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Title:

Changes in incidence of anogenital warts diagnoses after the introduction of HPV vaccination in Germany – an ecological study

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Short summary:

This study based on health insurance data demonstrated changes in the incidence of anogenital warts after the introduction of HPV vaccination for the first time in Germany.

Abstract:

In a large health insurance database, incidence of anogenital warts among 15 to 19 years old females decreased from 316/100,000 person-years in 2007 to 242 in 2008 (23% reduction, $p=0.0001$). The decrease started between the 1st and 2nd quarter of 2007 (HPV vaccination was introduced in March 2007).

Keywords: HPV vaccination, anogenital warts, incidence, health care database study, Germany

Text:

While the main focus of HPV vaccination is on prevention of cervical cancer, anogenital warts (AGW) (mainly caused by the HPV types 6 and 11) can cause emotional distress and substantial health care costs and are therefore an important secondary health outcome.(1-5) In clinical trials, a high efficacy of the quadrivalent vaccine against AGW was demonstrated.(6-9)

In March 2007, the German Standing Vaccination Committee (STIKO) recommended the HPV vaccination for the prevention of cervical cancer for girls between 12 and 17 years of age.(10) The STIKO recommendation does not distinguish between the bi- and the quadrivalent HPV vaccine. However, the quadrivalent vaccine is used predominantly in Germany (almost 90 % of sold doses).(11) Typically, the vaccination takes place towards the end of the recommended age range. In 2008/9, the coverage in the age group 16 to 18 years was estimated at about 40%.(12;13) Using the same database as in the current analysis, we

found that about 35% of 17 years old women received at least one HPV vaccine dose in 2008.

(14) Furthermore, the ratio of third doses to first and second doses administered in federal states where separate codes for the specific doses existed suggested that women usually completed the whole vaccination series.

The impact of the quadrivalent HPV vaccine on the reduction of AGW at population level has been investigated in Australia,(15-17) New Zealand (18) and the U.S..(19) These studies demonstrated a reduction of the AGW incidence soon after the introduction of national vaccination programmes, even with some evidence of herd immunity. We recently published a manuscript on the incidence of AGW in 2005 and 2006.(20) The aim of the current study was to assess whether there were changes in the incidence of AGW in the time period 2005-2008, during which HPV vaccination was introduced in Germany. We studied AGW anogenital warts incidence trends by age using a large health care database.

The database was the German Pharmacoepidemiological Research Database (GePaRD) which was described elsewhere.(20;21) In the current analysis, we used data from one large health insurance company (>6 million insured persons, 8% of the German population) for which data was available for the years 2004 to 2008. GePaRD contains demographic information, information on hospital admissions, ambulatory physician visits, and prescriptions. The hospital data contains information on admission and discharge dates, diagnoses and diagnostic and therapeutic procedures carried out in hospital with the respective date. Outpatient physician visit claims data include outpatient treatments, procedures, and diagnoses. Since outpatient physician visits are reimbursed quarterly, outpatient diagnoses can only be allocated to a quarter of the year.

We applied an open cohort design to assess the incidence of AGW. Cases of AGW were ascertained based on the ICD-10 German Modification (ICD-10 GM) code A63.0.(22) For the estimation of incidence rates, only cases with a preceding period of 12 months without

AGW diagnoses were included. Confidence intervals for incidence rates were based on Poisson distribution.

We estimated incidence rates for each quarter of the years 2005 to 2008, stratified by five year age group and sex and performed trend analysis with a Poisson model. We expected a change of trend in the incidence of AGW after the introduction of the HPV vaccination (“breaking point”). To explore this, we restricted the analysis to females aged 12 to 20 years and used a Poisson regression model with age, calendar time in quarters of the year (to allow for a general trend over time), calendar time within a year and calendar time since a breaking point. Adjusting for calendar time within a year was necessary to account for effects of aging in the respective cohort. We varied the time of the breaking point across the whole range of the studied period and used the Bayesian Information Criterion (BIC) to define the best fit for the breaking point.⁽²³⁾ In the next step, we applied the estimated breaking point in each of the one-year age groups for males and females separately. The reduction in the incidence after the breaking point was approximated by a linear trend. All analyses were conducted with SAS 9.2.

Overall, the incidence of anogenital warts in the age group 10 to 79 years increased by 17% from 2005 to 2008 (Table 1). In 2005, females had a 52% higher incidence than males; over time the difference decreased to 31% in 2008. In females, the incidence was highest in the age group 20 to 24 years, in males it was highest in the next older group (25 to 29 years) (Figure 1). In 2008, the peak incidence was 30% higher in women than in men. The general trend over time was an increase in the incidence, which was most visible for the age groups with high incidence. Despite the general upwards trend, there was a decrease in the incidence among females in the age group 15 to 19 years (316 per 100,000 person-years in 2007 and 242 in 2008, a 23% reduction, $p=0.0001$).

When focussing on 10- to 20-year-olds, a decreased incidence in 2008 could be seen for 16-, 17- and 18-year-old females, and less pronounced among the 15- and 19-year-olds (Figure 2).

In contrast, among 13-, 14- and 20-year-old women, there was some indication of an increased incidence. Generally, males had a much lower incidence in the age group 10 to 20 years, with some indication of a decreasing incidence among 16- and 17-year-olds over the whole study period.

Based on the lowest BIC, there was evidence of a change in trend in the incidence of AGW among females in the age group 12 to 20 years in the 2nd quarter of 2007 (data not shown). Evaluating the trend in one-year age groups, this change can be attributed to 16, 17 and 18 year old females (Table 2).

Based on the estimated decrease rate, the incidence among 16-year-old females was reduced by 47% in the end of 2008, by 45% among 17-year-olds, and by 35% among those 18 years of age compared to the incidence in these age groups before the breaking point. There was no clear breaking point in the incidence of AGW among males.

Our analysis demonstrated a reduction in the incidence of AGW after the introduction of HPV vaccination in Germany among 16- to 18-year-old females. The decrease started soon after the recommendation of HPV vaccination by STIKO and the reimbursement of HPV vaccination by health insurance companies.

Comparing same aged girls before and after the introduction of the vaccination showed a reduction of AGW of 35% to 47% (based on the estimated decrease rate). The reduction corresponds to the HPV vaccination coverage in the corresponding age groups.(12-14) Since in Germany the quadrivalent vaccine is predominantly used (it amounts to nearly 90% of all sold doses),(11) the vaccinated fraction can directly be translated into the protected fraction (assuming the probability of vaccination does not depend on the risk of HPV infection). In contrast, there was no evidence of a decrease in the incidence for males or older age groups of females.

To date, the newest data available for the project were from 2008, so we could not investigate whether the incidence remains stable after reaching the level of protection due to direct

effects of vaccination. Herd immunity effects could lead to a further decrease in the incidence, but these effects require more time.

The decrease in the incidence of AGW soon after the introduction of the vaccination in the current study is consistent with the observation that AGW develop within months of the initial infection.(15;24;25) Furthermore, while the complete vaccination schedule with three doses requires six months, there is some evidence that also two or even one dose of the bivalent HPV vaccine may already provide a substantial protection against HPV infections. (26) Similarly, protection against AGW provided by the quadrivalent vaccine might start soon after the initial vaccination, contributing to the short time period between introduction of the vaccine and the start of the decrease in incidence.

Three Australian studies with a smaller study population demonstrated reductions in the incidence of AGW after the introduction of HPV vaccination.(15-17) One further Australian study also showed a reduction in the incidence of cervical abnormalities.(27) In all these studies, the reduction in the incidence exceeded vaccine coverage and displayed a breaking point coinciding with the introduction of the vaccination programme. Recently, similar results were published for New Zealand,(18) and for the U.S.(19). Similarly to ours, these studies used ecological designs, evaluating the trend of incidence over time rather than comparing the risk in vaccinated and not vaccinated individuals. While such studies can be subject to ecological fallacy (drawing inferences for individuals from ecological level data), the evidence of a breaking point coinciding with the introduction of the vaccine and the fact that the observed decrease in the youngest age group accompanies a general increase in the incidence in the whole population support the causal interpretation.

References

Tables

Table 1. Incidence of anogenital warts in the age group 10-79 in Germany from 2005 to 2008

Table 2. Changes in the incidence of anogenital warts among females in the age group of 12 to 19 years for 2005-2008 (separate model in each line, with 2nd quarter of 2007 as a breaking point^a)

^a additionally adjusted for quarters within the year

^b in 1,000 person years

^c after the breaking point

Figures

Figure 1. Incidence of anogenital warts in Germany by sex and age group (age range: 10-79 years)

Figure 2. Incidence of anogenital warts in Germany by sex and age (age range: 10-20 years)