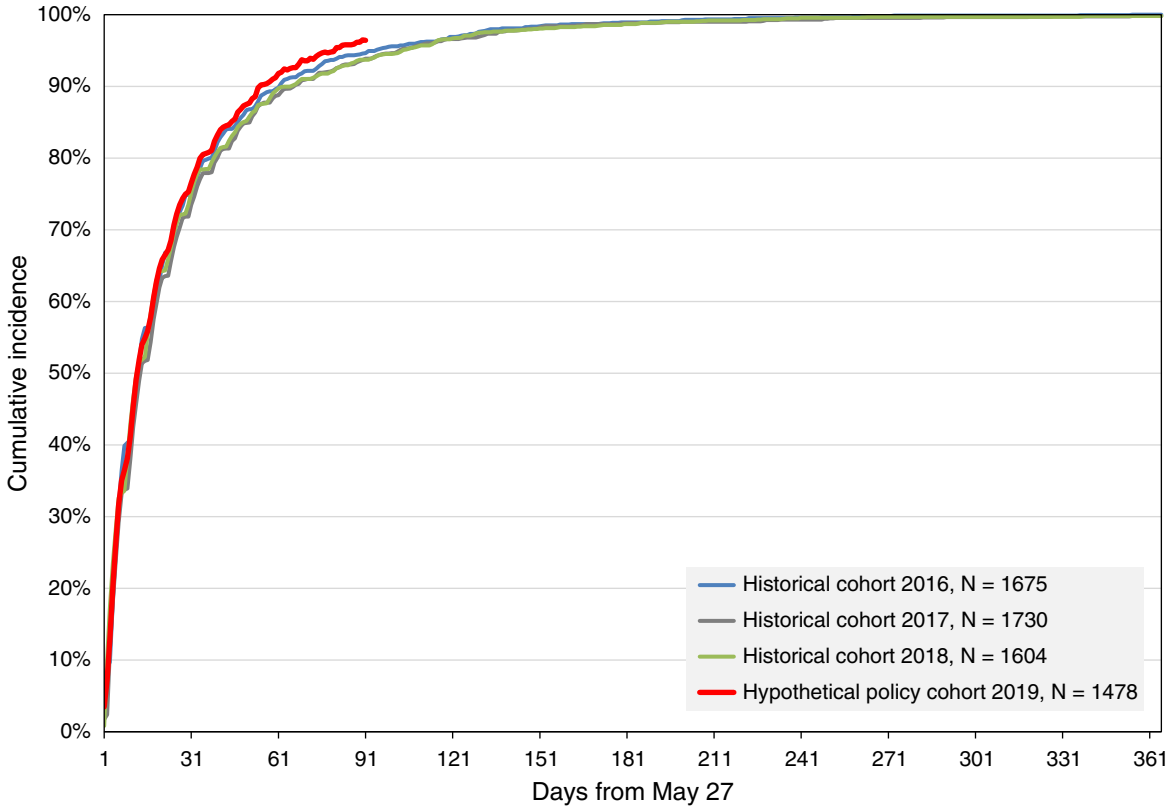

FIGURE 2 Cumulative incidence of first visits to a physician after implementation of the British Columbia Biosimilars Initiative (includes hypothetical data)

of likelihood ratios to evaluate common epidemiologic measures of association such as the risk difference have been published elsewhere.[11,12]

If repeated updates in any of the rapid monitoring analyses show a sustained likelihood ratio in excess of 7.1, we would conclude that the difference in the outcome between the policy cohort and the historical control cohorts is statistically significant. Figure 3 (A) shows an example of prescribing for angiotensin-2-converting-enzyme inhibitors after an update to the British Columbia RDP policy in 2016. Figure 3 (A) indicates the cumulative incidence of first admission to hospital in a policy cohort and three historical control cohorts. It is apparent from Figure 3 (A) that admissions to hospital were comparable and stable in all groups after the policy changes to the RDP program. Figure 3 (B) depicts the likelihood ratios that prevailed on each day of the follow-up period. Likelihood ratios were less stable in the early days of follow-up owing to a paucity of events. As follow-up progressed, likelihood ratios became more stable and showed a sustained pattern below the 7.1 threshold.

3 | DISCUSSION

This rapid monitoring plan will use the population-based de-identified linked claims data in British Columbia to provide policymakers with a rapid assessment of potential adverse consequences of the Biosimilars Initiative. This plan will not address several challenges that are often considered when conducting a carefully planned observational study and therefore it should only be regarded as a signal-detecting assessment. One of the limitations of this type of plan is the differences between cohorts over time. While we will describe patient characteristics in each cohort we will not control for differences if they exist. Applying methods to control for confounders may slow the analysis and prevent us from providing timely results. We have considered some differences between the cohorts. For example, loading doses may lead to increased cumulative incidence of the first refills of infliximab early in the postpolicy follow-up if the proportion of initiators is higher in the policy cohort. Another possible difference is in disease severity between the cohorts, which may lead to a difference in health services utilization and frequency of medication administration. However, in a preliminary analysis of trends in the historical cohorts, we observed similar trends between the historical control cohorts for most outcomes; hence, we assume that either the differences between the cohorts are small or such differences have a small effect on the outcome measures. If we observe a large difference between a postpolicy trend and historical trends, we would consider an additional analysis that will control for differences between the cohorts.

One of the limitations of studying a new policy is detection bias. Patients and physicians who are aware of the new policy are more likely to report symptoms and signs. This type of effect will bias the results away from the null. In the case of the Biosimilars Initiative, we also estimate that we will observe an increase in visits to

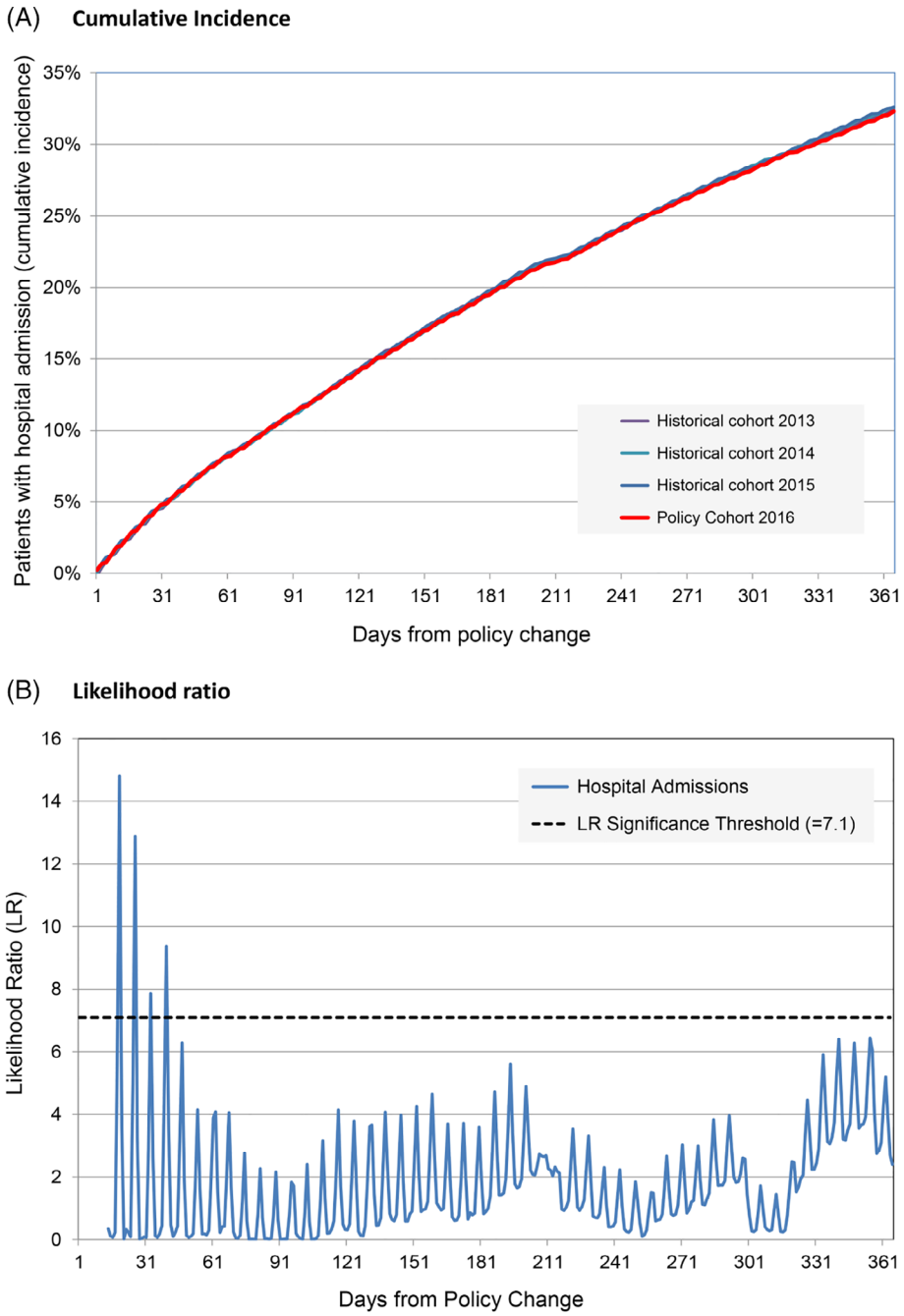

FIGURE 3 Rapid monitoring of angiotensin-2-converting-enzyme inhibitors after an update to the British Columbia Reference Drug Program in 2016. Plate A presents the cumulative incidence of first admission to hospital, for three historical cohorts and the policy cohort. Plate B shows the likelihood ratios corresponding to cumulative incidence differences over time

physicians and specialists to discuss switching to the biosimilar products.[13] We will consider these possible effects when interpreting the results of the rapid monitoring plan. Should the plan detect a trend in the postpolicy cohort that is significantly different from the historical control data, a carefully designed assessment will be undertaken.

We considered an alternative study design—the interrupted time series analysis—which has been used previously to assess the effect of a British Columbia drug coverage policy.[14] However, conducting this type of analysis requires longer follow-up after the policy is launched (at least 12 months),[15] and timely analysis is underpowered with this design.

The results of the proposed rapid monitoring plan will be used by policymakers to inform ongoing decision-making related to the Biosimilars Initiative, in terms of impacts on both patient health and health system utilization. We believe that this rapid monitoring plan will also provide assurance to the public that British Columbia is taking a precautionary approach to its biosimilars policy. Furthermore, results from early rapid monitoring will be useful for the design and implementation of more rigorous evaluations of the policy in future.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

Ethics approval was obtained from the University of British Columbia Clinical Ethics Research Board, certificate number H19-02377.

ACKNOWLEDGEMENTS

All inferences, opinions, and conclusions drawn in this paper are those of the authors, and do not reflect the opinions or policies of the Data Stewards. The BC Ministry of Health approved access to and use of BC data for this study. Data sources were as follows (http://www.popdata.bc.ca/data): British Columbia Ministry of Health [creator] (2019): Medical Services Plan (MSP) Payment Information File. BC Ministry of Health [publisher]. MOH (2019); British Columbia Ministry of Health [creator] (2019): Consolidation File (MSP Registration & Premium Billing). BC Ministry of Health [publisher]. MOH (2019); British Columbia Ministry of Health [creator] (2019): PharmaNet. BC Ministry of Health [publisher]. Data Stewardship Committee (2019); and Canadian Institute for Health Information [creator] (2019): Discharge Abstract Database (Hospital Separations). BC Ministry of Health [publisher]. MOH (2019). [Correction added on 22 January 2020, after first online publication: The acknowledgment section has been added in this version.]

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How to cite this article: Dormuth CR, Fisher A, Carney G. A rapid monitoring plan following a shift in coverage from brand name to biosimilar drugs for rheumatoid arthritis in British Columbia. *Pharmacoepidemiol Drug Saf*. 2020;1–7. https://doi.org/10.1002/pds.4957