**Author’s response to reviews**

**Title:** Impact of a direct-to-consumer information campaign on prescription patterns for overactive bladder

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Dr. Fabrizio Tediosi

BMC Health Services Research

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Dear Dr. Fabrizio Tediosi,

Ms. Ref. No.: BHSR-D-17-00935R1

Title: Impact of a direct-to-consumer information campaign on prescription patterns for overactive bladder
Please find attached a revised version of our manuscript titled "Impact of a direct-to-consumer information campaign on prescription patterns for overactive bladder" which we would like to resubmit for publication in BMC Health Services Research.

Your comments and those of the reviewers were highly insightful and enabled us to improve the quality of our manuscript significantly. In the following pages are our point-by-point responses to each of the comments of the reviewers.

Revisions in the text are tracked and underlined. In accordance with the suggestion of Reviewer 1, we added further explanations and relevant references for the delayed lag for the first-time prescription increase. We also corrected some inappropriate explanations in the text and removed some inappropriate results. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC Health Services Research.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Reviewer 1

The authors have extensively addressed the questions raised during the first review round. They decided to include an interrupted time series analysis on new endpoints (number of new diagnosis and number of newly diagnosed patients treated with medication from the cohort of the whole JMDC (during a limited period of time), as suggested.

Thank you.

#1. I still do have a number of questions, mainly related to the methodology and the conclusions drawn: The authors justify the delay they see in the effect of the original analysis by explaining that the average interval of clinic visits is 3 months for overactive bladder patients. However, one would assume that patients are evenly distributed over these intervals around time of the intervention. Indeed some patients may just have visited the physician before the intervention and any effect on their treatment will indeed take 3 months. But other patients are at the end of their 3-months interval and will visit the physician the day after the event. So I still have difficulties to really understand what causes the delay and therefore be sure that what we see is an effect of the intervention.

Thank you. Our cohort comprised patients who were diagnosed with overactive bladder before May 2010: i.e., at least 1.5 years before the start of the DTCI campaign in November 2011. Also, these patients did not receive any prescription for overactive bladder during the 1.5 years (from May 2010 to November 2011) prior to the start of the DTCI campaign. Therefore, we examined
the increase of the first-time prescription rate after the DTCI campaign among those who did not visit clinics regularly and those who visited clinics regularly but did not receive prescriptions for overactive bladder.

Under the most standard clinical guidelines for overactive bladder in Japan (The Japanese Continence Society 2015), it usually takes three months to prescribe a treatment drug for overactive bladder that is the "Step 4" in the guidelines. Namely, once a patient is diagnosed as overactive bladder, the patient first has to complete the following three steps: (Step 1) screening of other possible underlying diseases (e.g., cancer, infection, and urinary stones); (Step 2) fluid intakes (i.e., voiding diary) assessment; and (Step 3) physical treatment therapy (pelvic-muscle floor training). These three steps usually take three months in a regular clinical setting in Japan (The Japanese Continence Society 2015; Burgio 2013). Thus, even when a patient (previously diagnosed as overactive bladder but without a past prescription history prior to the DTCI campaign) returned to a clinic after being exposed to the DTCI campaign, a physician did not immediately prescribe a treatment drug (Step 4 under the guidelines) without completing the first three steps illustrated above.

Therefore, our key empirical findings regarding the timing of the DTCI campaign's impact (i.e., with a time lag of 3 months or 3 Periods in Year 1 in our main individual-level Cox model analysis presented in Table 2) aligned with the expected timeline of the standard clinical practices for patients with overactive bladder in Japan (e.g., the average time to prescribe the first treatment drug being 3-month and the average visit interval being 3-month) (The Japanese Continence Society 2015; Zaitsu 2011). For instance, for the patients who did not visit clinics routinely but was motivated to return to a clinic by the DTCI campaign (implemented in Period 1 in Year 1), their earliest clinic visit timing was Period 1 (weeks 1-5) in Year 1 that allows the earliest timing of the first-time treatment drug prescriptions between late Period 3 and Period 4 (around weeks 14-18) in Year 1 because of the clinical guidelines illustrated above. For the patients who visited clinics every 3 months regularly, the first visits after DTCI exposure should range from Period 1 to Period 3 (around week 13). Then, the second visits, or the first
prescriptions after three steps recommended in the guidelines, should range from the latter half of Period 3 (around week 13) to early Period 6 (around week 26), indicating the majority of the first prescriptions should be observed in Period 4 and Period 5 in Year 1. These estimated timelines were consistent with the larger impact of the DTCI campaign during Periods 4 and 5 in Year 1 (in terms of the hazard ratio magnitude) in our main individual-level Cox model analysis, compared to that during Period 3 and Period 6 in Year 1. The observed low rate in Period 3 can also be explained by the fact that some of the patients visited clinics in early Period 1 might not have truly exposed with the DTCI campaign since it was the very early days after the launch of the campaign. Moreover, our secondary aggregated-level interrupted time-series analysis (ITSA) also support these delayed effects. Namely, the ITSA showed that the first-time prescription rate was interrupted at Period 4 in Year 1 (i.e., intercept was significantly shifted upward in a regression model (p<.05)) in Table 3, and that the time periods representing Periods 4 through 5 in Year 1 were the two highest outlier periods (and that representing Period 6 in Year 1 was the third highest point) in Figure 2.

We have added these explanations in the text, and have added the literature to the reference list, and have updated the reference number accordingly, as follows:

Methods

P9, line 12

(ORIGINAL) "We set the interrupted time point of the intervention at Period 1 in Year 1. Additionally, to assess potential time lag regarding the impact of the DTCI campaign, we performed ITSA with various interrupted time points: from Period 2 to Period 5 in Year 1 (Period 5 corresponds to a 20-week delayed time lag); because a previous study in Japan suggests that an average interval of clinic visits is three months for overactive bladder patients (Zaitsu 2011)."
We set the interrupted time point of the intervention at Period 4 in Year 1 in our primary ITSA analysis. Our primary ITSA analysis assumed a three-month potential time lag partly because an average interval of clinic visits was suggested to be three months among overactive bladder patients in Japan by a previous study (Zaitso 2011) and also partly because it usually takes up to three months for overactive bladder patients to receive the first-time treatment drug prescription when their urologists follow the Japan's clinical guidelines that recommend other clinical procedures (i.e., screening of other possible underlying diseases, fluid intakes assessment, and pelvic-muscle floor training that may take up to three months in in a regular clinical setting in Japan) prior to the prescription (The Japanese Continence Society 2015; Burgio 2013).

Additionally, to assess potential different time lag regarding the impact of the DTCI campaign, we performed sensitivity analyses of the ITSA with various interrupted time periods: from Period 1 to Period 5 in Year 1 (Period 5 corresponds to a 20-week delayed time lag) besides the primary ITSA analysis.

Discussion

P13, line 16:

Our key empirical findings regarding the timing of the DTCI campaign's impact (i.e., with a time lag of 3 months or 3 Periods in Year 1) aligned with the expected timeline of the standard clinical practices for patients with overactive bladder in Japan (e.g., the average time to prescribe the first treatment drug being 3-month and the average visit interval being 3-month) (The Japanese Continence Society 2015; Zaitso 2011). For instance, for the patients who did not visit clinics routinely but was motivated to return to a clinic by the DTCI campaign (implemented in Period 1 in Year 1), their earliest clinic visit timing was Period 1 (weeks 1-5) in Year 1 that allows the earliest timing of the first-time treatment drug prescriptions between late Period 3 and Period 4 (around weeks 14-18) in Year 1 because of the clinical guideline (The Japanese Continence Society 2015). For the patients who visited clinics
every 3 months regularly, the first visits after DTCI exposure should range between Period 1 and Period 3 (around week 13) in Year 1. Then, the second visits, or the first prescriptions after three steps recommended in the guidelines (The Japanese Continence Society 2015), should occur between the latter half of Period 3 (around week 13) and early Period 6 (around week 26) in Year 1, indicating the majority of the first prescriptions should be observed in Period 4 and Period 5 in Year 1. These estimated timelines were consistent with the larger impact of the DTCI campaign during Periods 4 and 5 in Year 1 (in terms of the hazard ratio magnitude) in our main individual-level Cox model analysis, compared to that during Period 3 and Period 6 in Year 1. Moreover, our secondary aggregated-level ITSA also support these delayed effects. Namely, the ITSA showed that the first-time prescription rate was interrupted at Period 4 in Year 1 (i.e., intercept was significantly shifted upward in a regression model [p-value < .05]), and that the time periods representing Periods 4 through 5 in Year 1 were the two highest outlier periods (and that representing Period 6 in Year 1 was the third highest point)."

Endnote:


Similar: I do not understand why the authors used various interrupted time points. The choice to also present P4 as time of the event seems to be data driven, not driven by the point in time of the intervention.

Thank you. The choice of Period 4 is not data-driven. To address your concern, we revised the main text to clarify that we assumed that the earliest increase of the first-time prescription rate will be observed in Period 4 in Year 1 (corresponding to the period 3-months after the DTCI-campaign) due to two distinct clinical practice patterns in Japan, i.e., post-diagnosis clinical procedures (taking three months) prior to the first-time drug prescription and a the average clinical visit interval being three months (The Japanese Continence Society 2015; Burgio 2013; Zaitsu 2011) detailed in our response to your question #1 earlier. Our assumption about the three-month time lag of the DTCI campaign was confirmed by the main individual-level Cox model analysis indicating the earliest increase (of the first-time prescription rate) during Period 4 and the persistent increase (compared to the reference period prior to the DTCI campaign) up to Period 6 in Year 1 (Table 2).

The aggregated-level ITSA analysis also supported the earliest increase (of the first-time prescription rate) during Period 4, but did not indicate the continuing increase after Period 4 as observed in the Cox model analysis.

To clarify our modeling procedures, we revised the main manuscript as follows:

P9, line 12:

(ORIGINAL) "We set the interrupted time point of the intervention at Period 1 in Year 1. Additionally, to assess potential time lag regarding the impact of the DTCI campaign, we performed ITSA with various interrupted time points: from Period 2 to Period 5 in Year 1 (Period 5 corresponds to a 20-week delayed time lag); because a previous study in Japan
suggests that an average interval of clinic visits is three months for overactive bladder patients (Zaitsu 2011)."

(REVISED: Revised parts were underlined)

"We set the interrupted time point of the intervention at Period 4 in Year 1 in our primary ITSA analysis. Our primary ITSA analysis assumed a three-month potential time lag partly because an average interval of clinic visits was suggested to be three months among overactive bladder patients in Japan by a previous study (Zaitsu 2011) and also partly because it usually takes up to three months for overactive bladder patients to receive the first-time time treatment drug prescription when their urologists follow the Japan's clinical guidelines that recommend other clinical procedures (i.e., screening of other possible underlying diseases, fluid intakes assessment, and pelvic-muscle floor training that may take up to three months in in a regular clinical setting in Japan) prior to the prescription (The Japanese Continence Society 2015; Burgio 2013).

Additionally, to assess potential different time lag regarding the impact of the DTCI campaign, we performed sensitivity analyses of the ITSA with various interrupted time periods: from Period 1 to Period 5 in Year 1 (Period 5 corresponds to a 20-week delayed time lag) besides the primary ITSA analysis."

Endnote:


#3. Page 8, line 17: N=30 is unclear. 30 what? Similarly, what does N=25 mean on page 9, line 25.

Thank you. We meant the number of analyzed time periods. The analyzed population differed between main ITSA model (a cohort of overactive bladder patients) and supplementary ITSA model (the whole cohort of Japan Medical Data Center regardless of overactive bladder). We have clarified and distinguished these two analyzed time periods in the text, as well as footnotes of Table 3 and Supplementary Table 1 as follows:

P9, line 10:

(ORIGINAL) "(N = 30)"

(REVISED: Revised parts were underlined) "(N1 of analyzed time periods = 30)"

P10, line 18:

(ORIGINAL) "(N = 25)"

(REVISED: Revised parts were underlined) "(N2 of analyzed time periods = 25)"

Table 3, footnote:

(Original) "Sample size, N = 30."
"Sample size, N of analyzed time periods = 30. The aggregated data samples were extracted from 1,332 patients who were diagnosed with overactive bladder before May 2010 and who had not been prescribed a treatment drug during May 2010 to November 2010."

Supplementary Table 1, footnote:

(Original) "Sample size, N = 25."

(Revised: Revised parts were underlined) "Sample size, N2 of analyzed time periods = 25. The aggregated data samples were extracted from 795,370 enrollees covered by the Japan Medical Data Center from November 2010 to November 2012."

#4. Fig 2a +b: There seems to be a strange outlier in both graphs around P5 in year 1. Any idea why? How does this influence the results?

Thank you. In the original Figure 2's a and b, the highest outlier represents Period 5 in Year 1 that did not affect our overall conclusion. This was because our ITSA analyses (including its sensitivity analyses) indicated that only one ITSA model interrupted at Period 4 showed a statistically significant increase in the first-time prescription rate (Table 3). This increase during Period 4 in the ITSA analysis was consistent with the main Cox analysis, confirming our assumption of the three-month time-lag regarding the DTCI campaign's impact on the first-time prescription rate.

To address your point, we have added an explanation in the last part of the original discussion in Page 14, paragraph 2 as follows. Please note that the revised manuscript switched a and b in Figure 2, since our revised primary ITSA model assumed a three-month time lag:
"Although P5 in Year 1 (during March to April) seems to be an outlier, we did not observe a significant level change at P5 in Year 1 in ITSA as shown in the Results section and Table 3. Therefore, including P5 in Year 1 in the analysis does not influence the conclusion."

Endnote:
