Reviewer's report

Title: Prevalence of high-risk HPV types and associated genital diseases in women born in 1988/89 or 1983/84 - results of WOLVES, a population-based epidemiological study in Wolfsburg, Germany

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Reviewer: Marc Arbyn

Reviewer's report:

WOLVES is an important study assessing baseline findings and early effects just after the introduction of HPV vaccination in a German area. The authors describe prevalences of HPV infection (HR and type specific) and associations with explanatory risk factors as well as with cytological and histological cervical lesions in two young cohorts participating in cervical cancer screening. This is one of the rare reports currently available which are of importance in the surveillance of HPV vaccination effects.

Since the independent factors (infections, lesions) are dichotomic, the associations with explanatory factors could all be assessed by logistic regression (mono- and bivariate).

The study also contains data on vaccination status. The association between this status and prevalence of HPV1618, other hrHPV infection and the relation with lesions associated with these infections could be added. By doing this, the relevance of the paper in context of surveillance of HPV vaccination effects, will increase substantially.

Minor / more detailed comments

ABSTRACT

It should be mentioned that the HPV vaccination status is different between the studied cohorts.

1 decimal of ORs are sufficient. Confidence intervals should be added to the ORs.

Since only data are presented on CIN3+ outcome, it is better to limit conclusions only this outcome (instead of CIN2+).

INTRODUCTION

The authors could point to the causal relation between HPV infection and other than cervical cancers (see EUROGIN Roadmap 2011: Arbyn et al Int J Cancer 2012)

Page 4: “atypical screening results are reasonably common”. Statement is unclear. Do the authors mean that the prevalence of cytological abnormalities are
similar among sites? Or prevalence is quite high?

Last sentence: it is unclear what “dynamics of HPV infection” means.

METHODS.
1st §: adapt tense to the past.

The period where invitations took place should be defined.

Some explanations on the vaccination certificate could be given so that the reader can be informed about the reliability of this information. Do all women have this at hand? Does it contain all vaccination received? Who fills it in?

The authors could refer to European guidelines for collection of Pap smears (Arbyn et al Cytopathol 2007) and explain how local cytology terminology was translated into Bethesda terminology as recommended in European guidelines (Herbert et al Cytopathol 2007).

“Overall WOLVES will allow the investigation of individual changes in HPV infection during follow”. This objective is unclear.

“prevalence of HPV infections in different age cohorts over time”. Again this is unclear. “Age cohort” is a contradiction in terminis. One can consider differences at different ages within the same birth cohort, or, women at the same age but belonging to different cohorts (so measured at different calendar time points.).

Statistical analysis.

The parameters assessed (risk factors, prevalence hrHPV, prevalence cytological abnormalities and histological detection rates in two cohorts) and associations should be explicitly mentioned.

It would be interesting to add information of HPV vaccination status.

Logistic regression could be used for the assessment of the monovariate relation between HPV infection and explanatory factors instead of the MW U testing.

RESULTS

Table 1:
Add % besides the absolute numbers and p values for differences among cohorts.

“Cancer screening” in unclear. Is it “has had previous cervical cancer screening tests”?

Pap smear results: For an international journal it is necessary to translate into Bethesda equivalent terminology as done in table 3

Fig 1. Prevalence of LR HPV and mixed HPV can be dropped since LR HPV is mentioned as an object of another publication. The authors should explain in Methods how type specific HPV prevalences were computed (was there a
weighting to adjust for the genotyping on 10% hrHPV negative women?).

Fig 1 and 2. Statistical differences between cohorts could be assessed. HR HPV could be a couple of bars in fig 2 so that fig 1 can be dropped.

A lot of space is given to Mann Whitney U statistics assessing relation between type-specific HPV infections and possible explanatory factors. This can be reduced substantially. Figs 3a & b can be dropped since redundant.

Page 10: Type-specific univariate analyses of data from the 1983/84 cohort showed significant interactions between other specific HPV types and atypical Pap smear test results. Association is a better wording than interactions.

Colposcopic morphology
“All CIN3 lesions were associated with HPV16.” Redundant: already mentioned previously.

HPV vaccination
For surveillance of HPV vaccination effects this paragraph is the most interesting one. Differences in prevalence of hrHPV infection, HPV16/18 infection, hrHPV other than 16/18 and cytological lesions (overall and associated with HPV16/18) should be presented.

The authors could assess whether the difference in HPV16 infection between the cohorts is associated with vaccination status.

DISCUSSION
The words “dynamics” and “longitudinal” are for this cross-sectional data not allowed.
Differences in cross-sectional prevalence are better terms to use.

Page 13 “From a clinical perspective, there is still a significant population of young women infected with HR-HPV who will have a higher rate of cervical screening abnormalities and, ultimately, an increased risk of developing cancer”. It may be better to drop this sentence as it might be interpreted as a proposition to offer HPV-based screening at young women (<30 years).

“Nevertheless, the WOLVES data are in accordance with published data from similar European trials of HPV types commonly associated with atypical Pap smears/cervical neoplasia [27,28,36,37] and support the concept that HR-HPV infections leading to the development of cancer are acquired early in young women who have not been vaccinated.” This statement is speculative and may be dropped.

CONCLUSION
“The effect of cofactors for the risk of CIN3 and cancer, such as smoking and use of contraceptives, may not yet be apparent because these factors probably trigger
HPV persistency rather than acquisition." Better to drop this: acquisition and persistence cannot be derived from this one-time cross-sectional data set.

“Women with HPV16 infection have a high 16 risk of clinically relevant lesions that seems to increase over time (as the comparison of the two age cohorts shows) and there was a significant impact of HPV vaccination on HPV16 infections, although the majority of these women must have been sexually active already at the time of vaccination and, therefore, the efficiency must be considered to be suboptimal”. This sentence can be dropped.

In the conclusion, the lower prevalence of HPV16 in vaccinated vs non-vaccinated should be highlighted.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

MA: Participation at EUROGIN (Lisbon 2011) conference sponsored by organisers.