Paratuberculosis

Prophesy fulfilled

“The disease has, at present, a limited number of sources from which it can spread. .... These sources of infection will continually increase, unless agencies are operative to offset the constantly increasing commerce in cattle from such herds. ...if not controlled, it may become a more troublesome scourge for future generations than tuberculosis is for the present generation of cattle-owners.” (V.S. Larson, B.A. Beach & W. Wisnicky J. Amer. Vet. Med. Assoc. 80:446, 1924).

We (veterinary medicine and animal agriculture) had our chance to deal with paratuberculosis before it became an epidemic and we muffed it. In 1900 there were only scattered reports of paratuberculosis. A 1922 Agriculture Experiment Station publication in Wisconsin fully described the disease epidemiology, pathology and methods for diagnosis. It stressed that paratuberculosis (Johne’s disease) was seen in a small number of Wisconsin herds urging veterinarians and herd owners to act aggressively to eliminate the disease from infected herds and to protect those that were as yet not affected. Failure to heed these and other such warnings by veterinarians in Europe and the U.S. allowed the disease to insidiously and unrelentingly spread among herds, regions, and countries of the world.

As the famed bacteriologist Stanley Falkow once said: “The objective of a bacterium is to become bacteria”. The pathogen causing paratuberculosis, Mycobacterium avium subspecies paratuberculosis (M. paratuberculosis) has evolved very clever strategies allowing it to replicate inside macrophages, circumvent the host immune response, and persist in the environment waiting to be ingested by another susceptible host as a means of steadily increasing its numbers on the planet. Microbiologists have labeled Mycobacterium tuberculosis Complex (which includes Mycobacterium bovis), the cause of TB, the most successful pathogen on the planet. M. paratuberculosis is on track to one day take this title away.

Prevalence today

Today, 121 years since Heinrich Albert Johne described paratuberculosis in a Guernsey cow in Germany, well over half of all dairy herds in virtually all major dairy-producing countries are infected with M. paratuberculosis. The estimated herd-level true prevalence in the U.S. is now 91%. This infection, first seen in dairy cattle, has spilled over to cattle of all breeds and types. It also is prevalent in both meat and dairy goats and sheep. In the province of Ontario, Canada over half of sheep and goats herds are infected with M. paratuberculosis. Without question, paratuberculosis is a panzootic – and, it just might be a pandemic.

Myriad diagnosis and control tools

Scientists the world over have invested time, effort and millions of dollars toward a better understanding of the pathophysiology of paratuberculosis, its economic impacts, epidemiology, and diagnosis and control measures. Birth of the International Association for Paratuberculosis in 1988 helped foster scientific communication and collaboration. As a result, we bovine veterinarians and paratuberculosis specialists know this disease well and have numerous diagnostic tools at our disposal. We can detect
cattle in the more advanced, most infectious, stage of disease using very inexpensive antibody detection tests on serum or milk samples by ELISA technology. We can detect earlier stages of infection as animals just begin fecal shedding of *M. paratuberculosis* using genetic detection assays, commonly called PCR. We have multiple culture methods for isolation of *M. paratuberculosis*, if required. We have sequenced the entire genome of *M. paratuberculosis* and can effectively discriminate among *M. paratuberculosis* strains by an array of genotyping techniques or whole genome sequencing.

We have risk assessment tools that help evaluate *M. paratuberculosis* transmission risks in herds helping to focus herd management changes on those that will limit infection spread the most. At the University of Wisconsin, we have adapted the U.S. dairy herd risk assessment tool to an iPad App facilitating on-farm completion and submission of herd risk assessments. [http://www.vetmed.wisc.edu/dms/fapm/apps.htm](http://www.vetmed.wisc.edu/dms/fapm/apps.htm). Typically, herd risk assessments reveal the need for herd owners to focus on blocking fecal-oral infection transmission to calves; a task that improves overall calf health yielding significant pay-offs beyond paratuberculosis control.

**Impediments to action**

Why then does paratuberculosis continue spreading? Animal trade continues unabated and is the most effective means of infection spread among herds. Barrett et al. (Vet. Rec. April, 2011) showed that the #1 risk factor for dairy herds being found infected with *M. paratuberculosis* was the direct importation of cattle (OR 19.2, p<0.001). Rarely do cattle owners expanding their herds use appropriate pre-purchase infectious disease testing, especially not for paratuberculosis. The result is an ever increasing herd-level prevalence of paratuberculosis across the globe.

Spread of paratuberculosis between countries by animal trade as they enhance their dairy industry has been repeated over and over again. China is the current best example of this. Huge numbers of cattle being imported to China as it rapidly builds a dairy industry. These cattle come from countries well-known to have a high herd-level prevalence of paratuberculosis. The result is that *M. paratuberculosis* becomes added to the list of infectious diseases that these herds must cope with; a situation that is both unfortunate and preventable. Paratuberculosis control is an added cost to production as the infected herds must invest in routine diagnostics and herd management changes to deal with the problem. Antiquated import testing regulations based on old fashioned tests applied to individual animals (rather than herds of origin) facilitate this mistake. OIE (World Organization for Animal Health) is clearly at fault for failing to promote robust international trade testing protocols thereby allowing paratuberculosis spread to continue, decades after scientists described appropriate biosecurity measures for paratuberculosis; herd-level testing with purchase of herd replacements only from herds with a high probability of being *M. paratuberculosis*-free.

At the herd level, most owners perceive that the cost of the disease, paratuberculosis, is less than the cost of the programs to control it. As a result, only those owners who see obvious clinical disease in too many cows seek veterinary help to control the infection. The majority of commercial herds (herds not selling breeding stock) see no economic motivation to test for paratuberculosis or change management practices to limit its spread.

Cattle breeders fear that a paratuberculosis diagnosis will terminate their ability to sell breeding stock and so they intentionally avoid testing for the infection. Only when they eventually sell an *M. paratuberculosis*-infected animal to another breeder do they discover that their herd is infected. Some of those owners then take this “learning opportunity” to heart, seek veterinary help, and take appropriate actions to rid their herd of the infection; yes, it can be done! Others go into denial, discounting the importance of paratuberculosis, continuing “business as usual”, and thereby fostering the spread of paratuberculosis to other breeder herds whose owners are ill-informed about the importance of buying herd replacements only from test-negative herds.

**Consequences**

The largely uncontained global epizootic of paratuberculosis results in steadily increasing dissemination of *M. paratuberculosis* into the environment. This has consequences for both domestic animals and free-ranging wildlife. The list of wildlife found to be *M. paratuberculosis*-infected is long, and growing.
Examples include; North American Bison, deer, elk, Big Horn Sheep, Rocky Mountain Goats, raccoons and feral cats in the U.S.; fox, stoat, weasel, hare, badgers in Scotland; kangaroos and wallabies in Australia; Guanaco in Chile; and Fallow Deer in Spain. In zoos, paratuberculosis threatens multiple species of hoofed-stock and has also been diagnosed in nonhuman primates. It remains uncertain if *M. paratuberculosis* infections in wildlife are productive infections that threaten wildlife health and pose a risk for spread back to domestic species, or are simply dead-end hosts. For ruminant wildlife, *M. paratuberculosis* is definitely a health problem. Dead-end host or not, this partial list of susceptible animals highlights the capacity of *M. paratuberculosis* to jump species and the expanding impact of this pathogen on the health of all animals.

Humans apparently belong on the list of species susceptible to *M. paratuberculosis* infection. A meta-analysis by Feller et al. (Lancet Infect. Dis. 7:607, 2007) concluded that *M. paratuberculosis* is consistently associated with Crohn’s disease. The most recent study by Timms et al. in Australia (PLOS ONE DOI:10.1371, February 5, 2016) is typical of most such studies. They found that 6 of 21 (29%) Crohn’s patients were positive for *M. paratuberculosis* infection (PCR positive for IS900, and F57, and a 16s rRNA gene common to all mycobacteria). The organism also was successfully cultured from one of these infected Crohn’s patients.

While most in the medical community continue to discount the significance of these findings, it is almost certain that humans are becoming infected and that the most probable means of infection is via the food supply. Infected dairy herds yield *M. paratuberculosis*-contaminated milk. Pasteurization is not 100% effective at killing the organism as evidenced by multiple reports of culturing viable *M. paratuberculosis* from retail dairy products. Cattle, sheep and goats with clinical signs of paratuberculosis are slaughtered and in most all cases used for human consumption. Cooking meat to a well-done condition may effectively kill *M. paratuberculosis* but most foodies would agree that this is not the ideal way to enjoy meat.

Predictions
The 1924 prediction by Larson et al. was right; paratuberculosis has become a more troublesome scourge than tuberculosis (TB), at least in most developed countries. Like bovine TB, paratuberculosis will prove to be a zoonotic disease significantly impacting both animal and human health. Given that all pathogenic mycobacteria are zoonotic, this is not a great leap of logic.

Our strategies for dealing with this panzootic/pandemic will probably not resemble the approaches taken for bovine TB control, however. Countries can no longer afford national control programs like those employed for bovine TB and animal agriculture lacks political power to convince governments to spend the huge sums of money required for such programs. But, this should not paralyze us. Instead, we should find creative ways to foster paratuberculosis control at the level of the animal, herd, region, and internationally. In search of ways to motivate producers, some will say that we need more educational programs. I disagree. We have abundant educational materials in print and on the web and our community of bovine practitioners are well-versed in paratuberculosis and able to teach their producer clients. What we need is a better business plan.

Facing the facts
Producers run businesses that must make a profit if they are to survive. Saddling them with 100% of the cost to control a disease that has health and economic implications for the entire industry, and quite probably food safety and human health, is simply not fair and will never result in real progress. What will motivate producers? The answer is simple: money. We need to put in place economic drivers coupled with industry-driven regulations that make paratuberculosis programs work without creating complex, inefficient and costly governmental programs.

Paratuberculosis can be controlled and quite possibly even eradicated. It is a fecal-oral transmitted disease just like salmonellosis and a host of other infectious diseases. Blocking transmission is simply a matter of hygiene. To insure that hygienic measures are effective it is equally important to find the infectious cows in a herd using diagnostic tests and to cull the test-positives or isolate them away from susceptible calves. None of this is “rocket science”. We have herd risk assessment tools to identify
necessary herd management changes. We have excellent, commercially available diagnostic tests kits available internationally. We have skilled veterinarians to coach producers in the process and insure that they stay on track. The challenge is not in what to do. Rather, the challenge is in doing those things consistently for a long time, e.g. at least 6 years for most dairy herds.

The clock is ticking and time is running out. A large-scale, multi-national clinical trial is underway that may substantiate what case reports have already shown; treatment of Crohn’s disease with a cocktail of three anti-\textit{M. paratuberculosis} antibiotics can cure a high proportion of Crohn’s cases. No other therapy available today can make this claim. The ability to cure Crohn’s disease using anti-\textit{M. paratuberculosis} antibiotics may be the finding that tips the scale of scientific opinion. Consumers are concerned and Crohn’s patients are increasingly aware about the potential health risks of \textit{M. paratuberculosis} (http://thecrohnsinfection.org/). In addition to expecting high welfare standards for food-producing animals the public also should reasonably expect that these animals are healthy. And, animals with paratuberculosis are not healthy.

The way forward
- Veterinarians must be educators as well as guardians of animal and public health. Limiting animal and human exposure to \textit{M. paratuberculosis} starts on the farm; the critical control point. Bovine practitioners should make paratuberculosis a part of every herd health plan.
- Dairy processors should incentivize producers to test their herds. For example, a novel program in the UK offered to pay all of the testing costs for dairy herds that were found to be 100% test-negative.
- Dairy processors should pay producers more for milk from test-negative herds; thus enhancing product safety, insuring consumer confidence, and partially compensating herd owners for their efforts to attain and sustain a test-negative herd status.
- Breed organizations should implement requirements that cattle sold by their members come from test-negative herds. By announcing such programs well in advance and phasing rules in slowly, breed organization members can collectively move toward this ideal goal. For example: organizations could first require that cattle sold only originate from test-negative dams, then require that cattle sold come from test-negative dams in herds where 30 randomly selected adults are found test-negative, and eventually mandate that cattle for breeding purposes are only sold by herds with a history of being test-negative over multiple years. Programs can begin using low-cost, low-sensitivity tests like ELISAs and eventually move toward higher cost and higher sensitivity tests like PCR on fecal samples. Naturally, veterinarians are vital for insuring the integrity of the entire process beginning with sample collection. As the Chinese proverb states: A thousand mile journey starts with one step. It’s time for breeders to take that step.
- Governmental agencies should provide the infrastructure for these market-driven programs; educating veterinarians, licensing diagnostic tests, certifying laboratories and setting standards for herd classification based on likelihood of paratuberculosis-freedom. This infrastructure is already in place in many countries.
- The collective costs for paratuberculosis control will undoubtedly be passed along to consumers. There is nothing unfair about this. They will also be the ultimate beneficiaries of safer food from healthier animals.