PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Estimation of cost-based prices for injectable medicines in the WHO Essential Medicines List
AUTHORS	Gotham, Dzintars; Barber, Melissa; Hill, Andrew

VERSION 1 – REVIEW

REVIEWER	Lukas Radbruch Department of Palliative Medicine, University Hospital Bonn, Germany
REVIEW RETURNED	11-Dec-2018

GENERAL COMMENTS	The authors present a cost calculation for essential medicines and compare it with prices in the UK, South Africa and India. This is a follow-up paper on application forms for injection, as the authors have previously published on solid oral application forms. I did not find an explanation why the authors used data for API exports from India. Is this considered as the gold standard for low-cost manufacturing? In the discussion you compare percentages for current prices over estimated costs for injectable substances and later on absolute numbers for current prices over estimated costs for solid oral forms: I would have preferred if the same kind of data format would have been used so that I would be able to compare the shares for both settings. The authors state in the discussion that . As data collection for this analysis finished shortly before the publication in April 2017 of the 2017 EML, we use the second most recent iteration….” They should explain that there was no 2016 EML. No ethics board review is mentioned in the methods section. However, the authors used data publicly available and did not use any patient-related data, so ethical review would not be needed for publication. However, the authors should include information on ethical review board or why it was not presented for ethical review in the methods section. Page 4 line 21: spelling error: “Such significantly…” Page 6 line 30 and 33: FPP is used as an abbreviation but is introduced only later in the text Page 12 line 33: I did not understand the meaning of “…differences of costs individual manufacturing plants2

REVIEWER	Dr Syed Shahzad Hasan University of Huddersfield, UK
REVIEW RETURNED	24-Dec-2018

GENERAL COMMENTS	This paper can be submitted as a short/brief report

REVIEWER	Luke Vale & Vasilis Kontogiannis Newcastle University Newcastle UK
REVIEW RETURNED	22-May-2019

GENERAL COMMENTS	The authors have submitted a paper describing the process of developing an algorithm which aims to estimate the cost of manufacture for injectable medicines for which they use a similar approach to a previous paper carried out by the same authors for solid oral formulations. Given the high price of some drugs in the market, this is a very interesting topic which tries to shed light to the discrepancies found between the estimated prices using the algorithm and the actual prices currently in the market. The paper is presented in a clear and concise manner and written in a non-technical language which makes it easy to follow for a non-expert. There are some areas where some more explanation would be helpful. The paper could also benefit from more discussion of potential limitations of the work. With respect to these limitations the conclusions might be modified to reflect part of the discussion that the analysis might be appropriate as an initial exploration which may warrant a deeper exploration for specific circumstances. One general comment is that there are quite a number of abbreviations used. The clarity of the paper would be improved by removing these and writing out the term in full. The exceptions would be standard abbreviations and SI units. Noted below are further comments. These are not in order of importance but rather in terms of the order they appear in the paper. • Page 3. For the strengths and limitations four bullet points are given. It would be helpful if the authors could clarify which is a strength and which is a limitation. So is a conservative cost assumption a strength or limitation. • Methods, Page 6, line 34 " In general, we aimed to use conservative (high) assumptions in estimating the cost of production." In order to ensure clarity to readers I suggest being more explicit as the impact these assumptions have e.g. other things being equal they tend to increase the cost and hence minimise the 'excess' • Methods, Page 6, lines 39-40. For the general reader could you clarify what the distinction is between an ampoule and vial. • Page 6, line 40 to 44: The authors mention that "In some cases, the EML does not indicate whether formulation is as a vial or ampoule – for these items we assumed one or the other based on the more prevalent form found across the UK, South Africa, and India". It would be good to know for how many medicines they made assumptions for given the difference in costs between vial and ampoule. • Methods, Page 7, line 11-12 "We assumed that 10% more API is needed than the stated dosage, to account for loss of

	API in the vial/ampoule filling process and vial/ampoule overfill" This is a quite a strong assumption and probably needs some more justification. A cost conscious company would be expected to minimise this (comment based on personal communication from an engineer working with commercial weighing machines used in the manufacture of pharmaceuticals). • Methods Page 7, lines 22 to 29: The authors mention that "an analysis by IMS Health found that costs associated with import (transport, tariffs, other charges) were around 5% in most of the countries surveyed (e.g. Brazil, India, Russia), and that taxes represented around 10% of the final price". Although they increase the final margin for transportation costs to 10% they do not do the same for the margin accounting for taxation and they leave it as 10%. I would have expected an increase of 5% here. • Methods, Page 7, line 22-28. A fixed rate has been used for tax and transportation costs. As one use of the data for a reader is to draw comparisons between the countries an assumption of common mark-ups for these features may bias comparisons. Ideally, country specific data should be used, this should be possible given the limited number of countries considered. Even if it is not possible some discussion of the limitations of this assumption are needed. • Methods, Page 7, line 48. For unit prices country wide figures have been used for prices relevant to England (not I think the UK), and South Africa, but data has just been used for one state from India (Tamil Nadu). Some comment on the applicability of these data to India as a whole is warranted given the very wide variations in wealth and government between states within India. • Discussion, Page 10. The authors state "The great majority of medicines compared in this analysis are no longer under patent protection in the UK, South Africa, or India.[16]" The authors note one explanation of higher costs for these drugs which may represent diseconomies of scale. A further issue may the availability or otherwise of substitutes. This issue is worthy of some discussion. For some drugs (like some biologics) the process of producing a biosimilar agent is difficult and this may restrict market access by competitors. For other biologics like insulin, variants using other cell lines may still be protected by patent. • Discussion. The feature of companies exploiting a market position is mentioned elsewhere but the cause of this could be drawn out more. • Discussion. Some more exploration of market factors that may have caused this deviation in the estimated prices would have been useful. For example, there is little mention on competition and how the nature of the market in each country might have contributed to the high prices. What about generic drugs and what proportion of generic drugs is used in each country. If more generic drugs are used in India then this might be a reason for the low prices. • Discussion. What efforts is any have been used to validate the algorithm. The authors could useful draw distinctions between different notions of validity (both internal and external. Have the authors validated the algorithm in another dataset?

VERSION 1 – AUTHOR RESPONSE

REVIEWER #1

REVIEWER'S COMMENT:

The authors present a cost calculation for essential medicines and compare it with prices in the UK, South Africa and India. This is a follow-up paper on application forms for injection, as the authors have previously published on solid oral application forms.
I did not find an explanation why the authors used data for API exports from India. Is this considered as the gold standard for low-cost manufacturing?

AUTHORS' RESPONSE:

Thank you for this important point. Indeed, this clarification was missing. We assumed manufacturing in India both due to the fact that India is a major generics exporter, and because we have access to data on bulk prices for active pharmaceutical ingredient in India, but availability for data in other countries is limited. We have added this explanation on page 5.

REVIEWER'S COMMENT:

In the discussion you compare percentages for current prices over estimated costs for injectable substances and later on absolute numbers for current prices over estimated costs for solid oral forms: I would have preferred if the same kind of data format would have been used so that I would be able to compare the shares for both settings.

AUTHORS' RESPONSE:

If we have understood correctly the reviewer's suggestion, it was to make the absolute numbers (e.g. '214 of 277') into percentages, in the middle paragraph of page 11. We agree that this makes comparison easier and have converted into percentages.

REVIEWER'S COMMENT:

The authors state in the discussion that . As data collection for this analysis finished shortly before the publication in April 2017 of the 2017 EML, we use the second most recent iteration…." They should explain that there was no 2016 EML.

AUTHORS' RESPONSE:

Thank you – we have now clarified this in the limitations section on page 12.

REVIEWER'S COMMENT:

No ethics board review is mentioned in the methods section. However, the authors used data publicly available and did not use any patient-related data, so ethical review would not be needed for publication. However, the authors should include information on ethical review board or why it was not presented for ethical review in the methods section.

AUTHORS' RESPONSE:

This study relies exclusively on publicly available export, price, and trade data, for which ethics review was not necessary. The study did not involve human subjects or animals. We have added this note on page 8.

REVIEWER'S COMMENT:

Page 4 line 21: spelling error: "Such significantly…"

AUTHORS' RESPONSE:

Thank you – this was a typo and should have read "…such as significantly…". This is corrected on page 4.

REVIEWER'S COMMENT:

Page 6 line 30 and 33: FPP is used as an abbreviation but is introduced only later in the text fixed

AUTHORS' RESPONSE:

Thank you – this is now corrected on page 5.

REVIEWER'S COMMENT:

Page 12 line 33: I did not understand the meaning of "…differences of costs individual manufacturing plants2

AUTHORS' RESPONSE:

There was a typo in the sentence, it should have read "…differences of costs at individual manufacturing plants…". We also clarified further: costs differ at different manufacturing plants e.g. due to size of plant, location, machinery used, etc. We have added this point into the limitations section, on page 12.

REVIEWER #2

REVIEWER'S COMMENT:

This paper can be submitted as a short/brief report

AUTHORS' RESPONSE:

We agree that a short format is appropriate for this analysis. The manuscript is indeed already a relatively short paper at ~2500 words. There is no appropriate, shorter article format available at BMJ Open than the one we have selected, 'Research Paper'.

REVIEWER #3

REVIEWER'S COMMENT:

The authors have submitted a paper describing the process of developing an algorithm which aims to estimate the cost of manufacture for injectable medicines for which they use a similar approach to a

previous paper carried out by the same authors for solid oral formulations.
Given the high price of some drugs in the market, this is a very interesting topic which tries to shed light to the discrepancies found between the estimated prices using the algorithm and the actual prices currently in the market.
The paper is presented in a clear and concise manner and written in a non-technical language which makes it easy to follow for a non-expert. There are some areas where some more explanation would be helpful. The paper could also benefit from more discussion of potential limitations of the work. With respect to these limitations the conclusions might be modified to reflect part of the discussion that the analysis might be appropriate as an initial exploration which may warrant a deeper exploration for specific circumstances.

AUTHORS' RESPONSE:

Thank you – indeed it is important to emphasise that more detailed studies could (should) be undertaken for individual medicines or medicine groups. We had mentioned this in the original draft but have now made it more explicit, see page 12 in the Discussion.

REVIEWER'S COMMENT:

One general comment is that there are quite a number of abbreviations used. The clarity of the paper would be improved by removing these and writing out the term in full.

AUTHORS' RESPONSE:

Thank you – we have removed the abbreviations 'API', 'FPP', and 'SOF' and used full terms in all instances.

REVIEWER'S COMMENT:

• Page 3. For the strengths and limitations four bullet points are given. It would be helpful if the authors could clarify which is a strength and which is a limitation. So is a conservative cost assumption a strength or limitation.

AUTHORS' RESPONSE:

Thank you – we have added this in parentheses for each strength/limitation in the summary part, on page 3. Conservative cost assumptions could be seen as both a strength and a limitation: A strength because it decreases the risk that we are overestimating differences between current prices and estimated cost of production, but a limitation because we may be underestimating these differences. On balance, we consider it a strength of the study, as there is more emphasis on identifying cases where current lowest prices are significant ABOVE estimated cost of production, rather than cases that are significantly BELOW estimated cost of production.

REVIEWER'S COMMENT:

• Methods, Page 6, line 34 " In general, we aimed to use conservative (high) assumptions in estimating the cost of production." In order to ensure clarity to readers I suggest being more explicit as the impact these assumptions have e.g. other things being equal they tend to increase the cost and hence minimise the 'excess'

AUTHORS' RESPONSE:

Thank you – we have now clarified this at the bottom of page 6.

REVIEWER'S COMMENT:

• Methods, Page 6, lines 39-40. For the general reader could you clarify what the distinction is between an ampoule and vial.

AUTHORS' RESPONSE:

Thank you – we have clarified this on page 7. Ampoules are sealed glass containers, while vials generally have a removable cap.

REVIEWER'S COMMENT:

• Page 6, line 40 to 44: The authors mention that "In some cases, the EML does not indicate whether formulation is as a vial or ampoule – for these items we assumed one or the other based on the more prevalent form found across the UK, South Africa, and India". It would be good to know for how many medicines they made assumptions for given the difference in costs between vial and ampoule.

AUTHORS' RESPONSE:

Thank you – we have added this on page 7. Assumptions on whether the medicine is formulated as a vial or ampoule were made for 23% of items.

REVIEWER'S COMMENT:

• Methods, Page 7, line 11-12 "We assumed that 10% more API is needed than the stated dosage,

REVIEWER'S COMMENT:
to account for loss of API in the vial/ampoule filling process and vial/ampoule overfill" This is a quite a strong assumption and probably needs some more justification. A cost conscious company would be expected to minimise this (comment based on personal communication from an engineer working with commercial weighing machines used in the manufacture of pharmaceuticals).

AUTHORS' RESPONSE:

This margin of 10% accounts for both wastage during the filling process, and for overfill. (Overfill is where manufacturers fill the ampoule/vial with more than the labelled volume to enable the administrator to withdraw the labelled volume, as some volume will inevitably remain on the inside walls of the container, etc.). The United States Pharmacopoeia recommends, for example, 20-24% overfill for 0.5mL injectable containers, decreasing to 3-4% overfill for 30mL injectable containers.* As the container volumes of various EML items vary, we needed to choose a reasonable middle value.

*See https://www.drugfuture.com/pharmacopoeia/usp35/PDF/0765-0784%20%5b1151%5d%20Pharmaceutical%20Dosage%20Forms.pdf

REVIEWER'S COMMENT:

• Methods Page 7, lines 22 to 29: The authors mention that “an analysis by IMS Health found that costs associated with import (transport, tariffs, other charges) were around 5% in most of the countries surveyed (e.g. Brazil, India, Russia), and that taxes represented around 10% of the final price”. Although they increase the final margin for transportation costs to 10% they do not do the same for the margin accounting for taxation and they leave it as 10%. I would have expected an increase of 5% here.

AUTHORS’ RESPONSE:

We are grateful to the reviewer for highlighting this important point. On the one hand, the price of medicines with the locally applicable taxes is indeed the ‘real’ price borne by the buyer. On the other hand, for the purposes of comparing prices to estimated cost-based prices, upon reflection, we felt that it would be better to standardize tax rates to 0% across countries.

South African prices cited in the original submission included 15% value-added tax. Indian prices included 5% VAT. In order to standardize across countries, we adjusted these price data to a 0% VAT value. These adjustments had knock-on effects meaning most figures involving South African and Indian prices have changed slightly in the manuscript. We added a note in Methods on this adjustment to remove VAT (page 8). UK prices do not include VAT.

REVIEWER’S COMMENT:

• Methods, Page 7, line 22-28. A fixed rate has been used for tax and transportation costs. As one use of the data for a reader is to draw comparisons between the countries an assumption of common mark-ups for these features may bias comparisons. Ideally, country specific data should be used, this should be possible given the limited number of countries considered. Even if it is not possible some discussion of the limitations of this assumption are needed.

AUTHORS’ RESPONSE:

Thank you – as discussed in response to a different comment, above, we have adjusted calculations to remove the tax margin. For transportation costs, we consider country-specific assumptions not to be feasible, as there is not an official, specific margin that can be ascribed to medicines in each country (as there is with VAT for example), and data is very limited – even the cited IMS analysis only gives very rough figures, and does not provide details on how these figures were derived. Transportation costs will of course depend on the specific seller, distance, volume, mode of transport, and so on. We therefore prefer to use a single ‘one size fits all assumption’, and be clear about this as a limitation. This is discussed in the limitations section: “The main limitation of our analysis is that our estimates do not account for differences of costs across individual manufacturing plants due to heterogeneity in, for example, location, machinery used, and capacity, as well as different distribution costs (including tariffs) depending on the country of manufacture and the importing country, and changes in conversion cost depending on the volume of the unit. As argued above, this limitation would not preclude the use of a methodology such as this one to identify medicines that may have high profit margins, for closer ad hoc analysis.”

REVIEWER’S COMMENT:

• Methods, Page 7, line 48. For unit prices country wide figures have been used for prices relevant to England (not I think the UK), and South Africa, but data has just been used for one state from India (Tamil Nadu). Some comment on the applicability of these data to India as a whole is warranted given the very wide variations in wealth and government between states within India.

AUTHORS' RESPONSE:

It is not completely clear to the authors whether BNF indicative prices in fact cover only England or an average including, for example, Scotland.* We contacted the publishers to clarify this point but have not received a reply in time for submission of revised manuscript.

We agree with the reviewer that it is safer to change 'UK' to 'England' throughout, which we have done.

* http://services2.ascribe.com:8080/bnf/view/page/bnf/PHP39-prices-in-the-bnf.htm

We used two price sources for India – MedGuideIndia, which lists maximum retail prices (private market), and the Tamil Nadu tender database – choosing the lowest across the two. The maximum retail price is a nationally applicable value. About half of the prices cited were from one database, and half from the other (see full results table in appendix). The only Indian state tender data that we have been able to find is that for Tamil Nadu.

We noted this briefly in the original submission, but have now expanded and emphasised, on page 12: "Lastly, Indian prices were collected from two databases – one representing the private market and one representing Tamil Nadu state tenders (the lower price of the two was recorded). State tender prices are likely lower than private market prices, but the majority of health expenditures in India are out-of-pocket, and of these the majority are on medicines.[20] In addition, there are wide variations in wealth and access to health insurance between Indian states. The methodological approach of seeking the lowest available price in each country means that the price faced by patients when paying out-of-pocket in the private market may be considerably higher."

REVIEWER'S COMMENT:

• Discussion, Page 10. The authors state "The great majority of medicines compared in this analysis are no longer under patent protection in the UK, South Africa, or India.[16]" The authors note one explanation of higher costs for these drugs which may represent diseconomies of scale. A further issue may the availability or otherwise of substitutes. This issue is worthy of some discussion. For some drugs (like some biologics) the process of producing a biosimilar agent is difficult and this may restrict market access by competitors. For other biologics like insulin, variants using other cell lines may still be protected by patent.

AUTHORS' RESPONSE:

Thank you – none of the medicines included are widely protected by patent, to our knowledge. The reviewer's point regarding biologics is valid – we have now mentioned this in the Discussion, on page 12.

Regarding insulin – only human insulin is listed in the EML (and therefore included in the study), not insulin analogues. Human insulin is not believed to be covered by patents,* though other manufacturing and regulatory challenges remain.

*See
1. Luo J, Kesselheim AS. Evolution of insulin patents and market exclusivities in the USA. The Lancet Diabetes & Endocrinology 2015; 3: 835–837.
2. Kaplan WA, Beall RF. The global intellectual property ecosystem for insulin and its public health implications: an observational study. Journal of Pharmaceutical Policy and Practice 2017; 10: 3.

• Discussion. The feature of companies exploiting a market position is mentioned elsewhere but the cause of this could be drawn out more.

AUTHORS' RESPONSE:

We have now mentioned this important potential explanation for high prices in the Discussion on page 11.

REVIEWER'S COMMENT:

• Discussion. Some more exploration of market factors that may have caused this deviation in the estimated prices would have been useful. For example, there is little mention on competition and how the nature of the market in each country might have contributed to the high prices. What about generic drugs and what proportion of generic drugs is used in each country. If more generic drugs are used in India then this might be a reason for the low prices.

AUTHORS' RESPONSE:

Thank you. We consider that a detailed comparison of pharmaceutical market characteristics of the three countries is beyond the scope of the study. In addition, we did not measure the number of competitors for each item (though this may be an interesting follow-up study), so we believe we cannot draw conclusions on the relative level of competition in the three countries, which will also of course vary by product. However, we have added further notes pointing to some potential explanations of price differences, on pages 11 and 12.

• Discussion. What efforts is any have been used to validate the algorithm. The authors could useful draw distinctions between different notions of validity (both internal and external. Have the authors validated the algorithm in another dataset?

AUTHORS' RESPONSE:

Thank you – yes – there should indeed be a note on validation. We have added this note into limitations, on page 12.

VERSION 2 – REVIEW

REVIEWER	Lukas Radbruch Department of Palliative Medicine, University Hospital Bonn, Germany
REVIEW RETURNED	22-Jul-2019

GENERAL COMMENTS	The authors have considered all points of the review in their revision of the manuscript.