CORRESPONDENCE

The Efficacy and Duration of Vaccine Protection Against Human Papillomavirus: A Systematic Review and Meta-analysis

by Dr. med. Yvonne Deleré, PD Dr. med. Ole Wichmann, Prof. Dr. rer. nat. Stefanie J. Klug, Dr. Marianne van der Sande (MD, PhD), Dr. med. Martin Terhardt, Prof. Dr. med. Fred Zepp, Dr. med. Thomas Harder in issue 35–36/2014

Unethical Approach

The study forms the basis of the new immunization recommendations from Germany's Standing Vaccination Committee (STIKO) (1). Condom use (prevents 70% of infections and 100% of lesions) and smoking (increase of carcinoma in situ up to factor 27) were not considered as factors of influence (2, 3), in spite of STIKO's rules of operation (other options for prevention). This fact distorts the registration trial to an unknown degree, which means that its results are questionable because of bias. Evidence and evaluation cannot be attained in this way. It was unethical not to point out to participants the protective effect of condoms. The authors (some of whom are members of STIKO) mentioned adverse medication effects briefly, without any mention of the discussion on the future of immunization in Japan, India, Spain, and France—among others—because of adverse effects. The STIKO does not mention adverse effects at all in its recommendation. Publications about the importance of adjuvants—for example, by Shoenfeld (ASIA syndrome) and Exley—were completely ignored (4, 5). The past is catching up with authors of all study reports as adjuvants without the actual effective substance (virus-like particles) were used as a placebo. What was studied was not the safety of the vaccines, but whether the adjuvants trigger the same adverse effects as the full vaccine. The use of such a placebo is unethical because it can only be damaging, and it was—the rate of adverse events for the vaccine was at “placebo level.” Balancing risks and benefits, as well as a comprehensive clarification of what is known and what is not, are essential—scientifically, legally, and ethically. The study design has to make answers to questions possible. Postmarketing surveillance has to provide concrete answers about the rate of adverse effects: the product information for Gardasil reports “rate unknown” for seven out of 12 adverse effects.

DOI: 10.3238/arztebl.2015.0209a

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Conflict of interest statement

Jürgen Fridrich has received honoraria for coauthorship, conference delegate fees, travel and hotel expenses, and honoraria for preparing scientific conferences and a research project initiated by him personally for Libertas & Sanitas reg. assoc. He is chair of Libertas & Sanitas reg. assoc. and author of the book *Impfen mit den Augen des Herzens betrachtet – Tatsachen statt Expertenmeinungen* [Immunization studied with the eyes of the heart—facts rather than expert opinion].

Questionable Pooling of Data

The authors report a pooled efficacy of 84% against grade CIN2+ cervical lesions during short-term follow-up of HPV vaccination. They explain the observed heterogeneity with the fact that in some studies this outcome included only HPV 16– or HPV 18-positive lesions, whereas in others it included CIN2+ lesions irrespective of the type of HPV found in the lesion. Instead of scrutinizing, however, whether it actually makes sense to pool these data, the authors simply use a different statistical model. The question arises why they did not analyze either exclusively HPV16– or HPV18-positive CIN2+ lesions — these data have been reported in the PATRICIA study and by Konno et al. (1) —or exclusively any CIN2+ lesions, regardless of HPV type. An appropriate evaluation of the FUTURE studies relating to the quadrivalent vaccine was undertaken by Munoz et al. (2).

This “mixed” efficacy is compared with an efficacy against CIN2+ of 86% after seven years of follow-up, which was observed in an extension study. The fact that this data relates exclusively to HPV16- or HPV18-positive lesions was mentioned neither in the summary nor in Figure 3, but only in the actual text of the paper. Relating to CIN2+ lesions irrespective of HPV type, the extension study calculates an efficacy of 40.6%. Why did the authors not choose this data for their comparison?

In their conclusion, the 84% vaccination efficacy against CIN2+ in short-term follow-up is suddenly related to HPV16– or HPV18-positive lesions. It seems that the authors have lost track of their own data.

The analysis of the outcome “persistent infections” in the long-term follow-up is also incorrect. In the study by Villa et al. (3) which was analyzed in this context, for women in the placebo group who were actually

followed up for five years, only the data for the combined endpoint persistent infections OR CIN1+/genital warts are reported.

DOI: 10.3238/arztebl.2015.0

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Conflict of interest statement

The author belongs to the editorial staff of the independent drug information bulletin *arznei-telegramm*.

In Reply:

We included results from randomized clinical trials in our systematic literature review with meta-analysis on the duration of vaccine protection against human papillomavirus. We explained the studies and evaluation of results according to GRADE in as transparent a manner as possible.

Our study does not represent a general risk-benefit evaluation of HPV vaccination, even though the correspondent of the first letter to the editor wrongly interpreted it as such. Furthermore, our study did not aim to assess the likelihood of infection depending on the possible risk factors or protective factors, not did it aim at addressing possible adverse effects. For this reason, we did not discuss questions relating to the protection conferred by condoms or the influence of smoking. As we mentioned in our article, systematic literature reviews on the topic of adverse effects have been published. The first letter made a series of claims but did not cite any scientific sources in support of these. This includes, for example, the statement that the primary studies had been unethical because participants had not been informed about the protection conferred by condoms. In the primary studies, the question of the efficacy of the vaccine had been investigated in a setting of contraceptive methods as used by the participants. All studies had a positive vote from the ethics committee. Further studies are needed in order to establish whether, and to what extent, consistent use of condoms can actually prevent the development of persistent infection with high-risk HPV types.

The author of the second letter asks why we did not evaluate exclusively higher-grade CIN lesions, independent of the HPV type. We agree that higher-grade

CIN lesions correspond to an important end point, independently of the HPV type. For this reason, the data that were available were used and explained. Only where these data could not be extracted from the published studies did we additionally include results for lesions independent of HPV type in a separate group. On comparing the published data on effectiveness independent of HPV type in the article cited in the letter (1) with those from the long term study (2) on the same end point, the conclusion is that there are no indications for a gradual disappearance of the protective effect. As we explained in our article, however, the evidence backing the long term follow-up is, however, of low to very low quality.

We also have to take issue with the explanation in the last paragraph of the second letter. The analysis of the end point “persistent infections” is not incorrect. In the publication (3), Table 2 lists “infection and disease” as end points. Under this heading, separate data on “infection” and “disease” are reported, the latter subcategorized into “CIN-I-III” and “condyloma.” Data on end points by HPV type were added. We extracted data for our analysis from that particular latter part of the table, whereas a comparison with the top part of the table shows that these related almost exclusively to infections. This example shows that the included original studies had numerous problems relating to the presentation of the data. Searching for evaluable data in the context of a systematic review is time consuming and requires particular diligence. According to international standards, a minimum of two independent investigators should conduct the literature search and data extraction, which was the case in our study.

DOI: 10.3238/arztebl.2015.0210

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Conflict of interest statement

The authors declare that no conflict of interest exists.