2012-09-25-145 Paratuberculosis databases updated (2012-09-25)
To: (08) Mycobacterial diseases; (23) Veterinary education; (27) Scientific information

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Reference Laboratory for Paratuberculosis, Brno, Czech Republic

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CGN minireviews on mycobacteria as a public health risk
A new series, aimed at stimulating discussion on published literature dealing with the threat to public health posed by mycobacteria. Although some information of global significance has been known for decades, the risk posed by mycobacteria remains underestimated.

Prepared by the Reference Laboratory for Paratuberculosis and Avian Tuberculosis World Organization for Animal Health (OIE) and Biomedical Technology, Epidemiology and Food Safety Global Network operating in the Veterinary Research Institute, Brno, Czech Republic.

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(01) Do you know that mycobacteria may trigger asthma
(02) Mycobacteria are present in milk and dairy products, including dried milk for formula feeding
(03) A risk, even hypothetical, has to be treated as a risk
(04) How to assess MAP in retail milk

Go to COMMENTS – DISCUSSION – OPINIONS

New publications in the PARATUBERCULOSIS database (1278-1290)

1278 Das, K.M., Seril, D.N. (2012)
Mycobacterium avium Subspecies paratuberculosis in Crohn's Disease The Puzzle Continues
Journal of Clinical Gastroenterology, 46, 627-628

Abstract not available.

1279 Gitlin, L., Borody, T.J., Chamberlin, W., Campbell, J. (2012)
Mycobacterium avium ss paratuberculosis-associated Diseases Piecing the Crohn's Puzzle Together
Journal of Clinical Gastroenterology, 46, 649-655

The relation of Mycobacterium avium ss paratuberculosis (MAP) to Crohn's Disease (CD) and other MAP-associated conditions remains controversial. New data, coupled with the analogous Helicobacter pylori (H. pylori) story, has permitted us to piece together the MAP puzzle and move forward with a more scientific way of treating inflammatory bowel disease, particularly CD. As infection moves centre stage in inflammatory bowel disease, the dated "aberrant reaction" etiology has lost scientific credibility. Now, our growing understanding of MAP-associated diseases demands review and articulation. We focus here on (1) the concept of MAP-associated diseases; (2) causality, Johne Disease, the "aberrant reaction" hypothesis; and (3) responses to published misconceptions questioning MAP as a pathogen in CD

Bead-based microfluidic immunoassay for diagnosis of Johne's disease
Journal of Immunological Methods, 382, 196-202

Microfluidics technology offers a platform for development of point-of-care diagnostic devices for various infectious diseases. In this study, we examined whether serodiagnosis of Johne's disease (JD) can be conducted in a bead-based microfluidic assay system. Magnetic microbeads were coated with antigens of the causative agent of JD, Mycobacterium avium subsp. paratuberculosis. The antigen-coated beads were incubated with serum samples of JD-positive or negative serum samples and then with a fluorescently-labeled secondary antibody (SAB). To confirm binding of serum antibodies to the antigen, the beads were subjected to
flow cytometric analysis. Different conditions (dilutions of serum and SAB, types of SAB, and types of magnetic beads) were optimized for a large degree of differentiation between the JD-negative and JD-positive samples. Using the optimized conditions, we tested a well-classified set of 155 serum samples from JD-negative and JD-positive cattle by using the bead-based flow cytometric assay. Of 105 JD-positive samples, 63 samples (60%) showed higher antibody binding levels than a cut-off value determined by using antibody binding levels of JD-negative samples. In contrast, only 43-49 JD-positive samples showed higher antibody binding levels than the cut-off value when the samples were tested using commercially-available immunoassays. Microfluidic assays were performed by magnetically immobilizing a number of beads within a microchannel of a glass microchip and detecting antibody on the collected beads using laser-induced fluorescence. Antigen-coated magnetic beads treated with the bovine serum sample and fluorescently-labeled SAB were loaded into a microchannel to measure the fluorescence (reflecting level of antibody binding) on the beads in the microfluidic system. When the results of five bovine serum samples with the microfluidic system were compared to those analyzed with the flow cytometer, a high level of correlation (linear regression, r(2) = 0.994) was observed. In a further experiment, we magnetically immobilized antigen-coated beads in a microchannel, reacted the beads with serum and SAB in the channel, and detected antibody binding to the beads in the microfluidic system. A strong antibody binding in JD-positive serum was detected, whereas there was only negligible binding in negative control experiments. Our data suggest that the bead-based microfluidic system may form a basis for development of an on-site serodiagnosis of JD. (C) 2012 Elsevier B.V. All rights reserved

The 9th International Veterinary Immunology Symposium
Veterinary Immunology and Immunopathology, 148, 1-5

This special issue of Veterinary Immunology and Immunopathology summarizes the Proceedings of the 9th International Veterinary Immunology Symposium (9th IVIS) held August 2010, in Tokyo, Japan. Over 340 delegates from 30 countries discussed research progress analyzing the immune systems of numerous food animals and wildlife, probing basic immunity and the influence of stress, genetics, nutrition, endocrinology and reproduction. Major presentations addressed defense against pathogens and alternative control and prevention strategies including vaccines, adjuvants and novel biotherapeutics. A special Organisation for Economic Co-operation and Development (OECD) Co-operative Research Programme Sponsored Conference on "Vaccination and Diagnosis for Food Safety in Agriculture" highlighted the particular issue of "Immunology in Bovine Paratuberculosis". In April 2010 there was an outbreak of foot-and-mouth disease (FMD) in the southern part of Japan. This stimulated a special 9th IVIS session on FMD, sponsored by the World Organization for Animal Health (OIE) and the Ministry of Agriculture, Forestry and Fisheries (MAFF) of Japan, to discuss improvements of FMD vaccines, their use in FMD control, and risk assessment for decision management. The 9th IVIS was supported by the Veterinary Immunology Committee (VIC) of the International Union of Immunological Societies (IUIS) and included workshops for its MHC and Toolkit Committees. Finally VIC IUIS presented its 2010 Distinguished Service Award to Dr. Kazuya Yamanouchi for "outstanding contributions to the veterinary immunology community" and its 2010 Distinguished Veterinary Immunologist Award to Dr. Douglas F. Antczak for "outstanding research on equine immunology". Published by Elsevier B.V

Current strategies for eradication of paratuberculosis and issues in public health
Veterinary Immunology and Immunopathology, 148, 16-22

Paratuberculosis is a regional chronic enteritis caused by Mycobacterium avium subsp. paratuberculosis (MAP). The first complete description of this disease was made in 1895, but previous reports on clinical cases compatible with this entity can already be found in the literature of early 1800s. Its obvious similarities with tuberculosis gave it the name of paratuberculosis, although it was clearly recognized it was not the same entity as that caused
by mammal tuberculosis mycobacteria. Eradication has been considered the ideal goal for control of paratuberculosis, but the lack of efficient diagnostic tools and the high costs involved in testing and culling approaches have shifted the focus to control given the better benefit/cost ratios of more conservative strategies like vaccination. Up to now the control of paratuberculosis has been driven by its negative effects on the ruminant farming industry, however recent growing discussion on its links with human regional enteritis might require control strategies changes if a zoonotic role is considered by Public Health authorities.
Paratuberculosis was described nearly 40 years earlier than what is usually considered the first full type description of human regional chronic enteritis or inflammatory bowel disease (IBD) which is pathologically a similar entity. No microbiological evidence was found to link both entities until the 1980s in spite of a number of more or less serious attempts. Afterwards there have been numerous studies showing the association of MAP with human IBD. Microbiological, pathological, immunological, therapeutic and epidemiologic associations have not been considered proof of causality and, currently, no widely accepted consensus has been reached about the etiologic role of MAP in human cases. This puts ruminant farming under suspicion and causes a difficult balance between Public Health precaution and practical control measures. (c) 2011 Elsevier B.V. All rights reserved

Yoo, H.S., Shin, S.J. (2012)
Recent research on bovine paratuberculosis in South Korea
Veterinary Immunology and Immunopathology, 148, 23-28
Bovine paratuberculosis (Johne's disease), a chronic and debilitating disease of ruminants caused by Mycobacterium avium subspecies paratuberculosis (MAP), is a major cause of chronic ruminant enteritis. A national eradication program has been in place in South Korea since the first report of the disease in 1967; however, only limited data on bovine paratuberculosis in South Korea are available. Some research, such as investigations of the reactivity of animal sera against MAP antigens, has been done in localized areas and in limited animal species. Compared with the worldwide situation, the development of diagnostic methods in South Korea has shown similar results even though some data were obtained from international collaborative studies. MAP is considered by some to be zoonotic, noting an association with Crohn's disease, although this issue is still controversial; however, research into this association is limited. Decisions based on disease priorities have hampered active progress in research on the disease. In this paper, we reviewed the available results generated from South Korea compared with global research. Finally, we propose a theme for future research. (c) 2012 Elsevier B.V. All rights reserved

Whittington, R.J., Begg, D.J., de Silva, K., Plain, K.M., Purdie, A.C. (2012)
Comparative immunological and microbiological aspects of paratuberculosis as a model mycobacterial infection
Veterinary Immunology and Immunopathology, 148, 29-47
Paratuberculosis or Johne's disease of livestock, which is caused by Mycobacterium avium subsp. paratuberculosis (MAP), has increased in prevalence and expanded in geographic and host ranges over about 100 years. The slow and progressive spread of MAP reflects its substantial adaptation to its hosts, the technical limitations of diagnosis, the lack of practical therapeutic approaches, the lack of a vaccine that prevents transmission and the complexity and difficulty of the on-farm control strategies needed to prevent infection. More recently evidence has accumulated for an association of MAP with Crohn's disease in humans, adding to the pressure on animal health authorities to take precautions by controlling paratuberculosis. Mycobacterial infections invoke complex immune responses but the essential determinants of virulence and pathogenesis are far from clear. In this review we compare the features of major diseases in humans and animals that are caused by the pathogenic mycobacteria M. ulcerans, M. avium subsp. avium, M. leprae, M. tuberculosis and MAP. We seek to answer key questions: are the common mycobacterial infections of humans and animals useful "models" for each other, or are the differences between them too great to enable meaningful extrapolation? To simplify this, the immunopathogenesis of mycobacterial infections will be defined at cellular, tissue, animal and population levels and the key events at
each level will be discussed. Many pathogenic processes are similar between divergent mycobacterial diseases, and at variance between virulent and avirulent isolates of mycobacteria, suggesting that the research on the pathogenesis of one mycobacterial disease will be informative for the others. (c) 2011 Elsevier B.V. All rights reserved

Use of the johnin PPD interferon-gamma assay in control of bovine paratuberculosis
Veterinary Immunology and Immunopathology, 148, 48-54

Although the interferon-gamma (IFN-gamma) assay for measurements of cell-mediated immune (CMI) responses to paratuberculosis PPD (johnin) has been available for close to 20 years, the assay has not yet emerged as the long desired test to identify infected animals at an early time point. Among other issues, this relates to problematic interpretation of the test results and maybe an over-expectation of what can be deducted from this kind of test given the chronic nature and slow development of infection of paratuberculosis. Over a number of years a modified IFN-gamma assay with addition of recombinant bovine IL-12 to the PPDj stimulation of blood samples from the heifer group in more than 20 Danish dairy herds which also perform surveillance of MAP antibodies in milk have been performed. The results indicate that IFN-gamma assay results are specific for paratuberculosis, but the IFN-gamma assay result of an individual animal cannot establish whether the animal is infected or predict the future progression of disease in this animal. The IFN-gamma assay should thus be used on a group of animals to test the level of exposure to paratuberculosis bacteria the animals have experienced, and thereby assist in maintaining rational in-herd management procedures and in the establishment of paratuberculosis status of a given herd. Indeed, for any diagnostic test applied in paratuberculosis, both the diagnostic target condition and the purpose of the diagnostic testing must be considered before any meaningful estimates of sensitivity or specificity can be given. (c) 2011 Elsevier B.V. All rights reserved

Molecular pathogenesis of bovine paratuberculosis and human inflammatory bowel diseases
Veterinary Immunology and Immunopathology, 148, 55-68

Paratuberculosis (Ptb), caused by Mycobacterium avium subsp. paratuberculosis (Map), is a chronic enteritis that affects many ruminants and other wild animals worldwide. Ptb is a great concern in animal health and in etiology of human Crohn’s disease (CD). In the present study, we detected Map-specific insertion sequence IS900 of DNA in tissue sections surgically removed from lesions of patients with CD (29 samples), ulcerative colitis (UC) (17 samples), and non-inflammatory bowel disease (IBD) (20 samples). We then compared the histopathological findings of 29 CD and 17 UC cases with those of 35 cases of bovine Ptb, since few comparative pathological studies of human IBD and Ptb have been conducted. The QPCR examination indicated positive results in 13.37% of CD cases, 3.57% of UC cases, and 10% of non-IBD cases. Human CD tissues typically exhibited destructive full thickness enteritis with severe lympho-plasma infiltration and scattered additional granulomas; UC lesions exhibited much less inflammation than CD lesions. Non-IBD control samples did not exhibit pathological changes. Human CD and UC lesions were very different from Ptb lesions that are characterized by predominant granuloma formation. Immunohistochemistry for Map antigen and acid-fast staining were negative in all human IBD cases but were always positive in Ptb cases. Our present comparative study strongly suggests that we reconsider the previous hypothesis that "Map infection" causes CD, even though human intestines were considered to have been exposed to the Map antigen containing the DNA. (c) 2012 Elsevier B.V. All rights reserved
Classical causality models for infectious diseases have fulfilled an important role in the progress of medical sciences, however, new forms of association where weakly pathogenic agents cause widespread infections that mostly do not progress to disease, but that if they do so, cause protracted clinical courses where the host resources are exhausted fit better with the slow infection concept proposed over half a century ago. This model could show an infectious cause behind some diseases that have never fulfilled the conventional criteria. While new mechanisms of causation are defined, these diseases still need to be controlled to allow sustainable animal production. Here, I discuss the case of paratuberculosis control by vaccination as an example of the benefits of using a theoretically preventive treatment to modify the course of infection towards preventing clinical disease even though the infection itself might not be fully controlled. (C) 2012 Elsevier B.V. All rights reserved

Mycobacterium avium paratuberculosis (MAP), etiological agent of paratuberculosis in ruminants, is able to survive extreme conditions like very low pH (stomach), high temperature (pasteurization) or low temperature (refrigerated storage). Cheese, infant powder milk, cream and other milk and dairy products might thus be considered as possible sources of MAP for humans. The aim of this study was to investigate the survival of two MAP field isolates during fermentation of three different types of soured milk products (SMP; yogurt, acidophilus milk and kefir) under laboratory conditions. Pasteurized MAP-free milk was artificially contaminated with $10^6$ MAP cells/mL and survival and absolute numbers of MAP were monitored during fermentation (4 or 16 h) and after six weeks of storage at 4 degrees C by culture and quantitative real time PCR (qPCR). Viability of MAP was determined by culture using Herrold's egg yolk medium and Middlebrook 7H10 with antibiotics, supplemented with Mycobactin J and incubated at 37 degrees C for up to 12 weeks. The absolute numbers of MAP were quantified by previously published qPCR assays targeting F57 and IS900 loci in MAP genome. We herein confirm that MAP can survive pH reduction, however, longer exposure to pH below 4 in SMP seems to be critical because it inhibits growth. Therefore, it is suggested that probiotic cultures that can decrease pH below 4 during fermentation could provide better inactivation of MAP in SMP. (C) 2012 Elsevier B.V. All rights reserved

The aim of this study was to confirm clinical diagnosis of paratuberculosis in two cows showing suggestive clinical signs of the disease. Based on clinical signs, in culture and in IS900 PCR results from the individual milk samples it was possible to diagnose paratuberculosis in the cows studied

Mycobacterium avium subsp. paratuberculosis (MAP) is the etiological agent of Johne's
disease in ruminants. Recent studies have linked MAP to type 1 diabetes (T1D) in the Sardinian population. The aim of this study was to investigate the prevalence of MAP infection in a T1D cohort from continental Italy compared with healthy control subjects. 247 T1D subjects and 110 healthy controls were tested for the presence of MAP. MAP DNA was detected using IS900-specific polymerase chain reaction (PCR). The presence of antibodies towards a MAP antigen, heparin binding hemagglutinin (HBHA), was detected by ELISA. We demonstrated a higher MAP DNA prevalence in plasma samples from T1D patients and a stronger immune response towards MAP HBHA, compared with healthy control subjects. Moreover, in the recent onset patients, we observed an association between anti-MAP antibodies and HLA DQ2 (DQA1 0201/DQB1 0202). These findings taken together support the hypothesis of MAP as an environmental risk factor for the development of T1D in genetically predisposed subjects, probably involving a mechanism of molecular mimicry between MAP antigens and pancreatic islet beta-cells.

New publications in the **CROHN’S DISEASE AND PARATUBERCULOSIS database** (726-733)

**Nod2 improves barrier function of intestinal epithelial cells via enhancement of TLR responses**  
Molecular Immunology, 52, 264-272

Intestinal epithelial cells (IECs) form a physical barrier between the internal milieu and the intestinal microflora via the expression of tight junctions. TLR-mediated recognition of intestinal microflora by IECs is important for tight junction preservation, production of chemokines, and cell survival. Disturbance of the IEC barrier function results in bacterial invasion and contributes to the development of inflammatory bowel disease. We observed that muramyl dipeptide (MDP), a breakdown product of bacterial peptidoglycan, strongly enhances subsequent Toll-like receptor (TLR) responses in murine colonic epithelium cell lines. Prior exposure to MDP significantly increased the production of chemokines and cytokines and improved the barrier function induced by different TLR2 and TLR4 ligands. shRNA knockdown studies showed that MDP recognition by Nod2 mediated the enhancement of TLR responses. Our studies indicate that Nod2 stimulation by MDP significantly enhances TLR-mediated IEC barrier function and chemokine production. Failure of this protective mechanism may contribute to the increased risk of Crohn's disease in individuals with a loss-of-function mutation in NOD2. (C) 2012 Elsevier Ltd. All rights reserved

727  Das, K.M., Seril, D.N. (2012)  
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Practical immunoregulation: Neonatal immune response variation and prophylaxis of experimental food allergy in pigs
Veterinary Immunology and Immunopathology, 148, 110-115
The importance of environment in immune response is identified and the increase in prevalence of allergic, autoimmune and chronic inflammatory diseases reviewed. In particular, altered opportunity to acquire evolutionarily anticipated commensal microbiota is associated through the "hygiene hypothesis" with defective developmental and response signals to the innate and adaptive immune systems. Evidence of the detrimental effects of such environments is reviewed as is evidence for remediation using controlled exposure to bacteria or their active components such as LPS or peptidoglycan ligands for TLR and NOD-like receptors. Occurrence of major environmentally associated changes in porcine immune response phenotype are described. The prophylactic effects of heat-killed Escherichia coli given intramuscularly or of oral Lactococcus lactis on experimental ovomucoid-induced allergy in piglets are described in the context of altered immune response bias favouring reduced type-2 phenotypes. The high frequency of clinical tolerance to developing allergic signs even in the face of classical sensitization indicates possible function in this pig model of regulatory effectors such as Treg cells. (C) 2011 Elsevier B.V. All rights reserved

Bitti, M.L.M., Masala, S., Capasso, F., Rapini, N., Piccinini, S., Angelini, F., Pierantozzi, A., Lidano, R., Pietrosanti, S., Paccagnini, D., Sechi, L.A. (2012) Mycobacterium avium subsp paratuberculosis in an Italian Cohort of Type 1 Diabetes Pediatric Patients Clinical & Developmental Immunology, none, Article Number: 785262 DOI: 10.1155/2012/785262 Published: 2012-Mycobacterium avium subsp. paratuberculosis (MAP) is the etiological agent of Johne's disease in ruminants. Recent studies have linked MAP to type 1 diabetes (T1D) in the Sardinian population. The aim of this study was to investigate the prevalence of MAP infection in a T1D cohort from continental Italy compared with healthy control subjects. 247 T1D subjects and 110 healthy controls were tested for the presence of MAP. MAP DNA was detected using IS900-specific polymerase chain reaction (PCR). The presence of antibodies towards a MAP antigen, heparin binding hemoagglutinin (HBHA), was detected by ELISA. We demonstrated a higher MAP DNA prevalence in plasma samples from T1D patients and a stronger immune response towards MAP HBHA, compared with healthy control subjects. Moreover, in the recent onset patients, we observed an association between anti-MAP antibodies and HLA DQ2 (DQA1 0201/DQB1 0202). These findings taken together support the hypothesis of MAP as an environmental risk factor for the development of T1D in genetically predisposed subjects, probably involving a mechanism of molecular mimicry between MAP antigens and pancreatic islet beta-cells.

Defendenti, C., Grosso, S., Atzeni, F., Croce, A., Senesi, O., Saibeni, S., Bollani, S., Almasio, P.L., Bruno, S., Sarzi-Puttini, P. (2012) Unusual B cell morphology in inflammatory bowel disease Pathology Research and Practice, 208, 387-391 B lymphocytes express various different types of surface immunoglobulins that are largely unrelated to other hematological lines, although some reports have described a relationship between malignant B cells and other cells such as macrophages. Multiple genes of hematopoietic lineage, including transcription factors, are co-expressed in hematopoietic stem cells and progenitors, a phenomenon referred to as "lineage priming". Changes in the expression levels and timing of transcription factors can induce the lineage conversion of committed cells, which indicates that the regulation of transcription factors might be particularly critical for maintaining hierarchical hematopoietic development. The aim of this study was to evaluate the surface markers of particular IgM-positive and irregularly nucleated cells detected in patients with inflammatory bowel disease (IBD), and to assess their association with diagnosis and inflammatory cell recruitment. Small intestine, colon and rectal biopsy specimens of 96 IBD patients were studied. Immunoglobulinproducing cells (IPCs) were analyzed by means of immunofluorescence using polyclonal rabbit anti-human Ig and goat anti-human IgM. The specimens positive for B cells with irregular nuclei were assessed using monoclonal antibodies specific for CD79, and lambda and kappa chains in order to confirm their B cell nature. CD15+ cells, an important marker of inflammatory cell recruitment, were also evaluated. Statistical correlations were sought between the histological findings and clinical expression. 34 (35.4%) of the 96 patients (64 with ulcerative colitis and 32 with Crohn's
disease) presented a periglandial localization of IPCs with irregular nuclei, which showed surface markers specific for the B cell subset, such as IgM and CD79, but quantitative differences in lambda and kappa chains. These specimens also contained CD15-positive cells, which are usually absent in healthy controls. The quantitative aspects and localization of the CD15-positive cells correlated with the distribution of the IPCs with irregular nuclei. IPCs with irregular nuclei were significantly more frequent in those patients with Crohn's disease than in those with ulcerative colitis (p < 0.001). The finding of a subpopulation of cells that simultaneously showed irregular nuclei and B cell markers, such as functional surface IgM, in patients with IBD suggests that an unusual subgroup of B cells that correlates with CD15 expression and a diagnosis of Crohn's disease may be observed in the inflammatory process.

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