Biologic drugs have improved outcomes for individuals across a range of chronic medical conditions, including diabetes and rheumatic and gastrointestinal diseases. However, unlike conventional small-molecule pharmaceuticals, biologics are derived from living organisms, are structurally more complex, and have substantially higher costs. In 2018, biologics represented only 1.5% of Canadian public drug plan claims, but accounted for 27.3% of public drug costs. In addition to their generally higher list prices, utilization of biologics has grown substantially in the past decade. In Ontario, the total number of people taking biologics increased by 462% between 2010 and 2019, and total annual spending on these products was anticipated to reach $1.4 billion by 2021. Although biologics are improving outcomes for patients, their increasing use and high costs threaten the financial sustainability of public drug programs. The recent expiration of patents for some biologic drugs has created opportunities for the approval of new, lower-cost “biosimilars” — biologic medicines that are highly similar to an existing innovator biologic drug, with no clinically meaningful differences.
differences in efficacy, safety or immunogenicity. In 2010, Health Canada released a regulatory framework outlining the approval process for biosimilars. By building on the foundation of research and development already established by innovator biologics, biosimilars offer an opportunity for substantial cost savings for public and private drug plans. The first biosimilar was marketed more than a decade ago, but uptake of biosimilars has been modest in Canada relative to other Organisation for Economic Co-operation and Development countries. Consequently, Canadian public and private drug plans have begun to implement policies aimed at expanding the use of biosimilars.

In 2019, the Canadian provincial governments of British Columbia (BC) and Alberta announced policies mandating nonmedical substitution with biosimilars among people with rheumatic conditions and inflammatory bowel disease (IBD). It is estimated that these policies will save the BC and Alberta governments nearly $100 million each over the first 3 years of implementation. Despite these anticipated cost savings, concerns have been raised regarding potential destabilization of well-managed disease when medications are switched.

The objective of this study was to estimate the number of patients potentially affected by different biosimilar policy options and the cost implications of these policies in Ontario.

Methods

Design, setting and study population
We conducted a cross-sectional time series analysis of all Ontarians dispensed a publicly funded prescription for infliximab, etanercept or adalimumab, to manage rheumatic conditions (i.e., rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, and severe plaque psoriasis) or IBD (i.e., ulcerative colitis, Crohn disease) between Jan. 1, 2018, and Dec. 31, 2019. We analyzed data by month and projected forward to forecast utilization up to Dec. 31, 2020.

Three people with lived experience of using biologics participated on the study team. Their engagement included meetings throughout the project, input on the study design, interpretation of results and manuscript content.

Data sources
We used the IQVIA Drug Information File to identify relevant drug identification numbers for biologics and to categorize biologics into innovators and biosimilars, and the Ontario Drug Benefit (ODB) Program database to capture prescriptions for biologics reimbursed by the public drug program. In Ontario, individuals are eligible for ODB if they are older than 65 years, reside in a long-term care home, receive income or disability support, or have drug costs that are high relative to their income. Prescription cost data in the ODB Program database include the total amount paid by the government, and copayments and deductibles paid by the patient.

We excluded individuals who newly received public coverage for biologics during the extended Ontario Health Insurance Program (OHIP+) drug program (which temporarily covered all children and youth) on Jan. 1, 2018, but subsequently appeared to lose coverage after changes to the program on Apr. 1, 2019, so as to ensure projected costs reflected the current OHIP+ program. We used the OHIP Registered Persons Database to determine the age and sex of individuals included in the study.

The data sets we used have been shown to be of high quality (Appendix 1, eTable 1, available at www.cmajopen.ca/content/9/4/E1055/suppl/DC1), and were linked using unique encoded identifiers and analyzed at ICES.

Policy definitions and cost adjustments
We calculated total monthly costs for study biologics (infliximab, etanercept and adalimumab) in nominal Canadian dollars. This was calculated as the sum of the total paid by the Ontario Ministry of Health (i.e., the sum of the drug ingredient cost, compounding fee [if applicable], pharmacy markup and dispensing fee) and the copayments and deductibles paid by the patient. We adjusted these costs according to 2 potential reimbursement policy options, and 3 pricing considerations.

Reimbursement policy options
We considered 2 policy options that are aligned with those introduced elsewhere and that were found to be feasible and applicable within the Ontario public drug program. Specifically, these were a mandatory nonmedical substitution, whereby any patient receiving an innovator biologic has therapy substituted with the relevant biosimilar; and an enforced biosimilar requirement among new users of biologics only.

We modelled the mandatory nonmedical substitution by identifying all innovator biologic prescriptions dispensed each month and multiplying the medication ingredient costs by an adjustment factor (calculated as the median price paid by the Ontario Ministry of Health for biosimilar prescriptions reimbursed over the study period as a proportion of the cost reimbursed for the innovator biologic) to reduce the cost to that of the relevant biosimilar (Table 1). We then calculated the new pharmacy markup (6% for claims above $1000 and 8% for claims below $1000, aligning with current markup policies) and added it to the adjusted costs, along with dispensing fees.

In contrast, when modelling the biosimilar requirement among new users only, we applied these adjusted costs only to people newly starting an innovator biologic in the month of interest, or to people who had previously started an innovator biologic during our study period. This will accumulate cost implications over time as we assumed that new users from earlier months continued using the biosimilar in future months.

Pricing and policy expansion considerations
We combined the 2 policy options above with 3 policy considerations. First, we modelled the impact of the introduction of a biosimilar for adalimumab (which did not have a marketed biosimilar in Canada during the study period). In this

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In 2018, 14,089 individuals received a publicly funded biologic indicated for rheumatic conditions or IBD (Table 2). Adalimumab was prescribed most frequently (n = 5782, 41.0%), followed by infliximab (n = 4558, 32.4%) and etanercept (n = 3872, 27.5%). Overall, 54.3% (n = 7656) of users of biologics were women and 61.8% (n = 8703) were younger than 65 years, although these patterns differed by drug. For example, 63.4% (n = 2454) of users of etanercept were women, and 58.3% (n = 2258) were older than 65 years.

Among biologics with a biosimilar available in Ontario, 84.1% (n = 3256) of users of etanercept and 86.7% (n = 3954) of users of infliximab were treated with an innovator. However, when we considered new use, 39.5% (n = 305) of people starting etanercept and 59.8% (n = 459) of those starting infliximab began on an innovator.

Overall, the cost of biologics in 2018 was $280,782,091, and the average cost of biologics per person was $19,929, ranging from $16,034 per person treated with etanercept to $27,272 per person treated with infliximab.

Trends in monthly costs
The monthly costs of biologics for rheumatic conditions and IBD increased over our study period, rising from $21,883,713 in January 2018 to $26,331,208 in December 2019 (Figure 1). Monthly costs were forecasted to reach $28,246,752 (95% confidence interval [CI] $26,984,908 to $29,508,595) by December 2020 if current trends continued. In the sensitivity analysis that considered only public payer costs, monthly costs and patterns were similar over time (rise from $21,682,705 to $25,678,079 from January 2018 to December 2019). Assuming current reimbursement policies for biologics indicated for IBD and rheumatic conditions remained the same in Ontario, we anticipated that these medications would cost a total of $925,266,759 from 2018 to 2020.

Policy impact
The impact of policies on the number of patients affected and the resulting cost savings varied considerably depending on the policy selected (Table 3 and Figure 2). The fewest patients
were affected if only new users of etanercept and infliximab were required to use a biosimilar ($n = 757$ in 2018). This policy also led to the smallest percentage reduction in costs between 2018 and 2020 (3.7% reduction; $34 236 463$ in savings over 3 years). We estimated that a policy mandating nonmedical substitution for all users of etanercept and infliximab innovators would affect 7209 patients upon implementation, and save $238 589 858 over 3 years (25.8% cost reduction). In policies including insulin glargine, the number of patients affected would be considerably higher, reaching 115 895 in 2018 for mandatory nonmedical substitution, and 23 680 for a new user substitution. The percentage price reductions are similar for these policies as for those focusing on etanercept and infliximab; however, the absolute cost savings over 3 years are higher ($238 589 858$ for mandatory nonmedical substitution and new user substitution, respectively).

The impact of policies on costs varied depending on the availability of an adalimumab biosimilar and the degree of price negotiations, with the policy leading to the largest 3-year cost savings being a mandatory nonmedical substitution of 12 928 users of etanercept, infliximab and adalimumab innovators where prices are negotiated to 25% of the innovator cost (69.8% reduction; $645 879 599 over 3 years; Table 3).

### Interpretation

In this population-based study, we found that policies designed to increase uptake of biosimilars differed substantially in their impact on patients and government costs. In 2018, infliximab, etanercept and adalimumab cost the Ontario public drug program $280.8 million, 95.6% of which was attributed to innovator biologics. Depending on the policy implemented and negotiated biosimilar prices, we estimated the potential 3-year (2018–2020) cost savings of biosimilar reimbursement policies to range between $34.2 million (3.7% savings; enforced new user substitution for etanercept and infliximab only) and $645.9 million (69.8% savings; mandatory nonmedical substitution for etanercept, infliximab and adalimumab, each priced at 25% of innovator biologics). Similarly, the number of patients affected by the policies ranged from 757 to 115 895 annually, depending on the policy selected.

Overall, the considerable cost savings and number of patients affected by the biosimilar policy changes examined in this study are within the range of estimates found in other jurisdictions, both nationally and internationally. In Canada, BC and Alberta estimated their biosimilar policies would affect between 40 and 60 patients per 10 000 population and save about $1500 and $3000 per patient, respectively.

### Table 2: Characteristics of biologics use among people with rheumatic or gastrointestinal conditions, 2018

| Characteristic | Any biologic | Etanercept | Adalimumab | Infliximab |
|---------------|-------------|-----------|------------|------------|
| Sex           |             |           |            |            |
| Male          | 6433 (45.7) | 1418 (36.6)| 2664 (46.1)| 2405 (52.8)|
| Female        | 7656 (54.3) | 2454 (63.4)| 3118 (53.9)| 2153 (47.2)|
| Age, yr       |             |           |            |            |
| < 18          | 441 (3.1)   | 51 (1.3)  | 179 (3.1)  | 224 (4.9)  |
| 18–44         | 4310 (30.6) | 456 (11.8) | 1838 (31.8)| 2049 (45.0)|
| 45–64         | 3952 (28.1) | 1107 (28.6)| 1682 (29.1)| 1195 (26.2)|
| ≥ 65          | 5386 (38.2) | 2258 (58.3)| 2083 (36.0)| 1090 (23.9)|
| Patients treated with any innovator biologics | 12 928 (91.8) | 3256 (84.1) | 5782 (100) | 3954 (86.7) |
| New users     |             |           |            |            |
| Biologics     | 3219        | 773       | 1708       | 767        |
| Innovator biologics | 2924 (90.8) | 305 (39.5) | 1708 (100) | 459 (59.8) |
| Prescriptions dispensed |            |           |            |            |
| Biologics     | 98 070      | 27 920    | 41 582     | 28 568     |
| Innovator biologics | 91 261 (93.1) | 24 270 (86.9) | 41 582 (100) | 25 409 (88.9) |
| Total cost, $ |             |           |            |            |
| Biologics     | 280 782 091 | 62 083 387| 94 391 665 | 124 307 040|
| Innovator biologics | 268 348 355 | 57 336 774| 94 391 665 | 116 619 916|
| Average no. biologic prescriptions/person | 7.0         | 7.2       | 7.2        | 6.3        |
| Average cost of biologics per person, $ | 19 929      | 16 034    | 16 325     | 27 272     |

*Unless otherwise specified.
Our analysis found that a nonmedical substitution policy for etanercept, infliximab and insulin glargine (which is most similar to BC and Alberta’s policies) would affect about 80 patients per 10,000 population and save nearly $900 per patient in Ontario.

Although there have been many international studies examining the effect of biosimilars on the budget of public drug programs, primarily in Europe, many of these analyses are not directly comparable with this study owing to the variability of policies, product availability, populations studied and research methodology. A recent systematic review compiled 15 international studies and found that nonmedical substitution of biosimilars for etanercept, infliximab or adalimumab resulted in a wide range of cost savings (about €7 to €13,739 per patient per year). The variation between provincial estimates in Canada and international comparisons is likely a result of differences in the medications included in the biosimilar policies, the prevalence of associated diseases, and drug coverage before policy implementation. However, this international research suggests that policies requiring nonmedical switches or automatic substitutions with biosimilars generally lead to rapid shifts in dispensing patterns and large cost reductions for public payers, but potentially increased costs related to health services utilization. Although cost considerations can be an important driver of policy change, the way in which biologics are dispensed introduces an additional layer of complexity for optimal reimbursement policy. For example, although biosimilars have been shown to be effective and safe, some clinicians are concerned that substituting treatment for patients already stable on one therapy could cause anxiety among those who are experiencing benefit from their current medication and could destabilize their condition. This could both affect patient outcomes and incur costs to the health care system. This concern appears to be greater for patients with IBD, owing to uncertainty about destabilization of their condition and the more limited number of biologic options.

A unique aspect of biologic provision is that some patient care and medication administration costs (e.g., infusion clinics, laboratory tests, patient support nurses) are funded by biologic drug manufacturers. In addition, drug manufacturers often assist patients with their copayments. Therefore, any policies introducing mandatory changes in therapy need to allow for scaling-up of these services for the corresponding biosimilars. This includes anticipating funding to provide clinical support to patients when undergoing a change in therapy, and identifying potential implications for the patient copayments and financial support often provided by innovator biologics manufacturers.
Given the limited real-world evidence regarding the safety of mandatory nonmedical biosimilar substitution, particularly for patients with IBD, jurisdictions introducing these policies should monitor patient outcomes, including clinical consequences and costs, out-of-pocket expenses and quality of life.

**Limitations**

Although we used real-world data on publicly funded biologics to estimate the potential impacts of different biosimilar policies in Ontario, several limitations to this study merit discussion. In the absence of an available biosimilar for adalimumab, it would be possible that biologics prescribing could be channelled toward this product if a mandatory nonmedical substitution policy was introduced. Although we are unable to estimate the cost implications of such a change in clinical practice in our models, data after a similar policy change in BC suggest this did not occur.\(^27\)

Furthermore, in February 2021, adalimumab biosimilars became available on the Canadian market and were added to the Ontario public drug formulary in March 2021 at 60% of the price of the innovator. Therefore, all available innovator biologics now have a biosimilar available, thus reducing the potential for channelling.

The Ontario Public Drug Programs already has a policy requiring biosimilars among new users of infliximab or etanercept; however, when patients are started on medications in hospital or they receive their first dose at low cost from the manufacturer, these policies are circumvented. Therefore, although new-user policies are potentially more acceptable to patients, they may have limited effectiveness for public payers. As our model indicates, considerable additional savings could be achieved if the intended new-user biosimilar policy was fully enforceable, although it is not known whether this can be achieved when other factors remain outside government control.

Our study is limited to estimating the cost implications of biosimilar policy changes applied to the public drug program in Ontario, and therefore does not provide estimates of cost implications if similar policies were introduced by

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### Table 3: Cost implications of different policy scenarios, 2018–2020*

| Cost implications                                                                 | No. patients affected (2018)† | Savings 2018, $ | Savings 2019, $ | Savings 2020, $ | Total 3-year savings, $ | % Reduction costs |
|-----------------------------------------------------------------------------------|-------------------------------|----------------|----------------|----------------|--------------------------|------------------|
| Etanercept and infliximab only                                                    |                               |                |                |                |                          |                  |
| Everyone switches to currently available biosimilar                               | 7209                          | 75 711 829     | 79 753 211     | 83 124 819     | 238 589 858              | −25.8            |
| Only new users required to use currently available biosimilar                     | 757                           | 6 386 595      | 11 810 257     | 16 039 611     | 34 236 463               | −3.7             |
| Including adalimumab biosimilar†                                                 |                               |                |                |                |                          |                  |
| Everyone switches to biosimilar (adalimumab @ 60% innovator cost)                 | 12 928                        | 112 774 144    | 122 160 470    | 130 684 224    | 365 618 838              | −39.5            |
| Only new users are required to use biosimilar (adalimumab @ 60% innovator cost)  | 2443                          | 14 456 007     | 28 967 204     | 42 164 844     | 85 588 055               | −9.3             |
| New cost thresholds for all biologics (etanercept, infliximab and adalimumab)†    |                               |                |                |                |                          |                  |
| Everyone switches to biosimilar (all biologics @ 50% innovator cost)              | 12 928                        | 133 002 041    | 143 605 795    | 153 276 509    | 429 884 345              | −46.5            |
| Only new users are required to use biosimilar (all biologics @ 50% innovator cost)| 2443                          | 17 273 891     | 34 758 620     | 50 939 083     | 102 971 594              | −11.1            |
| Everyone switches to biosimilar (all biologics @ 25% innovator cost)              | 12 928                        | 199 861 495    | 215 784 478    | 230 233 627    | 645 879 599              | −69.8            |
| Only new users are required to use biosimilar (all biologics @ 25% innovator cost)| 2443                          | 25 965 104     | 52 250 289     | 76 614 092     | 154 829 485              | −16.7            |
| Etanercept, infliximab and insulin glargine†                                      |                               |                |                |                |                          |                  |
| Everyone switches to currently available biosimilar                               | 115 895                       | 94 857 347     | 96 465 505     | 97 410 407     | 288 733 259              | −25.3            |
| Only new users required to use currently available biosimilar                     | 23 680                        | 8 541 779      | 15 386 458     | 21 413 355     | 45 341 592               | −4.0             |

*Represents approximate numbers of people affected based on prevalence of new use of innovators or use of only innovators over the year.
†Secondary analysis.
private drug insurers who typically provide coverage to younger (i.e., < 65 yr) populations. However, younger patients with high drug costs are increasingly accessing Ontario’s catastrophic drug program (Trillium), which means that drug policy decisions made by public drug programs will affect them. We were unable to incorporate negotiated price reductions (rebates) already implemented in Ontario as these are confidential; the cost savings reported here therefore used the list price of the medications. Hence, we determined 2 potential thresholds for price reductions (25% and 50% of innovator cost) through consultation with policy-makers across Canada. Although achieving price reductions as low as 25% of the innovator cost may be unlikely, this provides a wide array of cost implications that can inform future price negotiations by public drug programs in Canada.

**Conclusion**

In this large population-based study, we found that policies designed to address the rising costs of biologics differ substantially in their impact on patients and cost savings. Given the complexity of the supply chain for these medications, including the role of manufacturers in drug provision, careful consideration of the balance between cost savings and patient access is warranted. Plans for enacting specific initiatives should consider forming partnerships with key stakeholder groups to ensure that patient and provider perspectives are incorporated.

### References

1. Biosimilar biologic drugs in Canada: fact sheet. Ottawa: Health Canada; 2019.
2. ICMRA statement about confidence in biosimilar products (for healthcare professionals). San Diego (CA): International Coalition of Medicines Regulatory Authorities [ICMRA]; 2019.
3. Biologics in Canada: part 1: market trends. Ottawa: Patented Medicine Prices Review Board; 2020.
4. Tadrous M, McCormack D, Martins D, et al. Current and prospective utilization of innovator biologics and biosimilars in Ontario. Toronto: Ontario Drug Policy Research Network; 2020.
5. Guidance document: information and submission requirements for biosimilar biologic drugs. Ottawa: Health Canada; 2016.
6. Kabir ER, Moreino SS, Sharif Siam MK. The breakthrough of biosimilars: a twist in the narrative of biological therapy. *Biomolecules* 2019;9:410.
7. Biosimilars initiative for patients. Vancouver: Government of British Columbia; 2019. Available: https://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmaceutical-for-bc-residents/what-we-cover/drug-coverage/biosimilars-initiative-patients (accessed 2020 May 14).
8. Biosimilars in Canada: current environment and future opportunity. Ottawa: Patented Medicine Prices Review Board; 2020.

9. Biologics in Canada: part 2: biosimilar savings. Ottawa: Patented Medicine Prices Review Board; 2020.

10. Biosimilar drugs. Alberta: Government of Alberta; 2020. Available: https://www.alberta.ca/biosimilar-drugs.aspx (accessed 2020 May 14).

11. Biosimilar initiative. Edmonton: Alberta Health; 2020.

12. Kaplan GG, Ma C, Seow CH, et al. The argument against a biosimilar switch policy for infliximab in patients with inflammatory bowel disease living in Alberta. J Can Assoc Gastroenterol 2020;7:33-42.

13. Crain J, Mawani M, Lee K, et al. Patient and health care provider input: non-medical biosimilar switch policy for patients with inflammatory bowel disease. Toronto: Crohn’s and Colitis Canada; 2019.

14. Levy AR, O’Brien BJ, Sellors J, et al. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol 2003;10:67-71.

15. Jensen TB, Bartels D, Saedder EA, et al. The Danish model for the quick and safe implementation of infliximab and etanercept biosimilars. Eur J Clin Pharmacol 2020;76:35-40.

16. Kalekar PS. Time series forecasting using Holt-Winters exponential smoothing. Mumbai: Kanwal Rekhi School of Information Technology; 2004:1-13.

17. Puertes EL, Henry B, Marfa F, et al. Trends in antibiotic utilization in Vancouver associated with a community education program on antibiotic use. Can J Public Health 2010;101:304-8.

18. Moorkens E, Vulto A, Huys I, et al. Policies for biosimilar uptake in Europe: an overview. PLoS One 2017;12:e0190147.

19. Liu Y, Yang M, Garg V, et al. Economic impact of non-medical switching from originator biologics to biosimilars: a systematic literature review. AdE Ther 2019;36:1851-77.

20. Broten L, Avitia-Zubieta JA, Lacaille D, et al. Systemic autoimmune rheumatic disease prevalence in canada: updated analyses across 7 provinces. J Rheumatol 2014;41:673-9.

21. Kaplan GG, Bernstein CN, Coward S, et al. The impact of inflammatory bowel disease in Canada 2018: Epidemiology. J Can Assoc Gastroenterol 2019;2 (Suppl 1):S1-S5.

22. Health Fact Sheets: Diabetes, 2017. Ottawa: Statistics Canada; 2018.

23. Campbell DJ, Manns BJ, Soril LJ, et al. Comparison of Canadian public medication insurance plans and the impact on out-of-pocket costs. CMAJ Open 2017;5:E808.

24. Jensen TB, Kim SC, Jimenez-Solem E, et al. Shift from adalimumab originator to biosimilars in Denmark. JAMA Intern Med 2020;180:902-3.

25. Barbier L, Ebbens HC, Declerck P, et al. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review. Clin Pharm Therapeut 2020;108:734-55.

26. Canadian Rheumatology Association (CRA) position statement on biosimilars. Mississauga (ON): Canadian Rheumatology Association; 2019.

27. Crosby M, Tadrous M, Gomes T. Potential cost implications of mandatory non-medical switching policies for biologics for rheumatic conditions and inflammatory bowel disease in Canada. Clin Pharmacol Ther 2021;109:739-45.

28. Tadrous M, Greaves S, Martins D, et al. Catastrophic drug coverage: utilization insights from the Ontario Trillium Drug Program. CMAJ Open 2018;6:E132-8.

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