Author's response to reviews

**Title:** Estimation of the incidence of genital warts and the cost of illness in Germany: a cross-sectional study

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**Version:** 2  **Date:** 15 April 2008

**Author's response to reviews:** see over
Reviewer's report
Title: Estimation of the incidence of genital warts and the cost of illness in Germany: a cross-sectional study
Version: 1 Date: 28 November 2007
Reviewer: Willem I. van der Meijsden

Reviewer's report:
General
This paper, with its limitations, adds to our knowledge with regard to the incidence and cost of genital warts in a major European country

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Abstract (Methods): just a question: why was recruitment not done in STI clinics, a well-known place for genital wart patients

Unlike the UK or the Netherlands where many patients seek free and anonymous treatment for sexually transmitted infections (STIs) at a STI clinic, in Germany such clinics are rare and are mainly used by people with 'high risk sexual behaviour'. Interviews performed with STI experts before the start of the study indicated that most female patients with genital warts go to a gynaecologist and most men either go to a urologist or dermatologist to be treated. As we wanted to have a representative sample of the German population with genital warts we felt that recruitment in the STI clinics would not allow us to fulfil this requirement.

2. Abstract (Results): 'For recurrent cases the highest incidence was observed in women...'. Since the incidence in males could not be calculated because of the small sample size, this cannot be stated in this way!

We wanted to highlight that the highest incidence of new cases was observed in women aged 14-25 years while for recurrent cases the highest incidence was observed in women aged 26-45 years. We did not aim to compare the incidence in women and men. This has been clarified in the text.

3. Introduction: 'HPV is a necessary cause of cervical cancer...': the word 'necessary' should be replaced with an alternative. Sounds a little strange.

A necessary cause is terminology used in epidemiology to assess the causality (i.e., logical relationship) between one event (called cause) (e.g. HPV) and another event (called effect) (e.g., cervical cancer) which is the direct consequence (result) of the first. Causes are often distinguished into two types: Necessary and sufficient.
**Necessary causes:**
If x is a necessary cause of y, then the presence of y necessarily implies the presence of x. The presence of x, however, does not imply that y will occur.

**Sufficient causes:**
If x is a sufficient cause of y, then the presence of x necessarily implies the presence of y. However, another cause z may alternatively cause y. Thus the presence of y does not imply the presence of x.

Extensive research by Munoz, Walboomers and others has shown that HPV was found in 99.7% of cervical cancers worldwide. Hence, most researchers in cervical cancer believe that HPV is a necessary cause of cervical cancer. We concur with this statement.

No changes in the text have been made.

4. page 5, 2nd paragraph: '...development of prophylactic HPV vaccines.' It is suggested to change 'development' into 'use'. The vaccine already exists! 

The change has been made in the text.

5. Methods: page 8, 1st paragraph(last sentence): why were new patients only evaluated by means of data collected at the first visit? In this way important data is missed. It could very well be that the cost incurred in case of new patients is considerably lower! 'Young and fresh warts' in general respond better to treatment than the older ones! This would have meant a prospective follow-up of let's say 1 year. Were the authors in a hurry to collect data? Please comment.

We fully agree with the reviewer that the best study to reach the two study objectives (i.e., to estimate the incidence of genital warts and to collect resource consumption) would have been to conduct a prospective 1-year follow-up study. However, such a study would be very time consuming and costly to do, so we decided to conduct a retrospective study. With such a study design, we capture resource use for existing patients (i.e. patients who are coming back for another visit). Some of these patients may have had multiple visits in the previous year or just one and therefore we capture the less complicated cases as well. The only resource use data we may miss are those for patients with only one visit that did not occur during the 2-month study period. However, the resource use of these patients is probably small compared with that for patients with multiple visits. This limitation is now mentioned in the discussion.

6. Results: page 10, line 6: I wonder why there is such a high number of warts with an 'unknown' status. This may lead to the assumption that the quality of the patient records from which data were extracted is suboptimal. Further in the paper the 'unknown' status warts are considered as 'existing'. Couldn't they also be 'new' warts?
In order to estimate the incidence GW in Germany, all investigators were asked to list information on all patients with GW seen in a 2-month period. The epidemiological survey classified patients as newly diagnosed (so called incident cases) or existing patients (previously diagnosed patients). Existing patients were further classified as either recurrent or resistant cases. If an investigator was not sure where a patient with existing warts had recurrent or resistant warts, the answer option “unknown” was available. Thus, the answer "unknown" was only possible for the existing cases and in total 15% (N=130) were listed as unknown. Therefore it may be possible that the incidence for recurrent cases calculated in our survey is underestimated since we had a high percentage of "unknown" cases. In the chart review the analyses were based on a detailed review of the patients’ records and fewer patients (10%, n=61) were listed as unknown.

7. page 12, first paragraph, halfway: 'internal' and 'external' should be properly defined, both in men and women! No data are given about the presence of genital warts at the vagina and cervix! These data are certainly needed, since experts agree that the presence of vaginal/cervical warts may to a large extent determine 'the difficulty' of getting rid of warts in female patients!

The following text has been added:

External lesions in women included lesions on the following anatomical sites: fourchette, labia minora and majora, clitoris, urethral meatus, perineum, anal area, vestibule, introitus (vaginal orifice), and vagina. Internal lesions were found on the ectocervix. Five-seven percent all women had genital warts on the perineum, followed by the introitus (35%), labia minora (35%), anal area (35%), labia majora (34%), and vagina (21%). Only a few women were reported to have lesions on the ectocervix (8%). External lesions in males included lesions on the following sites: glans, coronal sulcus, frenulum, foreskin, scrotum, groin, perineum, anal area, penile shaft, and meatus. Internal lesions were located in the urethra. In males, the shaft of the penis was often affected by genital warts (41%), followed by the glans (30%), the coronal sulcus (28%), foreskin (24%), anal area (21%), frenulum (19%) and scrotum (12%). Only a few men were reported to have lesions in the groin (6%), perineum (5%) or urethra (4%).

8. page 12, last but one line: 'Existing patients...' should be replaced with 'Patients with existing...'

This change has been made in the text.

9. page 13: reasons for hospitalization should be given. Will the readers understand why hospitalization of patients with 'resistant warts' was four times longer than the hospitalization of those with 'recurrent' warts? I don’t! Please comment. Maybe this has to be explained in the Discussion section.
We agree with the reviewer that the differences appear large. However, as the differences were based on only a few patients they have to be interpreted with caution: only seven patients with resistant GWs and ten patients with recurrent GWs were hospitalised. This has been added to the text. It may be better also to present the mean length of stay values here (e.g. three days for patients with recurrent GWs and five days for patients with resistant GWs).

10. page 15: what is the meaning of the last sentence of the paragraph 'Multivariable analysis'??

Multivariable (or multivariate) analysis is a statistical tool for determining the unique contributions of various factors to a single event or outcome. For example, numerous factors are associated with the development of coronary heart disease, including smoking, obesity, sedentary lifestyle, diabetes, elevated cholesterol level, and hypertension. These factors are called risk factors, independent variables, or explanatory variables. Multivariable analysis allows us to determine the independent contribution of each of these risk factors to the development of coronary heart disease (called the outcome, the dependent variable, or the response variable).

11. page 21: there are some mistakes in the initials of the authors which have to be corrected.

We have corrected the mistakes.


We have added this reference

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Discretionary Revisions (which the author can choose to ignore)
What next?: Accept after minor essential revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: 'I declare that I have no competing interests'.

Reviewer's report
Title: Estimation of the incidence of genital warts and the cost of illness in Germany: a cross-sectional study
Version: 1 Date: 21 January 2008
Reviewer: Maarten Postma
Reviewer's report:

1. Page 7: Some repetition on this page: AC Nielsen was said before, as was 600 Patients

   We have removed this sentence.

2. Page 11: Sexual contact data are scarce and valuable for dynamic models; please specify in more detail the distribution of the population over the number of new sexual partners in the previous year.

   We have added this information page 11

3. Page 13: median of 1 day in hospital is very short, was this a real overnight stay in all cases?

   Please see the answer to the 1st reviewer.


   This table has been added.

5. Major comment is on table 1, with GDP per capita used, this overestimates for the population investigated as these are younger than average, please apply age-specific GDP/capita estimates!

   This is an important comment for the calculation of indirect costs. We agree with the reviewer that this approach could lead to an overestimation of the costs. However, it seems that our estimate of 119 € by work day lost is low in comparison with other published German cost analyses. For instance, Banz et al. 2003\(^1\) estimated the cost per work day lost was 150 € in Germany. More interestingly, Stark et al. 2006\(^2\), considered in their cost analysis age- and sex-adjusted daily rate, as suggested by the reviewer (they used a different methodology than the GDP per capita). The cost per work day lost they obtained is presented in the table below. Except for the age group 15-19, the cost estimate of 119 €/work day lost is lower than for older age groups. For these reasons, we feel that our estimates of indirect cost are probably underestimated.

\(^1\) Banz et al. The burden of varicella. Eur J of Health Economics. 2004; 5: 46-53

Table published in Stark R. et al. 2006:

<table>
<thead>
<tr>
<th>Age group (y)</th>
<th>Daily rate of employee compensation (€)</th>
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<tbody>
<tr>
<td></td>
<td>men</td>
</tr>
<tr>
<td>15–19</td>
<td>132.77</td>
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<tr>
<td>20–24</td>
<td>169.89</td>
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<tr>
<td>25–29</td>
<td>205.12</td>
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<td>30–34</td>
<td>241.69</td>
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<td>35–39</td>
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