Author's response to reviews

Title: Hospitalization for diseases attributable to human papillomavirus in the Veneto Region (North-East Italy)

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Author's response to reviews: see over
Dear Editor,
We have revised the manuscript and would like to re-submit it for your consideration. We are grateful for the review, and your comments have resulted in a substantial improvement in the report. We hope that the revised version of the manuscript is now acceptable for publication in your journal. Please find the revised version and point-by-point answers to the reviewer’s remarks below. We look forward to hearing from you soon.
Yours sincerely,
Vincenzo Baldo

Replies to Reviewer 1

Major Compulsory Revisions:
1. Abstract:
   a. Conclusion about vaccination cannot be extracted from this study.
      - We have deleted this issue from the abstract

2. Methods section should be reviewed:
   a. It is said that the population in the region is stable during the study period (2000-2010) and as denominator for calculating the rates 2001 population data were used. By reviewing published data the population in Veneto region an increase of 10 % from 2000 (4.5 million) to 2010 (4.9 million) can be seen. It is not a stable population. Rates should be calculated again taking into account the population variability. It can be affecting the trends reported.
      - In the light of this comment, the rate was checked and calculated again, and data for the year 2011 were added. The materials and methods section has been revised accordingly.
   
   c. The statistics should be reviewed. “Linear regression models analyzing hospitalization rates as dependent variables and year as independent variables was used to evaluate the significance of any decreasing or increasing trends” the linear regression can inform of the goodness of fit of the data to a line, but not of the significant decrease or increase of a rate during a period of time. A Poisson model should be used instead.
      - We have revised the statistical methods and applied Joinpoint regression models instead of linear regression analysis to quantify the direction and magnitude of the trends using the average annual percentage of change (AAPC); a reference has consequently also been added (Stat Med 2000;19:335-51)

3. Results:
   a. New rates should be reported regarding the modification in the population.
      - The new rates have been reported by population year by year.
4. Discussion:
a. It is said “Our data show that the hospitalization rates dropped for women from 2000 to 2010. This decline regards cancer, and cancer of the uterine cervix in particular, and correlates with the introduction of organized screening programs in our region, that enable the detection and treatment of this disease.”
Could the author give any explanation on why the screening does not seem to decrease the number of genital warts in women and why have cases of anal cancer mainly occurring in MSM also decreased? The new rates should be discussed in more detail.

- The rates have been discussed and a possible explanation has been added for the trend of cancer of the anus in males and genital warts in females (page … , line …)

Minor Essential Revisions:
1) Title should include location
   - Done

2) Introduction.
a. “Human papillomavirus (HPV) represents the most frequent transmitted pathogen in the United States.” Please give epidemiologic data not only of USA, but of Europe or Global as your work is done in Italy.

We add new references also reporting Europe data

b. The use of the term “burden” should be carefully checked through the manuscript
   - Done

3) Methods:
a. Please define age groups to be study and its rational.
   - These are the age groups normally used in hospitalization studies in the Veneto Region, as listed in Table 1.

b. What proportion of the population in the Region (residents) was covered by the hospitals contributing to these study?
   - The phrase “concerning all discharges from all the hospitals in the region” has been added in the Materials and Methods.

c. Regarding: “the fact that it was impossible to check whether more than one discharges applied to the same person (which could contribute to an overestimation of the number of cases, but not the burden due to the HPV diseases).” Can the authors access other diagnosis positions? See comment of re-admissions above.

   - We agree with the observation that this issue could lead to an overestimation of the number of severe cases, but not of the burden on the hospital resources. We have used “hospitalization rates” instead of “cases”.
   - The aggregate data do not allow for us to access other diagnosis positions, but the first one is always the principal diagnosis for a given hospital admission.
4) Results:
a. Genital warts and cancer are very different outcomes. In terms of epidemiology, the age
groups affected and the time from infection to event are completely different. It would add
clarity to the text to split the analyses in two, at least in the figures (one for cancers and
one for warts).

- Figures 1 and 2 have been replaced by Fig. 1 for male cancer, Fig. 2 for female
cancer, and Fig. 3 for genital warts in both genders.

b. Please use the term “cases” or “hospitalizations” accordingly to previous
comment about readmissions

- The term hospitalizations or admissions has been used instead of “cases”

c. p=n.s. Please show value

- Please see the Material and Methods, as mentioned above

5) Discussion:
a. “Hospital records indicate that HPV-related diseases is an important public health issue
which could be prevented by vaccination strategies”. The records do not indicate that
HPV-related vaccines could be prevented by vaccination. A deeper analysis in the decline
of hospitalization before and after vaccine introduction could give some information. This
kind of sentences should be rewritten.

- The sentence has been omitted.

6) Figures:
a. Fig 1 and 2 are entitled “HPV-related hospitalization trend”, but the trend is difficult to
see due to the figure selected, that highlights the accumulative HPV-related disease and
only the “total” trend is finally showed. The cumulative effect is naively showed in figure 3,
so it would add clarity to the paper to see figure 1 and 2 reporting the individual rates and
its trend for each HPV-related disease. If possible separating warts.

- Figures 1 and 2 have been changed

Replies to Reviewer 2

- Major compulsory revisions
Introduction section
The role of oncogenic HPV types in cancers affecting cervix should be included. The
sentence "Many authors have also highlighted the involvement of HPV in cancers affecting
the oropharynx and oral cavity [3], Kreimer et al in 2005 conducted a systematic meta-
analysis to review the available literature in the field and ascertain the worldwide
prevalence of HPV in neck squamous cell carcinoma and the prevalence of HPV in neck
squamous cell carcinoma was estimated at 26% [4].“ should be re-written.

- The role of oncogenic HPV types in cancers affecting cervix was be included. The
whole paper has been revised by a native English speaker and rewritten.

The sentence "A number of studies in the literature estimate the burden of HPV-related
diseases by collecting data on primary care level, only an European Spanish study has
previously reported the burden of HPV-related hospitalization referring only to anal and penile neoplasm discharges [7]." should be re-written.

- The whole paper has been revised by a native English speaker and rewritten.

Methods section
The sentences "The attributable fraction to HPV was defined as a proportion of the cases of disease observed in all related hospitalizations attributable to HPV infection. In particular, all cases of cervical cancer and genital warts were assumed to be HPV-related, while for cancers of the male genitalia and anus the fractions considered were 50% and 88%, respectively, and for oropharyngeal cancer it was 26% [2-4]." should be re-written.

- The whole paper has been revised by a native English speaker and rewritten.

Results section
Showing the hospitalization rate in females, it could be useful to clarify which part of "genital cancer" is related to cervical cancer. The sentences "Over the whole study period, in the hospitalization rate for males was stable, from 16.1/100,000 in 2000 to 16.3/100,000 in 2010. The increase of cases were of genital warts (+81.7%; p<0.001), and the cases of genital cancer also increased (+10.0%; p=n.s.), while the anal and oropharyngeal cancers both dropped (-45.3% and -36.8%, respectively; p<0.05) (Figure 1)." should be re-written.

- The whole paper has been revised by a native English speaker and rewritten.

Discussion section
An ample debate on male vaccination is ongoing. As the implementation of male vaccination should be related to the achievement of a high VC% in females, it should be interesting to have included a comment on the coverage rate achieved in females in Veneto Region.

The reference n.19 should be updated and changed with: Giambi C. Stato di avanzamento della campagna vaccinale per l'HPV: dati di copertura vaccinale al 30/06/2012- rapporto semestrale www.epicentro.iss.it/problemi/HPV/pdf/aggiornamento
It could be useful to add a comment on the paper by Hartwig et al, BMC Cancer 2012, including this reference as well.

- A comment has been added, the reference has been changed, and the paper by Hartwig has been added.

Table 1
The total number of oropharyngeal cancer is 1,176 (and not 1,177)
Minor essential revisions
Introduction section
line 14 "Each year, genital warts is...." please change is with are
Methods section
line 10 "Condylomaacuminatum" please correct
line 14 "HPV -correlated", please correct as follows: HPV-related

Results section
line 2 "We identified 15,537 of.." please delete of

- We have modified the text in the light of these comments