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Title	Projected impact of biosimilar substitution policies on drug use and costs in Ontario, Canada. a cross-sectional time series analysis
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Reviewer 1	Loke, Yoon
Institution	University of East Anglia, Norwich Medical School
Reviewer comments and author response	**Reviewer: 1** **Comments to the Author** **Thank you for giving me the opportunity to review this submission. This is a straightforward study evaluating the monetary cost of biosimilar substitution at different stages of the patients' health care journey. The methods are simple and the calculations are appropriate.** We thank the reviewer for their supportive comments. **However, there are two major limitations to this piece of work.** **1. The first limitation is that it does not consider the resources required to switch patients over to the biosimilar product. In many instances, additional resource such as extra members of nursing staff or additional outpatient clinic time were required to make the transition as smooth as possible. Moreover, patients (some of whom are understandably anxious about coming off a treatment that had been helpful for many years) required additional counselling time so that the switch could be explained to them. This is less of a problem for new users.** We agree with the reviewer that any policy requiring changes to medication for large numbers of patients will incur short-term additional costs to support patients through this change. While we had mentioned this within our contextualizing factors (i.e., costs of infusion clinics, lab tests and patient support programs), we have now expanded this to explicitly speak to the clinical support required by patients during this transition. **Revised Text (Discussion, Contextualizing Factors; pg 11):** *Furthermore, a relatively unique aspect of biologic provision is that some patient care and medication administration costs (e.g. infusion clinics, lab 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 patient copayments and financial support often provided by innovator biologics manufacturers* **2. The second problem stems from the fact that some patients either do not tolerate or do not seem to have similar efficacy responses when they were switched to the biosimilar product. So, this required additional clinical staff and outpatient clinic time to manage these patients either by returning them**

	to the originator product or to explore different avenues of treatment. In summary, I feel that a study that evaluates only the monetary cost is a very limited exploration of what is a rather complicated situation in real life clinical practice. As such, I don't feel that this study (which focuses on monetary cost alone) adds a substantial amount to what is actually a complicated dilemma in practise when we are moving to a biosimilar product. We thank the reviewer for raising the concern of patient impact, which we agree is a major issue that overlays policy decisions in this field. We specifically designed this study to assess the economic impacts of biosimilar policy changes because these policies are being actively discussed, but have not yet been implemented in Ontario. Therefore, the intention of this study is to describe the cost implications of such changes, and to provide additional context to decision-makers when considering these changes, as identified by patient partners on this project. Although there is some evidence from outside of Canada that mandatory non-medical switching policies do not have broad negative clinical implications for patients, it is possible that some patients will not respond as well to the biosimilar which can lead to further downstream clinical interventions and related costs. Given the importance of this issue, we have included this in our discussion of contextualizing factors that we believe policy-makers must consider when implementing these policies. If biosimilar policies are implemented in Ontario, there will be an urgent need for ongoing monitoring and evaluation of their impact on patient outcomes and costs. **Relevant Text (Discussion; Contextualizing Factors; pg 11):** *Finally, given the limited real-world evidence regarding the safety of mandatory non-medical biosimilar substitution, particularly within patients with IBD, jurisdictions introducing these policies should monitor patient outcomes, including clinical consequences and costs, out-of-pocket expenses, and quality of life.*
Reviewer 2	Huang, Kun
Institution	University of British Columbia Faculty of Medicine, Rheumatology
Reviewer comments and author response	**Reviewer: 2** **Comments to the Author** **Gomes and colleagues presented a population based study to estimate the cost saving implication of different biosimilar policy options in Ontario, canada. Specifically, the authors used Ontario drug benefit (ODB) program database from Jan 1, 2018 to Jun 30, 2019 and projected forward to forecast utilization up to Dec 31, 2020.** **The manuscript is well written and organized. I enjoyed reading it.** We thank the reviewer for their supportive comment. **I just have to a few questions to ask the authors to clarify:** **1. Table 1 identifies the adjustment factors for biologic prices. It is unclear to**

	me how the authors reach the adjustment factor of 62.8% and 93.9%? These factors are based on median unit cost reimbursed for biosimilars as a proportion of the median reimbursed unit cost of the comparable innovator biologic. We have now clarified this in the manuscript. We also noticed an error in the adjustment factor listed in Table 1. The correct adjustment factor is 53.2% (this did not impact our calculations which used the correct adjustment factor – this was simply entered incorrectly in Table 1). Table 1 has been updated accordingly. **Revised Text (Methods; pg 5):** *We modeled the mandatory non-medical 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).* **2. is non-medical substitution or biosimilar enforcement amongst new users not mandatory so far in ontario? I am surprised to see that, amongst those with new start of biologics, 39.5% of people initiating etanercept and 59.8% of those initiating infliximab started on an innovator, rather than a biosimilar. There has been plenty study and real world data showing equivalency between biosimilars and originators. I am wondering what are the main reasons for hesitancy in physicians or patients to use a biosimilar for new start.** **In addition, my understanding is that OPDP requires biosimilar for new users of etanercept and infliximab. How could the uptake be so low if it is mandatory.** We thank the reviewer for raising this important point. As stated, there is technically a new user biosimilar policy in Ontario; however this policy can be circumvented by manufacturers of innovator biologics providing their products at low cost to hospitals (where many patients are first initiated on therapy), or providing them at low cost to the patient at initiation. Once a patient is then initiated on therapy with an innovator, they are eligible to continue to receive that product through the Ontario Public Drug Program. Because of these loopholes, we argue in our paper that the impact of new user biosimilar policies will be minimal unless they can directly address the issue of manufacturer funding of initial drug therapy. This is discussed in the limitations section of our manuscript. **Relevant Text (Limitations; pg 10):** *Second, the Ontario Public Drug Programs already has a policy requiring biosimilars among new users of infliximab or etanercept; however, when patients are initiated on medications in hospital or they receive their first dose at little 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.*

	3. table 3 projected largest 3 year cost savings being a mandatory non-medical substitution of all innovator uses of etanercept, infliximab and adalimumab where prices are negotiated to 25% of the innovator. I am a bit confused where the percentage of 25% or 50% comes from. It that a pure postulation from the authors or information from the pan Canadian pharmaceutical alliance? These numbers were identified in consultation with decision-makers within the pCPA and the Ontario Ministry of Health, and align with published average rebates. They were determined to be appropriate thresholds upon which policy-makers could compare their planned reimbursement strategies and price negotiations. We have expanded our discussion of this in the limitations section of our manuscript. **Revised Text (Limitations; pg 10):** *Finally, 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. Therefore, we determined two 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 undertaken by public drug programs in Canada.* **4. the ODB captures only those who are more than 65 years, reside in long term care home, receive disability or income support, or earn low income. So a large number of younger patients on biologics who have jobs and above low income line are not captured in this analysis. Potentially much more savings can be achieved at all comers level.** We would like to clarify, that patients eligible for Ontario's catastrophic drug coverage program (Trillium), who have high drug costs relative to their income, are included in this analysis. However, we agree that the broader cost implications of biosimilars extend beyond what we have studied in this manuscript. We approached this question from a lens of understanding the cost implications for Ontario's largest drug payer, the Ontario Public Drug Program, and therefore did not attempt to estimate costs for other payers across the province. Because these types of policies would be determined independently by drug insurers (public and private) across Ontario, we felt that it was appropriate to focus our analysis on one such payer. However, we anticipate the results would be generalizable to other drug insurers across Canada.
Reviewer 3	Name withheld
Institution	BC
Reviewer comments and author response	**Reviewer: 3** **Comments to the Author** **The study finds that introducing biosimilars will save the Ontario public drug program considerable cost and these will vary by the type of program and the costs negotiated. The strength of the study is the data and the simple but effective analysis. The weakness is that we could make these conclusions without the analysis, though the actual numbers between different programs**

	is a new contribution. I provide a few comments (in no specific order) that I hope will be helpful for improving the paper. **1. I think some readers will be surprised by the number of <=65 in the cohort and so suggest citing previous work on increasing utilization of trillium, and that many <= 65 in Ontario with private coverage are not included (but at age 66 will become eligible for ODB)** We thank the reviewer for suggesting this. We have now included discussion of the generalizability of these findings outside of the Ontario public drug program and the age implications to our limitations section of the revised manuscript. **Revised Text (Limitations; pg 10):** *Third, 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 private drug insurers who typically provide coverage to younger (i.e. <65 years) populations. However, younger patients with high drug costs are increasingly Ontario's catastrophic drug program (Trillium), which means that they will be impacted by drug policy decisions made by public drug programs.23* **2. I appreciate that most copays will be maxed, but given the noted patient involvement in the study, I was surprised not to see some description of the impact (or not in reality) of out of pocket patient costs.** Because of the high costs of these products, regardless of whether they are innovator biologics or biosimilars, differences in biosimilar policy will have little impact on copays made by patients. Furthermore, drug manufacturers typically offer copay cards to reduce or eliminate co-payments for patients prescribed their medication. As a result, this was not initially identified by our patient team members as a main area requiring discussion in this manuscript, given its focus on the impact of changing policy, and the anticipation that this would not impact copayments. However, based on this suggestion, we have expanded our discussion of the cost implications of mandatory non-medical switch policies to incorporate consideration of co-payment impacts (if, for example, biosimilar companies did not provide the same level of support for co-payments as manufacturers of innovator biologics). **Revised Text (Contextualizing Factors; pg 11):** *Furthermore, a relatively unique aspect of biologic provision is that some patient care and medication administration costs (e.g. infusion clinics, lab 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 patient copayments.* **3. The prices for biologics will not have included any of the rebates and should be acknowledged.**

	We agree that this is a limitation and have included it in the appropriate section of our manuscript. We have clarified in the text that we are referring to rebates negotiated between the government and drug manufacturers. **Relevant Text (Limitations; pg 10):** *Finally, 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.* **4. There are many studies from the US showing payors are not getting the biosimilar discounts that they expected. Some more justification on using 25% in the primary analysis is suggested – I think it is optimistic. The reality is that we don't know the actual price of the biologic or the biosimilar and so providing precise cost savings seems a little misleading.** We agree that biosimilar discounts vary, and that 25% is likely a low threshold for estimating potential cost implications. For this reason, our primary analysis did not use this threshold, but instead used the established cost reductions listed publicly by the Ontario Public Drug Program (Table 1; adjustment factors). We determined the thresholds of 25% and 50% of innovator cost following consultation with the pan-Canadian Pharmaceutical Alliance and policy-makers within the Ontario Ministry of Health who suggested that these two thresholds would provide them with guidance relevant for the policy discussions and price negotiations underway. We have expanded upon this in the limitations section of our manuscript. **Revised Text (Limitations; pg 10):** *Finally, 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. Therefore, we determined two 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 undertaken by public drug programs in Canada.* **5. The secondary analysis of insulin glargine is not fully described, likely due to space limitations. For example the setting states "We conducted a cross-sectional time series analysis of Ontarians dispensed a publicly-funded prescription for infliximab, etanercept, or adalimumab to manage rheumatic conditions or IBD between January 1, 2018 and June 30, 20". And so would suggest it is removed or properly included in all aspects of the paper.** We thank the reviewer for raising this important point. We struggled with the best way to present this analysis as the main elements of the manuscript focus on biologics indicated for RA and IBD; however because the British Columbia biosimilar policy was also applied to insulin, we felt it important to include this biologic in a secondary analysis to highlight its potential impact if implemented in Ontario. To aid the reader in understanding the full scope of our work, we have updated the Setting section of our manuscript to highlight early the inclusion of insulin glargine in our analysis.

	Revised Text (Methods; Setting; pg 4): *We conducted a cross-sectional time series analysis of Ontarians dispensed a publicly-funded prescription for infliximab, etanercept, or adalimumab to manage rheumatic conditions or IBD between January 1, 2018 and December 31, 2019. In a sensitivity analysis, this was expanded to include Ontarians dispensed insulin glargine over the same study period. Data were analyzed monthly and projected forward to forecast utilization up to December 31, 2020.* **6. There are a number of assumptions about how each of these policies will actually play out. There is likely to be ways for doctors to override mandatory switches, there could be channeling to drugs without a biosimilar. Some preliminary data from Europe and BC could inform this. Moreover, a nocebo effect could cause early withdrawal from biosimilar (particularly in GI). I personally think its unlikely, but its important with modelling studies to provide both sides on assumptions.** We thank the reviewer and agree that it is challenging to anticipate the dynamics of these policies once they are introduced. As a results, we have attempted to clearly elucidate some of these potential challenges in the discussion section of the manuscript. When submitting the manuscript originally, we were similarly concerned about the potential for channeling to alternatives without biosimilars, however data from BC does not suggest this is happening. Furthermore, since submitting our paper, a biosimilar for adalimumab has been approved in Canada and listed on the Ontario public drug formulary. Therefore, there are no longer options without biosimilars into which people could be channeled. We have expanded our discussion of this in the revised manuscript. **Revised Text (Limitations; pg 9-10):** *First, in the absence of an available biosimilar for adalimumab, it would be possible that biologics prescribing could be channeled towards this product if a mandatory non-medical substitution policy was introduced. Although we are unable to estimate the cost implications of such a change in clinical practice in our models, data following a similar policy change in British Columbia suggests this did not occur.22 Furthermore, in February 2021 adalimumab biosimilars became available on the Canadian market, and in March 2021 they were added to the Ontario public drug formulary at 60% of the price of the innovator. Therefore, all available innovator biologics now have a biosimilar available, thus reducing the potential for channeling.* **Relevant Text (Contextualizing Factors; pg 10-11):** *For example, although biosimilars have been shown to be effective and safe,23 there is a concern by some clinicians that substituting treatment for patients already stable on one therapy could cause anxiety among patients who are experiencing benefit from their current medication and could destabilize their condition, which could impact both patient outcomes and incur costs to the healthcare system. This concern appears to be greater for IBD patients due to concerns about destabilization of their condition and the more limited number of biologic options.13,24*
Reviewer 4	Bookman, Arthur
Institution	Toronto Western Hospital, Division of Rheumatology, Department of Medicine

Reviewer comments and author response	**Reviewer: 4** **Comments to the Author** **1. This is an important paper that is bound to affect government policy. There is the main concern that the authors do not have access to the government negotiated cost for purchase of innovator drug in Ontario, hence the cost savings could be highly overestimated. The paper is well written and the calculations are carefully considered, as are the caveats for making these calculations without the existence of a biosimilar for adalimumab. These cost estimates have been done before, and the savings have been considered by CADTH. As the authors point out, we cannot know the true savings until we get on with mandatory substitutions for ALL users, (not just initiators).** We thank the reviewer for their supportive comments, and agree with the limitations they have identified. We believe that our revised manuscript clearly outlines these limitations and the contributions of this work to the literature in this field.