

21 April 2010

Questions and answers relating to finding of DNA fragments of a porcine circovirus in Rotarix vaccine

What is the issue ?

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 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 ahead of print in the *Journal of Virology* on 7 April.

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

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. Two oral, live, attenuated rotavirus vaccines, Rotarix and Rotateq, are available internationally and are considered safe and effective in preventing gastrointestinal disease.

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. 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 to 13 serotypes of pneumococcus.

What is the significance of a DNA fragment of a porcine virus ?

The DNA fragments from PCV1 that have been detected in Rotarix are present as free DNA and could also be present as infectious virus. Studies are underway to determine whether this is the case.

The above-mentioned paper by Victoria AG et al states "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."

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.

Is Rotarix safe ?

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 DNA 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 PCV1 DNA, after distribution of 69 million doses, has not produced any signal of a safety risk attributable to the presence of PCV-1 DNA in the vaccine..

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, GACVS indicated that it had reviewed the safety data from both clinical trials and spontaneous reports, and found them both to support the continued safety of Rotarix. The Committee stated that it considers that the benefits of vaccination far outweigh any currently known risk associated with use of Rotarix. The Committee will continue to review data as it becomes available.

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

Yes, this issue was considered by the Group at its meeting of 13-15 April. Reports were provided by GACVS, regulatory authorities and virologists that are currently conducting investigations into the 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 asked to be regularly updated by GACVS as new information becomes available.

What is WHO's position ?

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

Rotarix is prequalified (determined by WHO to meet quality, safety and efficacy standards such that it can be supplied through United Nations agencies) by WHO, and the prequalification status remains unchanged.

The lyophilized (freeze-dried) formulation was prequalified on 26 January 2007. The liquid formulation was prequalified on 12 March 2009 for use in Europe and the Americas. Both formulations were granted an extension for procurement for other regions of the world on 7 May 2009.

Why has WHO not recommended suspension of the vaccine when some national regulatory authorities are recommending cessation of use pending further information ? (see background section)

WHO has not seen any evidence that the presence of DNA presents a risk to public health. WHO considered the potential increased disease from rotavirus which could occur if Rotarix is suspended, particularly in countries with a high burden of rotavirus disease, when making this recommendation. WHO is continuing to monitor the situation as more information becomes available.

Are further investigations ongoing ?

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

What about GSK's vaccines containing inactivated polio vaccine (IPV) ? Is PCV1 an issue with those as well ?

DNA fragments of PCV1 were also found in a cell bank which is used for the manufacture of GSK inactivated polio vaccines. Testing has not, however, identified DNA fragments in the 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.

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.

Has PCV1 also been found in other oral vaccines ?

No, the only oral vaccine in which PCV1 has been found is in Rotarix.

What action has WHO taken ?

On 22 March, timed with statements by the United States Food and Drug Administration (FDA) and the European Medicines Agency (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

WHO also 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 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

Since notification of the issue, WHO has been in extensive communication with the reference national regulatory authority for prequalification purposes, the EMA; the United States FDA, where the product is also registered; experts in testing for unexpected agents; and the manufacturer, 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 manufacturer, WHO has 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 *WHO Working Group on Adventitious Agents in cell substrates* will meet on

1-3 June and provide advice to WHO.

What action have national regulatory authorities 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/ucm205539.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 decision to suspend the use of Rotarix is at the discretion of national regulatory authorities. Some authorities have taken the decision to suspend use of Rotarix pending further information. When making such decisions, the authorities take into account considerations such as evidence of safety concerns, the burden of the disease against which the vaccine provides protection in their country, and the availability of alternative products.