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ARTICLE DETAILS

| TITLE (PROVISIONAL) | Low utilization of diabetes medicines in Iran, despite their affordability (2000-2012): a time-series and benchmarking study |
| AUTHORS | Sarayani, Amir; Rashidian, Arash; Gholami, Kheirollah |

VERSION 1 - REVIEW

| REVIEWER | Majid Davari |
| Tehran University of Medical Sciences, Tehran, Iran |
| REVIEW RETURNED | 14-Jul-2014 |

GENERAL COMMENTS

The subject of the manuscript is interesting and valuable for middle income countries. The results of regression model is not presented in RESULTS section. It would be good to present and discuss them. Physician's prescribing method could be a very important cause of low utilization of diabetes medicine in Iran and the authors may need more emphasis on it.

Physician's prescribing method could be a very important cause of low utilization of diabetes medicine in Iran and the authors may need more emphasis on it.

| REVIEWER | Richard Laing |
| Professor International Health |
| Boston University School of Public Health, |
| REVIEW RETURNED | 22-Jul-2014 |

GENERAL COMMENTS

Some English grammatical errors need to edited out. Overall a useful paper that will serve as a model for such a study to be repeated in all countries where such data exists. I think the conclusion of the abstract that the utilization of diabetes medicines was low is overstating the result. In a mixed environment such as Iran I would not think that 54% utilization was low. With many people living in rural areas compared to the OECD reference countries I think modifying the statement to relatively low would be reasonable. I am concerned that the term "with WHO recommendations" and "using WHO methodology" are used without clarifying which recommendations or methods are being referred to. In the introduction a single figure of diabetes prevalence of 8.7% in 2007. But the paper is about utilization between 2000 and 2013. What other information is there about rates over this time. Under methods the total retail price is reported as a variable collected from the Iran FDO database. I wonder if there is any information or validation whether this is a real
price or just a list price. In many countries the list price may bear little relation to the actual price or even the reimbursement price. Also this price is not the price charged to most of the patients as they only pay a copayment of about 30% for outpatient care. Or is the price quoted taking this co payment aspect into account. I wonder if the population data was only available in national aggregate figures or if the data could be disaggregated in such a way that regional consumption could be calculated. What software was used to calculate regression models? Reference 21 refers to a method not a WHO recommendation. Please clarify.

In the section on evaluating affordability the authors quote the Cameron et al article (24) that uses the daily wage of the lowest paid government worker to determine affordability. Only later on this page is an explanation used that the official minimum daily wage defined by the Social security Organization of Iran was used. This paragraph should be moved up to be part of the first paragraph of this section. The decision to use this metric rather than the Lowest Paid Government worker should at least be discussed. It makes this paper less comparable. In other countries these minimum wages may be unrelated to the realities of life in those countries and are often subject to political manipulation. That is why the Lowest Paid Government worker measure was used in the WHO/HAI manual.

On page 11 line 42 the sentence should read Nevertheless, the annual per capitaA10 utilization in Iran was consistently and substantially lower than those five countries during the benchmarking period (Fig. 4). On line 53 the text should read approximately half a minimum daily wage in 2012.

On page 12 it is not clear if the results only applies to insulin alone or takes into account the cost of syringes especially as some of these products come in pen syringes as the only dosage forms. Again daily wages should be reported as minimum daily wages.

In the discussion on page 13 there is no mention of other costs such as syringes or diagnostics being a barrier to utilization.

The sentence “Metformin use increased significantly during the study period; however, off-label uses including weight loss or polycystic ovary syndrome may result in overestimation of diabetes-related utilization but their contribution seems to be small” is confusing. What is the evidence for this statement? Are there referenced papers making this case? If not I would leave it out.

With regard to the references I am surprised that there was no reference to the important work done by David Beran on barriers to access to insulin. See articles at http://www.who.int/medicines/areas/policy/access_noncommunicable/ncd_med/en/index1.html

This is a good paper worthy of publication if the minor comments I have made are addressed.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer Name: Majid Davari
Reviewer’s comment: The subject of the manuscript is interesting and valuable for middle income countries.
Authors’ reply: Thanks for you encouraging comment.

Reviewer’s comment: The results of regression model is not presented in RESULTS section. It would be good to present and discuss them.
Authors’ reply: The ‘Add trend line’ tool in the Excel software was used to investigate trend of drug utilization over time. Exponential model revealed the highest R2 coefficients in A10, A10A, and A10B groups. The methods and results sections are modified accordingly.

Reviewer’s comment: Physician’s prescribing method could be a very important cause of low utilization of diabetes medicine in Iran and the Authors’ reply may need more emphasis on it.
Authors’ reply: We found few article on the quality of physicians’ diabetes management and
prescribing habits. However, the studies are cited in the discussion (references 29-31). The knowledge gap is also emphasized in the discussion.

Reviewer Name: Richard Laing

Reviewer’s comment: Some English grammatical errors need to edited out. Overall, a useful paper that will serve as a model for such a study to be repeated in all countries where such data exists.

Authors’ reply: We proof read the manuscript again to resolve language errors. Thanks for your encouraging comment about the paper.

Reviewer’s comment: I think the conclusion of the abstract that the utilization of diabetes medicines was low is overstating the result. In a mixed environment such as Iran I would not think that 54% utilization was low. With many people living in rural areas compared to the OECD reference countries I think modifying the statement to relatively low would be reasonable.

Authors’ reply: The proportion of people in Iran living in rural areas is smaller than what observed in many middle-income countries (28% in the last Census – 2011). Still we agree with the reviewer about the diversity of the population and health care access in Iran. We tried to find reliable utilization data for diabetes medicines in low and middle income countries but we were not successful. Hopefully, this study will serve as a basis for similar publications from LMIC countries. The term ‘relatively low’, as suggested by the reviewer, will be more appropriate in comparison to OECD countries, and we revised the text accordingly.

Reviewer’s comment: I am concerned that the term "with WHO recommendations” and "using WHO methodology” are used without clarifying which recommendations or methods are being referred to.

Authors’ reply: We modified the sentences in the abstract to resolve the ambiguities.

Reviewer’s comment: In the introduction a single figure of diabetes prevalence of 8.7% in 2007. But the paper is about utilization between 2000 and 2013. What other information is there about rates over this time.

Authors’ reply: Two references are added to this section in order to provide a clearer picture of diabetes burden in Iran during the study period.

Reviewer’s comment: Under methods the total retail price is reported as a variable collected from the Iran FDO database. I wonder if there is any information or validation whether this is a real price or just a list price. In many countries the list price may bear little relation to the actual price or even the reimbursement price. Also this price is not the price charged to most of the patients as they only pay a copayment of about 30% for outpatient care. Or is the price quoted taking this copayment aspect into account.

Authors’ reply: The price listed in the FDO database is based on the ‘retail price’ approved by the ‘Pricing Committee’ of the FDO. This price is printed on the medication box of locally produced pharmaceuticals, and is enforced in the country for all medicines. The prices charged by pharmacies are monitored by the. We are aware that in some low or middle income countries the actual prices of the pharmaceutical may greatly differ from the list prices. However this is not a concern in Iran. We compared our results with the available data from a survey in Iran (2007) on price and affordability of a group of medicines (http://www.haiweb.org/MedPriceDatabase). Glibenclamide, gliclazide and metformin prices were reported to be similar in the public and private sectors which could be an evidence of highly regulated prices in Iran. The cost of monthly treatment for the aforementioned medications in 2007 was comparable with our findings based on the DDD-based cost of treatment
In the present study, we did not focus on the effect of insurance coverage on the affordability as mentioned in the discussion section. If it had been included in the analysis, (formal co-payment of 30% for the insured – in practice people may pay from 40-60% of the total prescribing costs due to different surcharges and fees), we would have expected to observe a higher affordability of medications covered by insurance plans. As this did not affect the study findings and conclusion, it was not considered in the analyses and was referred to in the discussion section of the manuscript as noted above. Also please note that a valid inclusion of this factor in the analysis would have required primary data collection – because of the various fees and surcharges that affect the final paid amounts by the users - which was outside the scope of this study.

Reviewer’s comment: I wonder if the population data was only available in national aggregate figures or if the data could be disaggregated in such a way that regional consumption could be calculated.

Authors’ reply: This is an interesting additional inquiry that should be the focus of future studies, especially as to the best of our knowledge, our paper is among the first papers that have conducted such analyses in a low- or middle-income country.

Reviewer’s comment: What software was used to calculate regression models?

Authors’ reply: The ‘Add trend line’ tool in the Excel software was used to investigate trend of drug utilization over time. Exponential model revealed the highest R2 coefficients in A10, A10A, and A10B groups. The methods and results sections are modified.

Reviewer’s comment: Reference 21 refers to a method not a WHO recommendation. Please clarify.

Authors’ reply: This paragraph is modified to address the reviewer’s concern. The DU-90 is the method used to extract highly consumed medicines and the ‘Essential Medicines’ list was the reference to see the pattern of pharmaceutical market regarding essential and non-essential diabetes medicines.

Reviewer’s comment: In the section on evaluating affordability the Authors’ reply quote the Cameron et al article (24) that uses the daily wage of the lowest paid government worker to determine affordability. Only later on this page is an explanation used that the official minimum daily wage defined by the Social security Organization of Iran was used. This paragraph should be moved up to be part of the first paragraph of this section. The decision to use this metric rather than the Lowest Paid Government worker should at least be discussed. It makes this paper less comparable. In other countries these minimum wages may be unrelated to the realities of life in those countries and are often subject to political manipulation. That is why the Lowest Paid Government worker measure was used in the WHO/HAI manual.

Authors’ reply: We are not sure how this comment might affect our conclusions. Given that the medicines were generally highly affordable in our study, even if the lowest paid government workers were paid higher amounts – as it seems to be suggested by the reviewer, the study’s main conclusions would have remained the same. Furthermore, the minimum daily wages announced by the Social Security Organization of Iran is closely comparable to the lowest paid government workers in Iran. Legally in Iran the SSO is the organization that announces the minimum daily wages in the country, and the government employee’s minimum wages follow the same patterns. SSO’s minimum daily wage figures were available to us for the whole period of the study and were used to calculate affordability.

Reviewer’s comment: On page 11 line 42 the sentence should read Nevertheless, the annual per
capita A10 utilization in Iran was consistently and substantially lower than those five countries during the benchmarking period (Fig. 4). On line 53 the text should read approximately half a minimum daily wage in 2012.

Authors’ reply: Thanks for your corrections. The text is modified accordingly.

Reviewer’s comment: On page 12 it is not clear if the results only applies to insulin alone or takes into account the cost of syringes especially as some of these products come in pen syringes as the only dosage forms.

Authors’ reply: The cost of syringes required for conventional insulin or the cost of needles for pen injectors were not included in the affordability model. This is made clear in the methods section. The available literature on the affordability of insulin is also based on the price of insulin products alone (Mendis et al-2007, HAI medicines affordability database). This approach makes our study findings comparable with other countries.

Reviewer’s comment: Again daily wages should be reported as minimum daily wages.

Authors’ reply: The term ‘daily wage’ was replaced by ‘minimum daily wage’ throughout the manuscript, including figure 5 and figure 6.

Reviewer’s comment: In the discussion on page 13 there is no mention of other costs such as syringes or diagnostics being a barrier to utilization.

Authors’ reply: This limitation has now been highlighted in the discussion.

Reviewer’s comment: The sentence "Metformin use increased significantly during the study period; however, off-label uses including weight loss or polycystic ovary syndrome may result in overestimation of diabetes-related utilization but their contribution seems to be small" is confusing. What is the evidence for this statement? Are there referenced papers making this case? If not I would leave it out.

Authors’ reply: Thank you for highlighting this. We have now deleted it from the manuscript as suggested by the reviewer.

Reviewer’s comment: With regard to the references I am surprised that there was no reference to the important work done by David Beran on barriers to access to insulin. See articles at http://www.who.int/medicines/areas/policy/access_noncommunicable/ncd_med/en/index1.html

Authors’ reply: Thanks for reminding us about Beran’s works. We have used them to enrich our discussion.

Reviewer’s comment: Good paper worthy of publication

Authors’ reply: Thank you Prof Laing for the positive note, and valuable comments.