

## **Scientists in Germany call for a reassessment of the HPV vaccination and an end to misleading information**

As of autumn 2006, adolescent girls and women in Germany can be vaccinated against human papilloma virus (HPV). Ever since then there have been intense discussions about possible side effects and the costs of the vaccines, as well as the partly misleading promotional information which is given out to the public. The question of how effective the vaccines really are is hardly ever asked. Yet this crucial issue of efficacy – i.e., to what degree the vaccine actually lowers the rate of new cervical cancer cases – has not been sufficiently evaluated, and is the object of misleading information.

### **STIKO made its recommendations before the relevant studies were published**

In March 2007 the “Ständige Impfkommission” (STIKO) [Standing Vaccination Committee] of the Robert Koch-Institute recommended the HPV vaccine for all girls aged 12-17 years to decrease the burden of disease due to cervical cancer. However, at the time the recommendation was made, the results of the decisive studies had not yet been published.

It was not until May 2007 that the most important studies on the Gardasil<sup>®</sup> vaccine, FUTURE I and FUTURE II, were published in *The New England Journal of Medicine* (NEJM). The central message of an editorial published in this journal more than one year later was: “The bad news is that the overall effect of the vaccines on cervical cancer remains unknown” (Haug 2008)<sup>1</sup>. The most important study on the second vaccine, Cervarix<sup>®</sup>, was published in June 2007. Cervarix<sup>®</sup> has not yet been approved in the USA.

### **What do studies and other documents say about the efficacy of the HPV vaccines?**

Cervical cancer is closely associated with HPV infection. Of the approximately 100 known strains of HPV, at least 13 can trigger cervical cancer. Strains 16 and 18, which are the target of these two vaccines, are assumed to be responsible for 70% of all cervical cancer cases.

However, rather than assessing the effect of the vaccine against cervical cancer, the studies examined the incidence of high-grade cervical lesions (a potential precursor of cervical cancer) in 15-26 year-old women.

The vaccine did achieve a 98%<sup>2</sup> decrease in the precancerous stages associated with HPV 16 or 18 in women who had not yet been infected with these two strains. This gave rise to much optimism, and it was widely proclaimed that the 70% of cervical cancer cases associated with HPV strains 16 and 18 could be almost completely prevented (thus achieving a decline in all cervical cancer cases of almost 70%). This assumption, however, has so far not been confirmed by studies.

In analyses which included all women enrolled, FUTURE I found a decline of 7.8%<sup>3</sup> in the incidence of all high-grade cervical lesions (number extracted from EMEA [European Medicines Agency] 2008), and FUTURE II a decrease of 17%.<sup>4</sup> These evaluations have not yet been considered by STIKO. Regarding the second vaccine, Cervarix<sup>®</sup>, STIKO based its recommendations exclusively on data on the prevention of persistent infections. Data regarding the efficacy of Cervarix<sup>®</sup> against precancerous stages or cancer were not yet available.

The efficacy of Gardasil<sup>®</sup>, which has been described as “modest”, was partially explained by the fact that some of the women examined had already been infected with HPV 16 or 18. It is well known that the vaccine does not work once women have been infected. Hence it was

recommended that women should be vaccinated before they could be infected with HPV, i.e., before they become sexually active. STIKO, in its recommendation, set this age at 12-17 years. Data on the efficacy against early stages of cervical cancer, however, are only available for females aged 15-17 years, not for 12-14 year-olds.

To make up for this lack of data, the FUTURE studies conducted statistical analyses including only girls and women who tested negative for HPV 16 or 18 at the beginning of the study. This group was expected to approximate 12-year old girls. However, it remains unclear how Gardasil® affects the total number of high-grade cervical lesions in this group. Here, the only available data comes from a two-year follow-up of the FUTURE studies published by the FDA in 2006 which found an efficacy of 16.9%.<sup>5</sup> The FUTURE II study gives an efficacy estimate of 27%.<sup>6</sup> EMEA provides estimates of 37.9%<sup>7</sup> for 2006 and 46.1%<sup>8</sup> for 2008 for varying populations. However, in order to derive the figure of 46.1%, about half of the women enrolled were excluded *post hoc*.

When asked for additional data, Sanofi-Pasteur MSD Germany replied: “Unpublished figures and tables are only available to the colleagues who were immediately involved in evaluating the results, that is to say, at the headquarters in the USA. We do not have this data, and we will not get it, either.”

### **The STIKO recommendations for the HPV vaccine must be reassessed now**

The STIKO recommendations made in March 2007 were not based on explicit data on efficacy. Instead, STIKO mentions that “lifelong immunity” was 92.5%<sup>9</sup>, apparently based on its own extrapolations. No explanation was given for how this number was arrived at, nor was – or is – there any data on “lifelong” immunity. No study indicated an efficacy of this magnitude.

The STIKO recommendations must be reassessed immediately. STIKO should consider more recent study results and ask manufacturers for the missing data, which must then be included in a new evaluation. This evaluation should indicate clearly and precisely what efficacy STIKO expects of the vaccine, and what assumptions and data these expectations rest on.

### **Adolescent girls and women must be informed adequately**

The results of the studies clearly contradict many overly optimistic pronouncements. Adolescent girls and women are entitled to be adequately informed. We strongly object to stirring up fear regarding the risk of cervical cancer and feelings of guilt by disseminating incorrect information. We demand that gaps in the data be discussed openly. Assertions that a vaccine reduces the risk of cervical cancer by 70% or even 98% should simply not be made at this point in time. Instead, data should be used which is supported by sound research and which gives all those involved an opportunity to make an informed choice.

Prof. Martina Dören  
Charité, Berlin

Dr. Ansgar Gerhardus  
University of Bielefeld

Prof. Ferdinand M. Gerlach  
University of Frankfurt

Prof. Claudia Hornberg  
University of Bielefeld

Prof. Michael M. Kochen  
University of Göttingen

Prof. Petra Kolip  
University of Bremen

Prof. Wolf-Dieter Ludwig  
Charité, Berlin

Prof. Ingrid Mühlhauser  
University of Hamburg

Prof. Oliver Razum  
University of Bielefeld

Prof. Rolf Rosenbrock  
WZB, Berlin

Corinna Schach  
University of Bremen

Prof. Norbert Schmacke  
University of Bremen

Prof. Jürgen Windeler  
MDS, Essen

Contact: Dr. Ansgar Gerhardus, Universität Bielefeld, [ansgar.gerhardus@uni-bielefeld.de](mailto:ansgar.gerhardus@uni-bielefeld.de)

## References with exact positions of quotations and numbers

<sup>1</sup> Haug, CJ (2008) Human Papillomavirus Vaccination — Reasons for Caution. N Engl J Med 2008;359:861-62.

<http://content.nejm.org/cgi/reprint/359/8/861.pdf>

**Quotation** from p. 861, first paragraph

<sup>2</sup> **Number: 98%**

The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-1927.

<http://content.nejm.org/cgi/reprint/356/19/1915.pdf?ijkey=24cc07867ea2faad48e9e69c3463c8905ab010bf>

Abstract and page 1920. Table 3. Last Column

<sup>3</sup> **Number: 7.8%** (for FUTURE I study = Protocol 013)

EMA (2008): Gardasil: European Public Assessment Report. Scientific Discussion (May 2008):

<http://www.emea.europa.eu/humandocs/PDFs/EPAR/gardasil/EMA-H-703-II-13-AR.pdf>

Page 11. Table 6. 6th column, 4th row from below.

<sup>4</sup> **Number: 17%**

The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-1927.

<http://content.nejm.org/cgi/reprint/356/19/1915.pdf?ijkey=24cc07867ea2faad48e9e69c3463c8905ab010bf>

Abstract and page 1921. Table 3. Last Column

<sup>5</sup> **Number: 16.9%**

FDA (2006): Vaccines and Related Biological Products Advisory Committee. (VRBPAC). Background Document, May 2006

<http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.pdf>

Page 17. Table 25. 10<sup>th</sup> column

<sup>6</sup> **Number: 27%**

The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-1927.

<http://content.nejm.org/cgi/reprint/356/19/1915.pdf?ijkey=24cc07867ea2faad48e9e69c3463c8905ab010bf>

Page 1922. 2<sup>nd</sup> paragraph, 6<sup>th</sup> line

<sup>7</sup> **Number: 37.9%**

EMA (2006): Gardasil: European Public Assessment Report. Scientific Discussion (October 2006):

<http://www.emea.europa.eu/humandocs/PDFs/EPAR/gardasil/070306en6.pdf>

Page 28, 2<sup>nd</sup> paragraph following the heading “Population benefit integrated summary of efficacy”. Number refers to R-MITT-2-Population

<sup>8</sup> **Number: 46.1%**

EMA (2008): Gardasil: European Public Assessment Report. Scientific Discussion (May 2008):

<http://www.emea.europa.eu/humandocs/PDFs/EPAR/gardasil/EMA-H-703-II-13-AR.pdf>

Page 22. Table 15. R-MITT-2-population, 6th column.

<sup>9</sup> **Number: 92.5%**

Ständige Impfkommision (STIKO) am Robert Koch-Institut (2007): Impfung gegen humane Papillomaviren (HPV) für Mädchen von 12 bis 17 Jahren – Empfehlung und Begründung.

Epidemiologisches Bulletin 12/2007: 97-103.

[http://www.rki.de/clin\\_091/nn\\_195848/DE/Content/Infekt/EpidBull/Archiv/2007/Ausschnitte/HPV\\_\\_STIKO\\_O\\_\\_12\\_\\_07\\_templateId=raw,property=publicationFile.pdf/HPV\\_STIKO\\_12\\_07.pdf](http://www.rki.de/clin_091/nn_195848/DE/Content/Infekt/EpidBull/Archiv/2007/Ausschnitte/HPV__STIKO_O__12__07_templateId=raw,property=publicationFile.pdf/HPV_STIKO_12_07.pdf)

Page 101. 2<sup>nd</sup> paragraph following the heading “Mögliche Auswirkungen einer Impfung gegen HPV“