Author's response to reviews

Title: Nation-scale adoption of new medicines by doctors: an application of the Bass diffusion model

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Author's response to reviews: see over
Dear Dr Jigasha Patel,

Please accept the revision of our submission, titled "Nation-scale adoption of new medicines by doctors: an application of the Bass diffusion model", prepared as a research article for BMC Health Services Research. We have modified the manuscript according to the two referees’ comments and suggestions. The files attached include a revised manuscript, a highlighted version of the manuscript indicating where significant changes have been made, and an additional file with a new table replacing a figure.

Our response to the referees is attached as part of this document.

My co-authors include international experts in the areas of health informatics (Prof. Enrico Coiera, UNSW), patient safety (Prof. Bill Runciman), pharmacology and drug information (Prof. Ric Day, UNSW), and health services organisational research (Prof. Jeffrey Braithwaite). We hope that our work will make a valuable contribution to BMC Health Services Research.

Kind regards,

Adam Dunn
Response to Referees:
“Nation-scale adoption of new medicines by doctors: an application of the Bass diffusion model”

We thank the editors and referees for the thorough and useful reviews. What follows are our responses to the referees’ comments in order, and references to the corresponding changes. Page numbering relates to the highlighted version of the revised manuscript. Paragraph numbering starts from the first new paragraph on each page.

Referee 1:

“The paper presents a study that examined the adoption of innovative medicines in the Australian prescription market by using a bass diffusion model. It is here made a very interesting question and scientifically handled adequately. Yet I can not agree to publication of the present manuscript, unfortunately, and would ask for an urgent revision of the recommendations listed below. Major Compulsory Revision: 1. The background is represented in proportion to the whole article at great length. This applies especially to the basics of bass diffusion model, which will be provided to the interested reader as an existing knowledge or can be looked up in appropriate sources.”

We have modified the manuscript to reduce the length of the background section, particularly for the sections in which the Bass diffusion model is described – instead pointing the readers to the appropriate literature. (Pages 3, Paragraph 1, 2 and 3; Page 4, Paragraph 1 and 2)

“2. The same applies to the Conclusion that should be more concise and should make no reference to sources.”

We have modified the manuscript to reduce the length of the Conclusion, and removed the two references that were originally included. (Page 8, Paragraphs 3; Page 9, Paragraph 1)

“3. On page 5 is already referred to social networks, although later in the text, this is accomplished. The order should be changed here and the reference “see below” omitted. This would also avoid the two-time insertion of the reference Iyengar, van den Bulte and Valente.”

We have modified the order and removed the insertion of the reference to Iyengar et al. during the process of reducing the length of this section. (Pages 3, Paragraph 1, 2 and 3; Page 4, Paragraph 1 and 2)

“The individual chapters are not clearly separated from each other in content. For example, methods already included in results. Similarly, a detailed description of statins is not part of the study design. In results, however, the results are not presented purely factual, but discussed and placed in the overall context. The conclusion contains parts that are more suitable for discussion. This total should again be revised.”

We have modified the structure of the manuscript to more clearly delineate between background, methods, results and discussion, and place them in the order required by the journal. (Throughout)

“The Figure 3 is in very poor quality. It is unclear, contains too much information. The reader is overwhelmed with it.”

We have replaced Figure 3 with Table 1 in order to address the clarity and present the information in a standard way. (Figure 3 -> Table 1 in a separate file)
“**Minor Essential Revision:** 6. There is no source indicated on Figure 1. Was the figure created by the authors, based on what data?”

Figure 1 was created by the authors and uses values for p and q in the Bass diffusion model that are within the typical range of values found in empirical studies such as those examined by van den Bulte and Stremersch (reference below), to provide an example of the two types of forces that direct the adoption of a new product or service. We have not modified Figure 1 but we have modified the explanation of the figure to assure readers of the provenance of the figure. (Page 16, Figure Caption 1).


“7. In the title of Figure 2 occurs twice in.”

We have removed the title from figure. (Figure 2)

“8. The order of the manuscript is not right. According to the Guidelines for the authors: conclusion prior methods.”

We have modified the structure of the paper to conform to the journal standard, which is Background, Methods, Results and discussion, Conclusions. (Throughout)

**Referee 2:**

“**Minor Essential Revisions.** First line page 4: 90 months: is it correct?”

The article, Birkett and McManus [26] (see manuscript) states the range of 4.5 to 90 years to reach 50% of maximum utilisation – these are predicted from the model employed by Birkett and McManus. The discussion of the results found by Birkett and McManus have now been removed to avoid confusion. (Page 3, Paragraph 3)

“Second sentence last paragraph: Why does the sentence starts by “However?” It does not seem to be an opposition between evidence in first and second sentence of the paragraph?”

We have modified this paragraph during the process of reducing the length of background and this sentence no longer appears in the revised manuscript.

“**“Seminal work of Coleman” repetition with first paragraph on page 3.”**

We have avoided repetition of this phrase by re-writing the background to be more succinct. (Page 3, Paragraph 1)

“First paragraph on page 3: you stated only sporadic evidence following Coleman’s work but you give many following references on page 3.

Coleman and colleagues’ work was undertaken in the late 1950s and published in the early 1960s. In the fifty years since, work in the area has been sporadic and isolated, and we discovered thirteen examples of disparate but related work (about one article every four years). Moreover, the references discussed in this section do not cite each other, which highlights the disconnected nature of the research stream. We have modified the Background substantially, which should avoid confusion. (Pages 3, Paragraph 1, 2 and 3; Page 4, Paragraph 1 and 2)
“Major Essential Revisions.

Methods.
The methods are incomplete. I don’t understand how you calculated the p and q values in the model. No information is given on the statistical methods used and on the type of comparisons that are done.”

We have modified the manuscript to include the information suggested, including descriptions of the method for determining values for p and q that best fit the data, and the non-parametric test used to test the hypothesis that the two groups of drugs differ in their rate of adoption. (Page 5, Paragraphs 2 and 3)

“No information is given on the methods used to collect data that have helped you interpret the results of the modeling (eg relative effectiveness of drugs). No information is given on what are the methods used to conduct a “more detailed examination” of statins compared to other drugs.”

We deliberately avoided discussing the effectiveness (and safety) of drugs for the main group because the quality of evidence varies considerably across groups, so the confidence of any comparison would be greatly affected. We have modified the manuscript to clarify the use of the term “more detailed examination”, and modified the manuscript to avoid problematic discussions around the quality use of antihyperlipidemics. (Page 6, Paragraph 1; Page 7, Paragraph 1; Figure 3)

“Last paragraph page 9/ first paragraph page 10: the model does not account for the fact that drugs can be severely restricted or withdrawn after marketing, and that they have a different safety and efficacy profile. These are serious limitations of the model that should be discussed in the discussion and raise the question of why such the use of such a model could be envisaged in the first place. Moreover, drugs may be first in the class or me-toos and this characteristic is not taken into account in the model although it is highly likely to influence the diffusion rate.”

Referee 2 suggests limitations with the model that we agree with, however we respectfully disagree with the sentiment that the model should not have been used in the first place.

Referee 2 suggests that adoption rates may be partially correlated with the best available comparative effectiveness information, and the presence of competition. Other confounders may subsume this association. For example, evidence against the appearance of a difference between first in class and me-too drugs is provided by Cohen (reference below), who found no general pattern in this regard – more simply, drugs that were pioneers were adopted both faster and more slowly than their me-too counterparts, depending on the drug class.


We have modified the discussion to include the limitations described by Referee 2, and more accurately represent the value of the Bass diffusion model in the research stream aimed at understanding why there is such variety in patterns of adoption. (Page 7, Paragraph 2; Page 8, Paragraph 2)

“Results. Figure 3: no legend and no idea of how to interpret it!”

Figure 3 has been replaced by a table to make the results clearer. (Figure 3 is now Table 1)

“Figure 4: no legend, no idea of which drug is related to which curve.”
“A detailed look at statins: I suppose that many readers would jump on their chairs reading this analysis! The authors infer their statement of rosuvastatin superiority over other statins on a single reference on the risk of myopathy with high dose simvastatin (ref 54). In contrast a recent review of the 3 main trials comparing outcomes with higher and lower doses concluded “The results show that raising the dose of simvastatin or atorvastatin to 80 mg confers no mortality advantage, an increase in adverse reactions and only a slight decrease in myocardial infarctions and stroke versus a lower dose” (Spector and Snapinn 2011). To my knowledge there is no trial evidence showing that the greater potency of rosuvastatin translates into any clinically demonstrated benefit in terms of cardiovascular mortality and mortality compared to other statins. Some countries have used enormous resources to persuade prescribers to use low cost older statins instead of the newer most expensive ones as they think they do not provide any cost-effectiveness advantage. (Godman, B, Sakshaug, S, Berg C, Wettermark, B & Haycox, A 2011, ‘Combination of prescribing restrictions and policies to engineer low prices to reduce reimbursement costs’, Expert Review of Pharmacoeconomics & Outcomes Research, vol. 11, no. 1, Feb, pp. 121-129.). There is no information on the fact that rosuvastatin and atorvastatin were placed in the F1 PBS category with an important price differential compared to other off-patent statins in the F2 PBS category and that, as a consequence, these expensive drugs were heavily promoted by their respective manufacturers unlike off-patent statins.”

We have removed the sentence that states that “rosuvastatin has a higher efficacy than atorvastatin at the highest approved dose” and the sentence “the more efficacious drugs are adopted in larger numbers and more quickly.” We agree with Referee 2 that there is a lack of evidence to show that rosuvastatin is more effective or safer than all other statins with regards to cardiovascular outcomes.

The manuscript was modified to remove these claims and no longer discusses adoption rates in comparison to comparative effectiveness amongst this drug class. (Page 7, Paragraph 2)

“Discussion: It seems to be an underlying assumption that new medicines are all innovative. Confusing innovation with new seems to be the major issue in the paper. Several studies have shown that only a fraction of the new medicines are truly innovative and bring a therapeutic advantage (refs below). So a more interesting question to examine would be whether medicines with a demonstrated therapeutic advantage have a quicker adoption rate than me-tos. It does not make sense to raise a question “is adoption too low” for all new medicines, but only for the ones with a definite advantage.

References

We agree with Referee 2 that new drugs introduced into the Australian (and similarly, overseas) markets are often not safer, more effective or cheaper than the drugs that already exist to treat a given condition. We also understand that me-too drugs make up an increasingly large proportion of the market by number of drugs. We have modified the manuscript to make this clearer to potential readers, to avoid further miscommunication. (Page 5, Paragraph 1; Page 8, Paragraph 2)

“Conclusion
I don’t understand what the use of the Bass diffusion model adds to our understanding of the adoption of new
medicines by doctors. As stated earlier, its limitations and the fact that medicines are not ordinary goods but are heavily regulated goods raise doubt about the usefulness of this model for pharmaceuticals. I don’t think that the conclusion is supported by the results presented.”

The Bass diffusion model is routinely used as an indicator of the presence and proportion of endogenous and exogenous forces driving adoption and for that reason, was expected to be roughly indicative of the proportions of exogenous and endogenous forces in the adoption of medicines in Australia. In indicating the separation between exogenous and endogenous, the model suggests the relative importance of factors such as social contagion and regulation as an external force. We agree with Referee 2 that the model is not explicitly linked to the adoption of new prescribing practices by individual clinicians.

We show, in accordance with the aims, that the Bass diffusion model has limited value in explaining the causal factors in adoption (linking individual decision-making with the population-level prescription patterns) but does help us describe the range of adoption times for subsidised drugs in Australia. We have modified the discussion and conclusions to better reflect the aims, and reflecting the concerns of Referee 2 (Page 4, Paragraph 2; Page 7, Paragraph 3; Page 8, Paragraph 3).