

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Cross Sectional Study Estimating the Burden of Illness Related to Genital Warts in South Korea
AUTHORS	Lee, Taek Sang; Kothari-Talwar, Smita; Singhal, Puneet; Yee, Karen; Kulkarni, Amit; Lara, Nuria; Roset, Montserrat; Giuliano, Anna; Garland, Suzanne; Ju, Woong

VERSION 1 - REVIEW

REVIEWER	Marek Petráš Charles University in Prague, Second Faculty of Medicine, Czech Republic
REVIEW RETURNED	31-Oct-2016

GENERAL COMMENTS	<p>The topic of the manuscript is not without merit and it should be published. However the current manuscript requires an additional revision by authors. It is important to reevaluate GW rate expressed as incident rate. The text of "Results" and "Discussion" has to be modified and completed. The number of figure and tables must be reduced and make them more readable.</p> <p>Major comments</p> <p>pg 6 " treated ≥ 75 patients in outpatient visits in a typical week..." there are about 387 patients per one physicians in two weeks in Busan region how it results from table 2. It seems that number of patients varied in large range dependently of outpatient clinic and therefore it would be important to summarised average numbers of patients in every region/city to facilitate reading. Moreover, the test of sensitivity among all clinical sites could be performed. The GW incidence among sites where marginal number of patients were recruited should be discussed with respect to GW occurrence.</p> <p>pg 10 If the new GW cases were the reason why patients visit physicians then the crude incidence of new GW cases could be approximately 2.2 per 1,000 patients (163 new cases per 71,655 patients). The cross-section study was performed as prospective one. Therefore the prevalence could be replaced by an incidence (expressed per 1,000 patients or person). Authors could distinguish an incidence of GW acquisition and one of the GW recurrence. The study results benefit from this modification.</p> <p>Minor comments</p>
-------------------------	--

pg 4

More recently studies are missing (for example “Rates and predictors of genital warts burden in the Czech population, International Journal of Infectious Diseases 2015”)

pg 5-8

Study Design

Subheads “ Prevalence” and “Statistical Analysis” contain the identical information about weighing of GW proportion. The aim of this procedure should be probably a standardisation of GW rate, shouldn't it? The reported method is common and it does not merit more attention. The description in the subhead “ Statistical Analysis” is more than sufficient.

pg 8

Statistical Analysis

The statistical tests used for comparison between groups are missing. The reported tests are not sufficient to understand for what comparison were used. I am afraid that multiple tests are omitted.

“Referral patterns for GW patients were reported descriptively for the last 20 male and last 20 female patients. Reported were number” this paragraph does not belong to “Statistical”.

pg 9

Table 1

The row “Valid n” is identical to n under specialty - double information.

pg 11

Table 2 - why are there reported two same columns (All patients and Patients with identified GW status)?

Column “Patients with New or...” is probably prevalence.

pg 12

Table 3 - which statistical test was used, and which of groups were tested? Why multiple test was not used?

pg 14

“Cryotherapy was more frequently used by DERM (50.6%, 18.5% of patients) than by PCP (40.7%, 5.4% of patients) ...” percentage in parentheses should be explained.

pg 16

“OB/GYN used most of the tests more frequently, including the Pap smear (26.38%; $p < 0.001$), colposcopy (9.92%; $p = 0.0430$), ...” the explanation is missing - more frequently than what.

pg 17

“However, significant differences by physician specialty for diagnostic tools and techniques, in-office treatment and procedure costs, and topical medication prescription costs for at-home use (p -values: < 0.0001 , 0.0073 and 0.0037, respectively) were observed.” - P -values are referred to what? Which comparison?

Generally

Authors reported p -values in different forms - they use either $p < 0.05$ or p with appropriate calculated value. In discussion, the 95% CI could be omitted, especially when the results of other publications are referred. In addition, the value should be unified to one or two

	<p>decimals (better to one decimal). The text should be reviewed by an English language writer. There are some instances where the meaning of the text is difficult to understand. Limitations of survey are not sufficiently described.</p>
--	--

REVIEWER	Susanne Hartwig Sanofi Pasteur MSD France
REVIEW RETURNED	09-Nov-2016

GENERAL COMMENTS	<p>Methods</p> <ul style="list-style-type: none"> - page 5 line 47 to 52: representativity of the sample of physicians: only physicians from clinics that could be identified through the IMS database were included. Are these private clinics? Is their a public health system in Korea and if yes, patients attending private and public health institutes might be very different. Please explain a bit more the health system in Korea. - page 5 line 52: the dabase covers 5,098 clinics. Please add the total number of clinics for the five target specialities in Korea - page 5 line 54: ... for five target specialities... which are those target specialities? Later you select four of them, right? Please clarify - general comments for the methods section: <ul style="list-style-type: none"> --it is not detailed how the data were extrapolated to the overall country population (which population data were used for the catchment area of the physician and the overall country population) --it is not mentioned if the study was submitted to an ethics committee <p>Results</p> <ul style="list-style-type: none"> - page 10 : results are described for different endpoints (new cases, existing case, recurrent case,). These objectives and case definition are not described in the methods section. Please add - page 11 table 11 results are described by "region". In the methods section those "regions" are called "cities" and in the in the footnote a of table 2 "countries" are mentioned. Please harmonize the wording throughout the manuscript - page 13 table 3: nb of "hospitals": in the methods section "clinics" are mentioned. Please use the right term throughout the manuscript - page 17 to 20 (discussion): <ul style="list-style-type: none"> -- references should be inserted whenever cited (ex; page 18 line 30, line 36, ...references are missing) -- comparison to the results form other studies should be better structured to improve readability (a table with comparison data could be included) - potential limitation: <ul style="list-style-type: none"> --nothing is said regarding a potential double-counting of patients who might have attended more than one physician. Please discuss --nothing is said regarding the short time period of two weeks. Was this period sufficient to get a representative picture of the rate of GW patients? Please discuss
-------------------------	--

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Marek Petráš

Institution and Country: Charles University in Prague, Second Faculty of Medicine, Czech Republic

Please state any competing interests: None declared

Please leave your comments for the authors below

The topic of the manuscript is not without merit and it should be published. However the current manuscript requires an additional revision by authors. It is important to reevaluate GW rate expressed as incident rate. The text of “Results” and “Discussion” has to be modified and completed. The number of figure and tables must be reduced and make them more readable.

Thank you for your feedback on our study. To begin, we have abbreviated and reduced Table 3. Page 16

Major comments

pg 6

“ treated ≥ 75 patients in outpatient visits in a typical week...” there are about 387 patients per one physicians in two weeks in Busan region how it results from table 2. It seems that number of patients varied in large range dependently of outpatient clinic and therefore it would be important to summarised average numbers of patients in every region/city to facilitate reading. Moreover, the test of sensitivity among all clinical sites could be performed. The GW incidence among sites where marginal number of patients were recruited should be discussed with respect to GW occurrence.

We made the following changes to Table 2: We deleted the column: “Patients with identified GW status y/n, and added a column showing the “average number of patients per physician” (Page 10).

pg 10

If the new GW cases were the reason why patients visit physicians then the crude incidence of new GW cases could be approximately 2.2 per 1,000 patients (163 new cases per 71,655 patients).

The cross-section study was performed as prospective one. Therefore the prevalence could be replaced by an incidence (expressed per 1,000 patients or person). Authors could distinguish an incidence of GW acquisition and one of the GW recurrence. The study results benefit from this modification.

Although this was a prospectively performed cross-sectional study, the number of patients included both new and existing patients. That is the main reason we named prevalence instead of incidence.

Minor comments

pg 4

More recently studies are missing (for example “Rates and predictors of genital warts burden in the Czech population, International Journal of Infectious Diseases 2015”)

Thank you for your suggestion. We have added the following references to our manuscript: Int J Infect Dis. 2015;35:29-33. Rates and predictors of genital warts burden in the Czech population. Petráš M, Adámková V.” (Discussion section, page 22)

pg 5-8

Study Design

Subheads “ Prevalence” and “Statistical Analysis” contain the identical information about weighing of

GW proportion. The aim of this procedure should be probably a standardisation of GW rate, shouldn't it? The reported method is common and it does not merit more attention. The description in the subhead "Statistical Analysis" is more than sufficient.

Yes, the procedure is a standardization of GW rates. We removed the subtitle "prevalence" and its contents, and the section has been subtitled as "Statistical Analysis".

pg 8

Statistical Analysis

The statistical tests used for comparison between groups are missing. The reported tests are not sufficient to understand for what comparison were used. I am afraid that multiple tests are omitted.

We have reviewed the section and added the following:

"All study outcomes were summarized descriptively. P-values were calculated for comparison between groups ie, region, age, sex, and physician specialty using t-tests or the Mann-Whitney U-test for continuous variables; Chi-square tests or Fisher Exact tests were used for binary or categorical variables.

"Referral patterns for GW patients were reported descriptively for the last 20 male and last 20 female patients. Reported were number" this paragraph does not belong to "Statistical".

We have revised this section and removed the entire paragraph "Referral patterns ~ using Mann-Whitney U tests"

pg 9

Table 1

The row "Valid n" is identical to n under specialty - double information.

This has been addressed in the manuscript; we replaced "valid n" with "Total Patients" in Table 1.

pg 11

Table 2 - why are there reported two same columns (All patients and Patients with identified GW status)?

Column "Patients with New or..." is probably prevalence.

This has been addressed in Table 2, Column "patients with identified GW status" was deleted and replaced with the "average number of patients per physician"

Also "Patients with new or existing GW" represent prevalence in the region.

pg 12

Table 3 - which statistical test was used, and which of groups were tested? Why multiple test was not used?

We used the Mann-Whitney test to compare only the DERM cohort and the URO cohort because the variables from both groups were independent of each other, and we felt this was an appropriate test to compare the two cohorts.

pg 14

"Cryotherapy was more frequently used by DERM (50.6%, 18.5% of patients) than by PCP (40.7%, 5.4% of patients) ..." percentage in parentheses should be explained.

Thank you for your suggestion. To improve readability, we removed the first percentage highlighted in red, the other percentage represents patients treated with cryotherapy by a dermatologist or urologist.

We revised as follows:

"Cryotherapy was more frequently used by DERM (18.5%) than by PCP (5.4%) or URO (2.7%; $p < 0.001$). Electrosurgery was more frequently used by URO (57.2%; $p < 0.001$) compared to DERM

and PCP.” Also we corrected the typo in Figure 3 to Figure 2. (Page 18)

pg 16

“OB/GYN used most of the tests more frequently, including the Pap smear (26.38%; $p < 0.001$), colposcopy (9.92%; $p = 0.0430$), ...” the explanation is missing - more frequently than what.

We have revised this section as follows “There were differences in the use of particular diagnostic tools and techniques. OB/GYN used most of the tests more frequently than DERM”

pg 17

“However, significant differences by physician specialty for diagnostic tools and techniques, in-office treatment and procedure costs, and topical medication prescription costs for at-home use (p -values: < 0.0001 , 0.0073 and 0.0037 , respectively) were observed.” - P -values are referred to what? Which comparison?

We apologize for the confusion. We have revised this section. The comparison is between DERM and URO physicians, and we attached the p -values to the respective treatment procedures.

Generally

Authors reported p -values in different forms - they use either $p < 0.05$ or p with appropriate calculated value. In discussion, the 95% CI could be omitted, especially when the results of other publications are referred. In addition, the value should be unified to one or two decimals (better to one decimal).

For the p -values, we reported the appropriate calculated values as reported from the analysis. The p -values < 0.0001 were reported from the analysis as p -values < 0.0001 and we reported as such in the manuscript, while the other appropriate calculated p -values were approximated to the 4th decimal points.

The 95%CI has been omitted from the reference articles in the discussion section and the values have been revised to one decimal point.

The text should be reviewed by an English language writer. There are some instances where the meaning of the text is difficult to understand.

An English language writer has revised the manuscript.

Limitations of survey are not sufficiently described.

The potential limitations of our study have been added to the discussion section.

Reviewer: 2

Reviewer Name: Susanne Hartwig

Institution and Country: Sanofi Pasteur MSD, France Please state any competing interests: I am an employee of Sanofi Pasteur MSD, MAH of Gardasil vaccine in Europe

Please leave your comments for the authors below

Methods

- page 5 line 47 to 52: representativity of the sample of physicians: only physicians from clinics that could be identified through the IMS database were included. Are these private clinics? Is their a public health system in Korea and if yes, patients attending private and public health institutes might be very different. Please explain a bit more the health system in Korea.

We have revised this section; an explanation regarding the overall health care system in Korea has been added to the manuscript.

- page 5 line 52: the database covers 5,098 clinics. Please add the total number of clinics for the five target specialities in Korea

This section has been revised as follows: "The database covers 5,098 clinics for five targeted specialties in five major cities in South Korea: Seoul, Busan, Daegu, Kwangju, and Daejeon. It is mandatory for all the clinics to be enrolled in the National insurance system, which can be monitored exhaustively by HIRA in Korea."

- page 5 line 54: ... for five target specialities... which are those target specialities? Later you select four of them, right? Please clarify.

The targeted specialties are general practice, family medicine, OB/GYNs, UROs, and dermatologists (DERMs).

- general comments for the methods section:

--it is not detailed how the data were extrapolated to the overall country population (which population data were used for the catchment area of the physician and the overall country population) --it is not mentioned if the study was submitted to an ethics committee

We have revised the methodology section, adding more specific details of the study design, and including the ethics committee entities who approved this study.

Results

- page 10 : results are described for different endpoints (new cases, existing case, recurrent case,). These objectives and case definition are not described in the methods section. Please add

"The number of new or existing GW cases..."

Thank you for pointing out the oversight. We added the following to the Methods/Study Design Section: "In addition, patients diagnosed with GW were stratified as new, existing, recurrent, and resistant cases." (Page 5)

- page 11 table 11 results are described by "region". In the methods section those "regions" are called "cities" and in the in the footnote a of table 2 "countries" are mentioned. Please harmonize the wording throughout the manuscript.

We have revised the manuscript to use "region" to describe demographic-related results throughout.

- page 13 table 3: nb of "hospitals": in the methods section "clinics" are mentioned. Please use the right term throughout the manuscript

Thank you for calling attention to this detail. To further define hospital vs office/clinic: In this context, a "hospital" represents a larger health care center than an "office" or clinic. Also, we have changed "office" to "clinic" throughout the manuscript, to make the description clearer and to avoid confusion.

- page 17 to 20 (discussion):

-- references should be inserted whenever cited (ex; page 18 line 30, line 36, ...references are missing).

Citations for the references have been added to the discussion section.

-- comparison to the results form other studies should be better structured to improve readability (a table with comparison data could be included)

The discussion section has been revised to improve readability.

- potential limitation:

--nothing is said regarding a potential double-counting of patients who might have attended more than one physician. Please discuss --nothing is said regarding the short time period of two weeks. Was this period sufficient to get a representative picture of the rate of GW patients?

Please discuss

The potential limitations of the study have been added to the discussion section of the manuscript. We believe that it is less likely for the patients to be counted double because the patients who received the same questionnaire at another clinic might have been highly likely to raise a question to the doctor who gave it to the patient.

VERSION 2 – REVIEW

REVIEWER	Marek Petráš Charles University in Prague, Second Faculty of Medicine, Czech Republic
REVIEW RETURNED	22-Jan-2017

GENERAL COMMENTS	I am agree with the current revision of the manuscript.
-------------------------	---