ACM/1068

ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF FOOD

WORKING GROUP ON NEWLY EMERGING PATHOGENS

CONSIDERATION OF BOVINE NEONATAL PANCYTOPENIA (BNP)

Background

The National Expert Panel on New and Emerging Infections (NEPNEI) asked the ACMSF to consider whether there were any food chain risks associated with BNP (an emerging disease in calves) in July 2010. The issue was referred to the ACMSF's Working Group on Newly Emerging Pathogens who met twice to consider the available information on BNP including published papers, a UK case control study and data presented by the Animal Health and Veterinary Laboratories Agency (AHVLA). The Group were asked to assess whether there was a risk to human health from products from BNP affected calves and from dams with BNP affected calves entering the food chain, specifically;

- milk from dams with affected calves
- meat from recovered calves and dams with affected calves.

The Group were also asked to identify whether there were any data gaps which needed filling and to recommend whether the ACMSF and/or the FSA needed to take any further action.

Microbiological risk assessment

On the basis of the evidence available the Group concluded there were no microbiological risks associated with meat and milk from BNP affected animals. Investigations to identify a microbiological cause have not led to the identification of any microorganisms consistently associated with cases of BNP. These investigations have included histological examination, electron microscopy, cell culture, PCR, microarray and deep sequencing studies designed to detect a wide range of viral and bacterial pathogens [1,2,3,4]. The expanding body of evidence from recent investigations strongly suggests that BNP has an immune-mediated rather than an infectious microbiological aetiology.

Immunological risk assessment

Recent research to understand the pathogenesis of disease has indicated that BNP is associated with alloantibodies present in the dams' colostrum. Susceptible calves exposed to these maternal colostral antibodies become pancytopaenic[5,6,7,8]. Further studies have proposed that these maternal alloantibodies are induced by a bovine viral diarrhoea virus (BVDV) vaccine and are able to bind surface antigens on bovine leucocytes[5,9]. The UK case control study demonstrated a strong association between BNP in calves and vaccination of the mothers with this BVDV vaccine prior to birth[4]. However, the majority of calves born to vaccinated cows do not appear clinically

affected (it is estimated that the incidence for BNP in the EU between 2004 and 2009 was 0.016% based on a single dose)[10]. It has therefore been suggested that there is a genetic component to the disease with recent research proposing a role for allogenic MHC class I antibodies[11,12]. Use of the implicated BVDV vaccine, PregSure BVD vaccine, was discontinued in the EU in June 2010 and its marketing authorisation was subsequently suspended.

The Group felt it was appropriate to consider whether there could be any immunological risks to the foodchain associated with BNP on the basis of the available evidence, recognising the issue of immunological food safety was at the edge of the Committee's remit and expertise. More specifically they considered whether the antibodies that are thought to cause BNP in calves could represent any risk to human health through the foodchain (particularly through meat and milk). Using principles that would be applied in the case of a microbiological risk assessment a number of factors were identified that may reduce any risk to human health from antibodies which cause BNP if present in the foodchain.

UK Cattle Population

Different levels of risk are likely to be associated with different cattle populations depending on whether or not Pregsure BVD vaccine has been administered and whether or not a dam's calf has been affected by BNP. It was suggested that Pregsure vaccinated cows who have had an affected calf (estimated at around 500-600 cases in the UK), would present a higher potential risk than Pregsure vaccinated cows that have not had an affected calf. Unvaccinated cows would pose a negligible risk.

Information on the percentage of the UK cattle population that received Pregsure BVD vaccine prior to its withdrawal was not available. It was estimated that around 60% of UK dairy cows are vaccinated against BVDV but it was noted that two other BVDV vaccines were available at the same time as Pregsure. If the number of doses of Pregsure BVD vaccine administered in the UK and the total UK cattle population were known[1] it would be possible to estimate the number of cattle in the different groups defined above to provide a more quantitative estimate of risk.

The use of Pregsure BVD vaccine was discontinued in June 2010. The peak period for BNP associated alloantibodies entering the foodchain in milk or meat was before the vaccine was withdrawn. Since the withdrawal of the vaccine the risk will have been reducing in proportion with turnover within the cattle population and the introduction of unvaccinated cows into the UK herd. The average lifespan of a UK dairy cow is around 5-6 years. For beef cattle the lifespan is usually at least 7-8 years but can be much longer. Antibody levels in affected dams are also likely to decline in the absence of further administration of the vaccine.

[1] The UK beef herd is currently estimated at 1.6 million and the dairy herd estimated at 1.8 million http://www.defra.gov.uk/statistics/files/defra-stats-foodfarm-landuselivestock-farmstats-dec11-120308.pdf

Meat

Due to the high mortality associated with BNP, affected calves would be excluded from the food chain. There is however the potential for alloantibodies in meat from dams of affected calves, meat from vaccinated cows with unaffected calves and meat from clinically unaffected or recovered calves whose mothers were vaccinated to enter the foodchain. The level of antibody in muscle and therefore meat is likely to be lower than antibody levels in milk. The heat treatment applied when cooking meat is also likely to reduce the functionality of the antibodies present.

Milk

BNP associated alloantibodies may be present in colostrum and in milk from dams vaccinated with Pregsure BVD vaccine whether or not they have produced an affected calf. Milk is routinely withheld from entering the bulk milk tank for 96 hours following calving to ensure colostrum does not enter the bulk milk. Antibody levels in milk are greatly reduced compared with antibody levels in colostrum. Studies have shown antibody levels in cows' colostrum are around 6.0%, dropping to 0.09% in whole cows' milk[13].

Any BNP associated alloantibodies present in milk would be diluted with milk from other cows in the herd and possibly with milk from other herds which would reduce the concentration of antibody present. Antibody levels would be further reduced by processing of the milk. Pasteurisation may damage antibodies but not necessarily destroy them. However, Ultra High Temperature (UHT) pasteurised milk contains little detectable antibody[14]. Milk based infant formulas are subject to high temperature processing (90-110°C for 1-2 mins (or an equivalent UHT process) and spray drying at 90°C for 10-30 secs)[15] which is likely to reduce the level of antibody present.

Antibody absorption in humans

It is not known whether there is any human cell surface protein target that would be recognised by BNP associated alloantibodies. However, if BNP associated alloantibodies were present in meat or milk it was considered unlikely that fully functioning antibodies would persist in the presence of digestive processes in the gastrointestinal tract, be transported across the human gut into the blood stream, evade the immune system and have a sufficiently high affinity for antigens on the surface of human haemopoetic cells to exert an antibody dependent cell cytotoxicity. There is thought to be only very limited uptake of antibody across the post-natal human gut as the majority of maternal to foetal antibody transport occurs across the placenta. This is in contrast to cows where antibody transfer to the calf is through the mothers' colostrum before the calf's stomach becomes impermeable to antibody which occurs around 24 hours after birth.

Human surveillance

There have been no reports of any change in the pattern of aplastic anaemia in humans in the UK in the last four years.

Conclusions

On the basis of the evidence available the Group concluded there were no identifiable microbiological risks associated with meat and milk from BNP affected animals. The Group considered that the immunological risk to human health associated with BNP and the foodchain was very low based on a number of identified factors. The estimated incidence of BNP is low and levels of BNP associated bovine alloantibody in milk and meat once diluted/processed/cooked were likely to be low minimising potential human exposure to any antibodies in meat and milk. Evidence suggests there is minimal transport of antibody across the human gut, with the possible exception of neonates. Given the processing applied to infant formulae exposure of neonates to functional bovine antibodies was likely to be minimal. Additionally it was considered unlikely that sufficient functional antibody would cross the human gut, have a high affinity for a human target antigen and be able to exert a cytolytic effect in humans. As the implicated vaccine has been withdrawn from use any potential risk would be declining and finite. The absence of reports of recent changes in the incidence of aplastic anaemic in humans suggests the emergence of BNP in cattle has not had any observable effects within the human population.

The Group recognised they were on the limits of their remit and competence in terms of assessing immunological food safety risks (rather than microbiological ones). External expert immunological advice was sought and the response suggested that there is no reason to believe that alloimmune disease in cattle represents any risk to humans. These antibodies will be reactive only with bovine antigens and will pose no greater risk to human health than general bovine gamma globulins[16].

It is suggested that the identified factors are relevant ones to consider in terms of a risk assessment but it is recommended that the conclusions reached and any assumptions made are confirmed by a Committee with appropriate immunological expertise. In addition there are implications in relation to stimulation of alloimmunity that should be considered by the relevant authorities for future vaccine authorisation/licensing of viral vaccines produced using a cell line derived from the target species.

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