The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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QUESTIONS AND ANSWERS ON BOVINE SPONGIFORM ENCEPHALOPATHIES (BSE) AND VACCINES

Find below questions and answers related to BSE and vaccines for human use which are used in the EU.

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I. Questions and answers on Bovine Spongiform Encephalopathy (BSE) and variant CJD

What is BSE?

BSE (Bovine Spongiform Encephalopathy) is a disease of cattle which is commonly known as Mad Cow disease. BSE belongs to a group of diseases called TSEs (Transmissible Spongiform Encephalopathies). BSE was recognised for the first time in 1986 in the UK. A similar disease in sheep, called scrapie, has been recognised for over two centuries. As of July 2000, more than 176,000 cases of BSE were confirmed in the UK.

All TSE diseases are associated with the appearance of tiny particles in brain and nerve cells. The particles responsible for TSE diseases are called 'prions'. The most obvious symptoms of TSE diseases are in-coordination of movements and mental deterioration. Once a TSE disease becomes established, it becomes progressively more serious.

TSEs are said to be 'transmissible', because if certain tissues of an affected animal are given by injection or by mouth to other animals, the disease may be passed on to them. Brain and spinal cord are the tissues which are the most risky in this respect.

How did the outbreak appear in animals?

The outbreak probably started as a result of feeding of animal derived meat-and-bone meal to cattle. There is strong evidence and general agreement that the outbreak was then amplified by the continued feeding of meat-and bone meal prepared from infected cattle

Does this kind of diseases occur in humans?

Yes, but these human diseases are very rare. They include classical Creutzfeldt-Jakob Disease (CJD), variant CJD, Kuru (transmission via cannibalism in Papua New Guinea), fatal familial insomnia. Classical CJD has been well studied for more than 70 years and occurs sporadically worldwide at a rate of about 1 case per 1 million people.

Can BSE be transmitted to humans?

In 1996, the first cases of a variant of Creutzfeldt-Jacob Disease (vCJD) were reported in the UK (Lancet, 1996, 347: 921-925). There is now strong scientific evidence indicating that vCJD and BSE are caused by the same infectious prion agent. The Spongiform Encephalopathy Advisory Committee (SEAC) of the UK has suggested that contaminated food might account for these vCJD cases. As of March 2001, 95 cases of vCJD have been reported in the UK, two in France and one in Ireland.

vCJD affects younger people (average age of onset: 28 years) than classical CJD and the clinical symptoms are different.

What are prions?

Prions are proteins found in all animal species and in humans. Abnormal forms of prion protein are found in TSEs such as BSE, scrapie and CJD. Abnormal forms of prion proteins are closely associated with the spread of the disease. Unlike other infectious particles such as bacteria or viruses, prions do not carry any genetic material. Prions are extremely difficult to destroy: they are resistant to high temperatures and chemicals, which would normally kill bacteria and viruses.

How do prions cause BSE?

Spongiform encephalopathies (also known as prion diseases) are degenerative neurological disorders characterised by the presence of massive amounts of structurally abnormal forms of prion proteins. For an unknown reason, the normal protein can be transformed into a different conformation, by contact with another modified prion protein. This can happen in the brain

where a cascade of progressive degeneration may start. It is thought that the ingestion of a critical amount of this modified protein could trigger the disease.

There is no diagnostic test available yet to identify the disease prior to the start of clinical symptoms and the development of a characteristic neurological pattern. However, diagnostic tests are available and are used for detecting BSE in slaughtered animals.

No medicinal product is available to combat the disease, and no vaccine has been developed to protect animals or people.

Why is the risk of BSE transmission being raised in relation to vaccines for human use?

Material of animal origin, including bovine derived materials, is used in the manufacture of some medicinal products, including vaccines.

However, the European Agency for Evaluation of Medicinal products (EMEA) has been advised by a panel of international experts that the risk of BSE contamination of vaccines used in the EU is extremely low. There are no indications that vCJD is linked to the use of medicinal products, including vaccines, and it is felt that the risk posed by the use of bovine material is very remote and theoretical.

II. Vaccines and risk of BSE transmission

II-1. Questions and answers on bovine materials used in the manufacture of vaccines

What are vaccines and how do vaccines work?

Vaccines are medicinal products, which are given to protect individuals against viral or bacterial infections. Some contain small amounts of inactivated viruses or bacteria, while others may contain micro-organisms which, although alive, no longer cause disease (live attenuated vaccines). Vaccines may also be composed of purified fractions of these micro-organisms or of components derived from recombinant DNA technology. Vaccines act by stimulating the body's own defences (the immune system), so that when he or she comes in contact with the relevant virus or bacterium, he/she will be protected against infection. Tetanus vaccine is an example of a bacterial vaccine and measles vaccine is an example of a viral vaccine.

How are vaccines manufactured?

Vaccines are made by growing large quantities of these viruses or bacteria. These are then inactivated by chemical treatment or used in very small quantities if they are attenuated (live, but no longer able to cause the disease). Bacteria require complex culture media ("culture broths") for their growth. Viruses need to grow in cells and these cells also require complex culture media. The culture media provide numerous nutritious elements and growth factors, obtained from materials of animals origin, such as serum, milk and milk derivatives, gelatin, meat extract of extracts from other muscular tissues ("peptones").

After the processes of bacterial fermentation or viral growth in cell cultures are completed, there is a purification process reducing these growth supplements to trace amounts.

The bacterial or viral components of the vaccine are then diluted to the desired strength and prepared into a finished product, which can be administered to an individual. Vaccines are presented in vials or pre-filled syringes containing the desired bacterial or viral components together with ingredients such as stabilisers.

Are any materials of bovine origin used in the manufacture of vaccines?

Yes, bovine derived materials are used at some stages in the manufacture of most vaccines, but not of all vaccines. These bovine materials are the usual source of nutrients and growth

factors for the growth of bacteria or for the cells used to grow viruses. These elements are essentially provided from materials of animal origin.

Generally they are used only in the early stages of the manufacturing process of the vaccine component(s), and then they are reduced to trace amounts during the further purification and dilution steps.

In other cases, highly processed derivatives of a bovine material are used, e.g. as a stabiliser of the finished product. For example polysorbates, which are manufactured using very high temperature and extreme chemical treatment, are used in a small number of vaccines.

Manufacturers of vaccines strictly control the quality of the materials derived from animals and obtain them from known sources.

Is it possible to replace bovine materials used in the manufacture of vaccines with non-animal materials?

Over the past years there have been many attempts to find a way to replace growth media containing bovine derived materials by more "synthetic" media. Unfortunately, not all the attempts have succeeded in providing bacteria, viruses or cells with all the nutrients present in the bovine material. The use of synthetic culture media sometimes resulted even in the production of a vaccine, which differs from the one expected and may be of inferior quality.

In some cases, it has been possible to replace most or all of the animal materials used during the production of vaccines. Researchers continue their efforts to eliminate materials of animal origin in the manufacturing process.

As a general precautionary measure, manufacturers of medicinal products are encouraged not to use materials of bovine origin if possible, and if possible not to use materials of animal origin at all.

How safe is the bovine material used in the manufacture of vaccines?

Gelatin

Gelatin is extracted from different tissues (usually from skin and bone) from different animal species (usually from cattle and pig). It is used directly in medicinal products, for example in capsules. Gelatin is not a high risk material (a specified risk material -SRM) like brain or spinal cord, but it cannot be excluded that some small amounts of SRM could be found amongst bones from which gelatin is extracted.

The production of gelatin from bones involves grinding, degreasing, heating followed by a hydrochloric acid bath for several days. The gelatin may then be further treated with strong alkali (the preferred manufacturing process for bone gelatin). These processes have been shown to help to reduce or eliminate any contaminating BSE prions. An additional safeguard includes using bones of animals from countries where BSE does not exist, or with a very low number of BSE cases.

Bovine serum

Bovine serum is very rich in vitamins, growth factors and other components necessary to grow the cells needed for viral vaccine production. The safety of serum regarding the risk of transmission of contamination with BSE is ensured by the following elements:

- It has not been possible to detect the presence of the BSE prion in the blood of cattle, either sick or incubating the disease. This is why bovine blood (from which the serum is obtained) has been classified category IV by World Health Organisation (WHO). Category IV is for tissues in which no infectivity has been detected..
- Bovine serum is obtained only from countries with no BSE or with a very low number of BSE cases.

- The cells used for vaccine production and which are cultivated in the presence of bovine serum cannot replicate the prion protein if it were present in the serum. The only cells able to replicate the prion are nerve cells, which are not used for the production of vaccines.

Milk and milk derivatives (for example lactose)

Milk has always been considered as non-infectious, regardless of the country of origin. Like calf serum, milk is classified in category IV (no detectable infectivity). Lactose is a natural sugar present in milk. Milk used for lactose production must be collected under the same conditions as milk for human consumption. This ensures that milk comes from healthy animals, controlled by veterinary welfare systems.

Meat extracts

Meat extracts are derived from beef or other muscular tissues. Most of the tissues are classified category IV by the WHO (tissues for which infectivity is not detectable), and they are collected from countries with a low number or no cases of BSE. Taking these criteria into consideration, meat extracts do not represent a risk of BSE transmission.

Polysorbate (Tallow derivatives)

Tallow derivatives are prepared from tallow (fat)which is derived from animal fat tissue, by separating it from the protein fraction. It has been shown that BSE infectivity (experimentally added to the animal fat tissue) is never found in the tallow fraction, but can be found in the protein fraction. The second step is the manufacture of tallow derivatives, which involves high temperatures and extreme chemical treatment. Tallow derivatives are extremely unlikely to pose any risk of transmitting BSE. Examples of tallow derivatives are stearates (used in many tablets) and polysorbate (used to stabilise vaccines).

II-2. Questions and answers on vaccines and the measures taken to prevent the transmission of BSE

What measures are applied to vaccines to prevent BSE infection?

All medicinal products, including vaccines, have been thoroughly evaluated before they are authorised to be marketed. To receive this authorisation to market their product, a pharmaceutical company has to describe in detail (in a dossier) the results of all the studies demonstrating the quality, safety and efficacy of the medicinal product. The dossier also documents the method of production and control of each component of the medicinal product. In this part of the dossier, all factors concerning the risk of BSE transmission are presented. The dossier is evaluated by the relevant National Authorities or the EMEA, in the light of all existing guidelines. It is only when a dossier is complete and fully satisfactory that a marketing authorisation for a medicinal product is granted.

For all bovine materials used in the manufacture of vaccines (and all other medicinal products) an assessment is made of the risk of BSE contamination. This is carried out in accordance to the European *guideline on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.* This guideline was first applied in 1991, and has been regularly updated since. Factors taken into special account are:

- The country of origin of the animals used,
- The nature of the tissue used (for example, brain is considered the highest risk, serum and muscle tissue are of the lowest risk),
- Information on traceability (origin and follow-up of herds, type of feed, etc...)

- Whether the manufacturing processes of both the materials of bovine origin and the vaccine can reduce or destroy any BSE which may be present.

Therefore, safety related to the risk of transmitting BSE is assessed from a set of criteria taking into account not only the geographical origin of animals but also their feeding, their age at slaughter, technique of slaughter and carving, nature of tissues used, as well as manufacturing processes which must comply with European guidelines and recommendations. It is the assessment of all these criteria, which ensures the BSE safety of a medicinal product, before it is authorised and marketed.

In June 2000, the European Agency for the Evaluation of Medicinal Products (EMEA) conducted a review of the safety of all vaccines on the EU market with respect to BSE contamination and concluded that all vaccines are indeed safe.

What is the risk with vaccines received before the measure of 1991?

It is necessary to point out that experts in the field of Creutzfeldt-Jakob disease and BSE agree that the highest risk arose from food consumed between 1980 and 1996, mainly in the UK. Although they do not have evidence for this, experts believe that certain types of meat (mechanically recovered meat) or certain high risk tissues (brain) used in the preparation of industrial minced meat could have played a major role in spreading the human form of mad cow disease (vCJD). These types of tissue were not used in the manufacture of vaccines. So it is extremely improbable that vaccines could have played a role in spreading the disease before 1991.

Why was an oral vaccine against poliomyelitis withdrawn in the United Kingdom at the end of October 2000?

The withdrawal by the Department of Health of the UK of a specific oral polio vaccine was a precautionary measure undertaken because the vaccine manufacturer had not followed the European recommendations on the use of bovine products of British origin during manufacture. More precisely, the Company had used foetal bovine serum (FBS) at some stage during the growth of the cells used for vaccine production. This FBS had been collected in the UK before 1990.

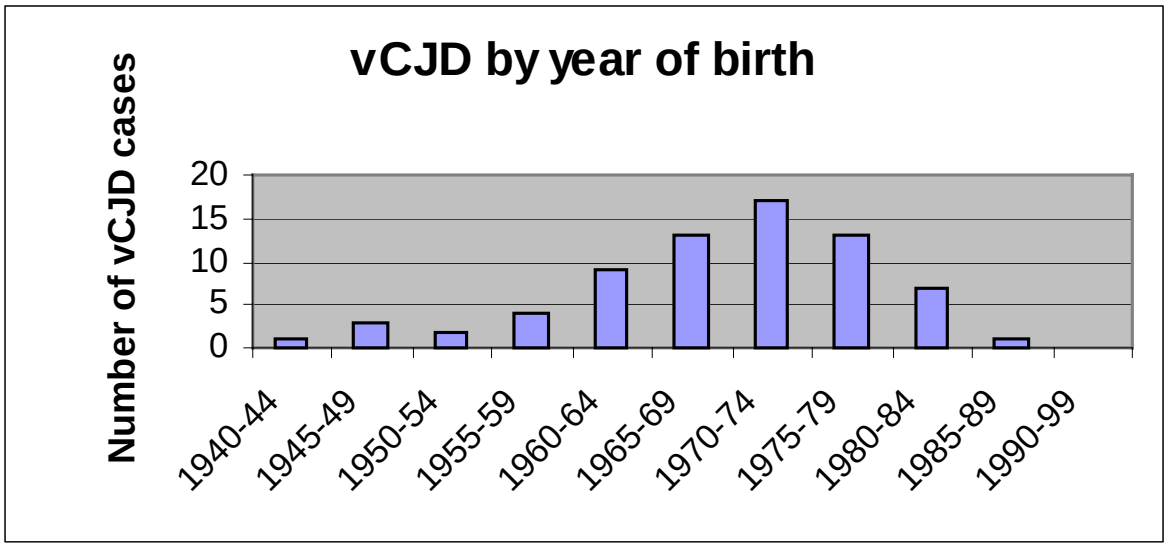
Although the FBS is eliminated during the manufacturing process and is not present in the vaccine itself and although FBS has been classified by WHO and the EU authorities as category IV (no detectable infectivity), the vaccine was withdrawn from the market as a precautionary measure.

Bovine material of UK origin is not used in the routine manufacture of any vaccine. Where bovine material is present in nutritional media used in the fermentation process, it is not of UK origin.

II-3. Questions and answers on the evidence that vaccines do not transmit BSE.

What evidence is there that vaccines do not transmit BSE?

The relationship between the date of birth of the UK v-CJD patients and their probable date of vaccination has been analysed. This study has shown that the majority of the first 74 cases of vCJD observed in the UK were born and would have been vaccinated prior to the occurrence of BSE in British herds. (Most vaccines are given in the first two years of life.) Thus, the vaccines used to immunise the vCJD patients, even if they contained bovine materials, had been produced in the years prior to the BSE epidemic. The vaccines administered are therefore not linked to the appearance of vCJD. The data are summarised in the graph below.



Additional proof that vaccines cannot be associated with any transmission of BSE is the fact that the same vaccines are used throughout the world whereas the nearly all cases of vCJD have appeared in the UK.

What is the experts' opinion on the safety of vaccines with respect to BSE?

Vaccines have played, and continue to play, a crucial role in the prevention and eradication of viral infectious diseases, such as measles, mumps, rubella, polio and smallpox, and of bacterial infectious diseases such as diphtheria, tetanus and pertussis. Vaccines currently in use have an excellent safety record. A reduction in use of vaccines is likely to result in the spread of damaging or fatal diseases.

The European Agency for Evaluation of Medicinal products (EMEA) has been advised by a panel of international experts that the risk of BSE contamination of vaccines used in the EU is vanishingly small. There are no indications that vCJD is linked to the use of any medicinal product, including vaccines, and it is felt that the risk posed by the use of bovine materials is very remote and theoretical.