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## Questions and answers relating to finding of porcine circoviruses in rotavirus vaccines

### What is the issue ?

Two oral, live attenuated rotavirus vaccines, Rotarix and RotaTeq, are approved for use internationally for the prevention of gastroenteritis in children. Unexpectedly, porcine circovirus has been detected in both vaccines.

### Rotarix (produced by GSK Biologicals, Belgium)

A United States academic research team discovered the presence of DNA fragments of a porcine circovirus (PCV1) — a small, animal virus — in two batches of the GSK Biologicals' (hereafter referred to as GSK) oral, live attenuated rotavirus vaccine, Rotarix, during a study using a new technology for detecting viral genetic material.

On notification by the researchers of their findings on 9 February, GSK initiated tests to confirm the results and investigate further. These tests confirmed the presence of DNA in the two finished vaccine lots previously tested, and in the working cell bank and viral "seed" (starting materials) from which the vaccine was derived — confirming that the material had been present since the early stages of product development, including in the vaccine used during clinical trials.

WHO was informed of the issue by GSK on 16 March. The article by the research team, headed by Professor Eric Delwart, was published online on 7 April ahead of print in the *Journal of Virology*. Victoria JG et al., Viral nucleic acids in live-attenuated vaccines: detection of minority variants and an adventitious virus. *Journal of Virology*, 2010, doi: doi:10.1128/JVI.02690-09

### RotaTeq (produced by Merck and Co., Inc., USA)

On 5 May 2010, WHO was informed by Merck and Co., Inc. that, following testing that the company had undertaken at the request of the U.S. Food and Drug Administration (FDA), fragments of DNA from both PCV1 and porcine circovirus 2 (PCV2) had been identified in its oral, live attenuated rotavirus vaccine, RotaTeq.

The tests were undertaken following the identification of the DNA fragments of PCV1 in Rotarix.

### Why is immunization against rotavirus important ?

Rotaviruses are the most common cause of severe diarrhoeal disease in young children throughout the world, with an estimated 527 000 deaths among children under five years old, most of whom live in low-income countries.

### What are porcine circoviruses ?

Circoviruses are animal viruses with small, circular, single-stranded DNA genomes. They are known to infect birds and pigs. Mammalian circoviruses are porcine circovirus 1 and 2 (PCV1 and PCV2,

respectively), infecting pigs. Porcine circovirus 1 (PCV1) is not known to cause disease in animals (including pigs) or humans. Although PCV2 can cause disease in pigs, it is not known to cause disease in humans. Since both PCV species are highly prevalent in healthy pigs, human dietary and respiratory exposure to this virus is common through pork consumption.

### **Is there any relationship between PCV1 and 2 and PCV7, 10 and 13 ?**

The abbreviation "PCV" is also used for pneumococcal conjugate vaccines. In this case, the number affixed to the abbreviation denotes the number of serotypes of pneumococcus contained in the vaccine. There is no relationship between PCV1 and 2 referred to here (which refer to porcine circovirus types 1 and 2) and PCV7, 10 and 13, which refer to licensed pneumococcal conjugate vaccines containing 7, 10 and 13 serotypes of pneumococcus.

### **What is the significance of these findings ?**

The initial study on Rotarix by Victoria et al used a method that detected DNA fragments and gave no information on the infectivity of this DNA for humans. The authors stated: "In view of the demonstrated benefit and safety of Rotarix the implications (if any) on current immunization policies of the detection of PCV1 DNA of unknown infectivity for humans needs to be carefully considered." Large-scale clinical trials were conducted prior to licensure and samples from infants immunized with Rotarix containing PCV1 are available for study. These are being analysed to determine if vaccination has resulted in human infection with PCV. The initial conclusions from these studies are that human infection with PCV1 has not occurred after vaccination.

The finding of PCV1 and PCV2 in RotaTeq is more recent than the detection of PCV1 in Rotarix. Therefore less information is currently available. Studies are being designed to investigate the findings.

### **How could such contamination have happened?**

Many vaccines are manufactured in complex living systems, such as cells. These cells require the use of biological reagents such as serum and trypsin (an enzyme used to help propagate cells). Regulators require that precautions be taken to minimize the risk of contamination of both the cell substrates and the reagents used for vaccine production. However, scientific knowledge of potential contaminants is imperfect. New viruses continue to be discovered. New techniques to detect new viruses continue to be developed. This is what has happened in this case. The producer was complying with all regulatory requirements at the time the vaccine was licensed by authorities around the world and prequalified (deemed to meet all quality, safety and efficacy requirements for supply to countries through international agencies) by WHO. New regulatory requirements are now being developed in response to this event.

### **Are the vaccines safe ?**

#### *Rotarix*

The current Rotarix safety profile is based on extensive placebo-controlled clinical trial data, including monitoring of non serious and serious adverse events, in 20 studies, with over 50 000 people vaccinated with Rotarix. Vaccines manufactured from the working seed lot and working cell bank in which PCV1 has been identified were used for these trials. Only a few adverse events of mild severity were found to be causally related to Rotarix: diarrhoea, flatulence, abdominal pain, irritability

and dermatitis.

The company's post-marketing surveillance safety data, from vaccines which also contained PCV, after distribution of 69 million doses, has not produced any signal of a safety risk attributable to the presence of PCV1 in the vaccine.

### *RotaTeq*

The safety profile of RotaTeq has been documented through clinical trials and post-marketing surveillance. Clinical trial data comes from the REST study — with nearly 70 000 infants enrolled, and from Bangladesh, Ghana, Kenya, Mali and Vietnam — including a total of more than 7 500 subjects. Post-marketing surveillance comes from several industrialized countries in which the vaccine has been used since introduction in early 2006. Most data, particularly from the post-marketing studies and spontaneous reporting, relate to use in developed countries.

Overall, monitoring of RotaTeq safety has not, to date, identified any signal that suggests a safety risk attributable to PCV.

### **What is the position of the WHO Global Advisory Committee on Vaccine Safety (GACVS) ?**

In its statement published on 26 March:

[http://www.who.int/vaccine\\_safety/topics/rotavirus/rotarix\\_statement\\_march\\_2010/en/index.html](http://www.who.int/vaccine_safety/topics/rotavirus/rotarix_statement_march_2010/en/index.html), GACVS indicated that it had reviewed the safety data from clinical trials and spontaneous reports relating to Rotarix, and found that all data supported the continued safety of the vaccine. The Committee stated that it considered that the benefits of vaccination far outweighed any currently known risk associated with use of Rotarix. The Committee continues to review new and related data as it becomes available, and will issue updates as appropriate.

### **Has this issue been considered by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization ?**

Yes, data relating to the finding of DNA fragments of PCV1 in Rotarix were considered by the Group at its meeting of 13-15 April. The findings on RotaTeq were not known at the time of the meeting. Reports were provided to SAGE by GACVS, regulatory authorities and virologists that are currently conducting investigations into the Rotarix finding, and from the manufacturer.

In the absence of any known risk, SAGE strongly recommended the continued use of Rotarix for immunization programmes, in particular in those parts of the world with elevated under-5 mortality associated with rotaviruses. SAGE is being regularly updated by GACVS as new information becomes available.

### **What is WHO's position ?**

WHO encourages all countries using either vaccine to carefully consider the significant benefits of continued use of rotavirus vaccine in any decisions about further use. WHO concurs with the views of the U.S. FDA and the European Medicines Agency (EMA) that the findings do not present a threat to public health — the withdrawal of rotavirus vaccine would potentially pose a threat to public health. Thus WHO does not recommend any change to use of rotavirus vaccine. WHO is continuing to liaise closely with both the manufacturers and regulatory authorities as the situation evolves. Updated statements will be issued as appropriate.

Both Rotarix and RotaTeq are prequalified (determined by WHO to meet quality, safety and efficacy standards such that they can be supplied through United Nations agencies) by WHO, and the prequalification status of both remains unchanged.

WHO encourages the development of PCV-free rotavirus vaccines and is working with the regulatory authorities to provide guidance to manufacturers on how this might be achieved.

**Why did WHO not recommend suspension of the vaccine when some national regulatory authorities temporarily recommended cessation of use ? (see background section)**

The decision to suspend the use of vaccines is at the discretion of national regulatory authorities. When making such decisions, the authorities take into account considerations relevant to their country, such as the risk tolerance of society, the burden of the disease against which the vaccine provides protection, and the availability of alternative products.

WHO considers that the presence of PCV in rotavirus vaccines presents a theoretical risk to public health. On the other hand, WHO considers that there will be a real increase in disease from rotavirus, which would otherwise be preventable, if rotavirus immunization is suspended, particularly in countries with a high burden of rotavirus disease.

**Are further investigations ongoing ?**

Yes, there are a number of further tests ongoing. WHO is continuing to liaise closely with both the manufacturers and regulatory authorities as the situation evolves. All new data received are being critically evaluated and changes will be made to existing positions if warranted.

**What about other vaccines ? Is PCV1 an issue with those as well ?**

The cell bank used for the manufacture of Rotarix vaccine is the same as that used for the manufacture of GSK's inactivated polio vaccines (IPV). Testing has not, however, identified DNA fragments of PCV1 in the IPV vaccines themselves, due to the purification and inactivation processes undertaken. Furthermore, a review of clinical and post-marketing data does not suggest any relationship between GSK IPV-containing vaccines and hypothetical PCV infection in humans.

Other vaccines and other biological products produced from different cell banks are being evaluated.

**BACKGROUND**

**What is WHO's position on rotavirus vaccination ? (December 2009 WHO position paper)**

WHO recommends that rotavirus vaccine for infants should be included in all national immunization programmes. In countries where diarrhoeal deaths account for  $\geq 10\%$  of mortality among children aged  $< 5$  years, the introduction of the vaccine is strongly recommended.

The use of rotavirus vaccines should be part of a comprehensive strategy to control diarrhoeal diseases; this strategy should include, among other interventions, improvements in hygiene and sanitation, zinc supplementation, community-based administration of oral rehydration solution and overall improvements in case management.

## **What action has WHO taken ?**

Since notification of the issues relating to both Rotarix and RotaTeq, WHO has been in extensive communication with: the reference national regulatory authorities for prequalification purposes (the EMA for Rotarix, and the U.S. FDA for RotaTeq); experts in testing for unexpected agents; and the manufacturers; in order to gather further information.

In order to evaluate in real time the product-specific issues generated by regular reports of new data received from the manufacturers, WHO convened: (a) an ad hoc prequalification advisory committee; and (b) a sub-committee of GACVS.

To evaluate the broader issues of the new testing methodologies, the already established *WHO Working Group on Adventitious Agents in cell substrates* has been considering the issues and is providing advice to WHO. This advice will be considered by the Expert Committee on Biological Standardization in due course.

On 22 March, timed with statements by the U.S. FDA and the EMA, WHO published a statement on its web site indicating its preliminary position - see

[http://www.who.int/immunization/newsroom/news\\_rotavirus\\_vaccine\\_use/en/index.html](http://www.who.int/immunization/newsroom/news_rotavirus_vaccine_use/en/index.html)

WHO convened (by teleconference) on 25 March the Global Advisory Committee on Vaccine Safety (GACVS) — see [http://www.who.int/vaccine\\_safety/about/indepth/en/index.html](http://www.who.int/vaccine_safety/about/indepth/en/index.html) for more information on the Committee — to review the available safety data. GACVS issued a statement on its web site on 26 March

[http://www.who.int/vaccine\\_safety/topics/rotavirus/rotarix\\_statement\\_march\\_2010/en/index.html](http://www.who.int/vaccine_safety/topics/rotavirus/rotarix_statement_march_2010/en/index.html)

WHO's Strategic Advisory Group of Experts (SAGE) on Immunization also reviewed data relating to the finding of DNA fragments of PCV1 in Rotarix at its meeting of 13-15 April. A preliminary statement on the issue was published on the SAGE web site on 21 April — see

[http://www.who.int/immunization/Interim\\_report\\_Flu\\_Rotarix\\_16\\_Apr\\_draft\\_v1.pdf](http://www.who.int/immunization/Interim_report_Flu_Rotarix_16_Apr_draft_v1.pdf)

WHO will continue to communicate closely with the manufacturers of both Rotarix and RotaTeq, national regulatory authorities and WHO advisory committees, on currently-available and new data relating to this issue and will issue additional statements regarding their use as appropriate.

## **What actions have the reference national regulatory authorities for prequalification taken ?**

On 22 March, the U.S. FDA issued a statement recommending that clinicians and public health professionals in the United States temporarily suspend the use of Rotarix while the agency learned more about the situation.

<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm205540.htm>

On the same day, the EMA issued a press release indicating that the Agency's Committee for Medicinal Products for Human Use (CHMP) had undertaken an initial review of the findings and concluded that no action was necessary at that point.

<http://www.ema.europa.eu/humandocs/PDFs/EPAR/rotarix/18935010en.pdf>

On 26 March, the EMA issued a further press release, following a meeting of the CHMP on 25 March, indicating the EMA's conclusion that DNA of PCV1 in batches of Rotarix "does not present a risk to public health" and that there was no need to restrict the use of Rotarix.

<http://www.ema.europa.eu/humandocs/PDFs/EPAR/rotarix/20192310en.pdf>

The U.S. FDA's Vaccines and Related Biological Products Advisory Committee met on 7 May to discuss additional data relating to the finding of DNA fragments of PCV1 in the Rotarix vaccine, and also the finding of DNA fragments of PCV1 and 2 in the RotaTeq vaccine. At this meeting, the U.S. FDA was informed by the Advisory Committee of its view, based on available evidence, that the benefit of using both Rotarix and RotaTeq outweighs any theoretical risk.

On 14 May, the U.S. FDA issued a statement advising clinicians and health-care professionals in the United States of America to resume the use of Rotarix and to continue the use of RotaTeq.

<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm212140.htm>