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Review Article

Mycobacterium avium Subspecies Paratuberculosis and Global Health An Infectious Disease Incorporated Perspective

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Abstract

Infectious diseases have long been a primary focus of public health concern. The enhanced virulence that occurs when an organism jumps from one species to another species obligates the resultant public health threat to be aggressively addressed: antimicrobial therapy and/or vaccine development. What has received considerably less attention are zoonotic infectious disease organisms already embedded within the human biosphere. Being limited in impact, public health measures tend to be subordinated to overriding economic considerations. Rather than being proactive, these agencies tend to be more reactive in which disease becomes the opportunity that prevention missed.

The thesis of how a government agency allowed *Mycobacterium avium* subspecies *paratuberculosis* presence within nations' food supply to be transformed into a global pandemic is derived from a 20-year collaboration between Infectious Diseases Incorporate and the University of Florida.

Keywords: *Mycobacterium avium;* Food and Drug Administration (FDA); United States Department of Agriculture (USDA)

Introduction

In the United States, the public welfare is mediated through two federal agencies, the United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA). Each agency functions under its specific mandate.

USDA is a sophisticated, massive bureaucracy whose primary focus is the protection and advancement of U.S. agribusiness.

The Rio Declaration on Food Safety and the World Trade Organization Agreement's Precautionary Principle place the obligation to protect the public welfare on the FDA. FDA is a federal agency that has responsibility for population welfare. Its scopes of function are largely encompassed by three Supreme Court rulings: the Federal Meat Inspection Act (21 U.S.C.601et seq.), the Poultry Protection Act (21m U. S. C. 451 et seq.) and the Federal Food, Drug and Cosmetic Act (21 U.S C. 321 et seq). These laws identify a food as being adulterated if it bears or contains any poisonous or delirious substance which may render it injurious to health and is not neutralized by its subsequent processing. By law, such adulterated products cannot enter commerce for food consumption.

To navigate through standing laws and treaties, the FDA has created its own rules of governance. For a food to be labeled as being potentially hazardous to the public health, the proof must be both evidence-based (data derived from multi-million-dollar double blind, randomized comparative studies) and must be absolute. Rigid adherence to this requisite by the agency gives industry a major say over the preponderance of evidence-based knowledge upon which FDA can act.

Avoidance of potential zoonotic adulteration of foods and food-based products has been primarily a producer's responsibility. When a threat to the public health emerges i.e., L*isteria monocytogenes* in ice cream, USDA's intervention is primarily focused on preserving the agribusiness reputation and marketability of the product. Historically, long-term prevention of disease tends to be subordinated to short-term plication of perception of a threat to the public welfare.

Crohn's disease demonstrates how failure to address a zoonotic threat on a national level can have global health consequences.

Crohn's disease

Crohn's disease (CD) is a chronic disease of the human gastrointestinal tract that affects an estimated three to four million individuals within industrialized nations. In 2019, the Centers for Disease Control and Prevention (CDC) identified it as a disease of unknown etiology. What is now established is that CD is an immune-mediated disease whose creation and then disease induction are a function of the widespread presence of viable *Mycobacterium avium* subspecies *paratuberculosis* (MAP) in the food supply within industrialized nations [1].

Results

Viable mycobacteria in milk

When viable MAP isolates were demonstrated in pasteurized milk and commercial milk products, the potential threat to the public welfare was initially viewed through the prism of *Mycobacterium bovis*.

Mycobacterium bovis (MB) produces a chronic, progressive infectious disease primarily of the gastrointestinal tract of cattle. Infected animals shed mycobacteria into their milk. MB infection attained through the ingestion of MB adulterated milk and milk products resulted in potentially lethal gastrointestinal human disease. Between 1912 and 1937, an estimated 65,000 individuals in England and Wales died of gastrointestinal disease contracted from ingestion of milk and milk-products containing MB. The threat to commerce was such that when an infected animal was detected within a herd, the entire herd was destroyed. This threat to agribusiness was resolved when it was demonstrated that MB could be destroyed by pasteurization.

MAP's use of the same vehicle, milk, to access humans put USDA in a dilemma of attempting to balance public health concerns against safeguarding the economic status of milk agribusiness. The number of MAP-infected animals rendered Its prior policy of testing animals and culling infected animals unsustainable.

USDA's initial response was the publication of a paper which stated that pasteurization in the United States effectively destroyed MAP [2]. The paper's experimental design was overtly criticized [3]. MAP presence was then quickly affirmed in pasteurized milk [4]. USDA certified MAP diagnostic tests whose low sensitivity underestimated the prevalence of infection [5]. McKenna., *et al*. showed that the commercial MAP ELISA tests identified only 6.8% to 8.8% of tissue positive cattle [6]. Pinedo., *et al*. demonstrated that MAP ELISA tests had a poor correlation with the documented presence of MAP in the corresponding milk [7]. Cows whose milk tested positive for MAP had negative or inconclusive MAP titers in 23.5% and 11.8% of the cases respectfully.

In the 2001 United Kingdom's report to the Queen, Lord Justice Phillips wrote "Where the likelihood of a risk to human life may appear remote, where there is uncertainty, all reasonably precautionary measures should not be played down on the grounds that the risk is unproven". That same year, the United Kingdom Food Standards Agency wrote "There is undoubtedly sufficient cause for concern (referring to MAP and CD) for further action to be urgently taken to determine what the available data means …. .". In step with the United Kingdom, the U. S. Congress determined that sufficient evidence exists to warrant substantial funding to "increase the knowledge base so that future decisions may be made upon more information". Congress gave USDA sole stewardship of determining whether viable MAP in the nation's milk and food constituted a hazard to the public welfare.

One epidemiological fact that had been in evidence was that MAP had to become widespread in milk-producing herds before CD appeared in the general population. World War II and then the Iron Curtain isolated the Czech Republic [8,9]. Prior to 1950, MAP infection was virtually unknown within its milking herds. Economic hardship obligated most mothers to breastfeed their babies. Following the collapse of the Iron Curtain, some 30,000 heifers were imported from countries whose herds contained animals with paratuberculosis. As the local economy improved,

women began abandoning breast feeding in favor of infant formula. Initially, infant formula was produced from local herds. The single local producer was bought by an international company and local production stopped. Between 1995 and 2004, the incidence of CD in the Czech Republic increased 4.5-fold among 19+ year old and 6.5-fold in 65+ year old individuals.

In 2000, USDA created the Volunteer Bovine Johne's Disease Control Program and in 2001, instituted a five-year Johne's Disease Prevention Dairy Herd Demonstration Program [10,11]. Despite evidence that other mycobacteria on the evolutionary transition from *Mycobacterium avium* subspecies *avium* (MAA) to MAP caused Johne's-like disease in domestic animals, USDA held fast to its pre-requisite that a positive MAP test should only identify animals with the IS900 insertion [12-14].

The U.S. national standard for animal product warranty is addressed through the animal's health certificate. From 2000-to date, USDA has opted not to make an animal's MAP serological status part of an animal's certificate of health. The Code's language in 9 CFR chapter 1 sub-chapter C restricts the inter-state movement of infected livestock. Revisions to Part 71 and 80 of the Code of Federal Regulations (CFR) are intended to specifically restrict the interstate movement of MAP-infected animals. Certifying MAP ELISA tests to be but an insensitive statement of probability of developing Johne's disease rather than a valid measurement of the presence or absence of anti-MAP antibody and not requiring that an animal's MAP serologic status be known resulted in dissemination of infected animals into uninfected herds and secondarily increased the presence of MAP in the milk supply.

In 2000, an estimated 20% of bovine milking herds contained MAP infected animals. By 2007, USDA acknowledged that an estimated 70% of U.S. dairy herds contained MAP infected animals [15]. By 2012, the World Organization for Animal Health attempted to remove paratuberculosis (MAP) from the Terrestrial Animal Health Code because "MAP infection is so widespread, continued recognition of MAP as an animal pathogen would only cause economic losses through the restriction of international trade". Not requiring an animal's MAP status on an animal's certificate of health allowed MAP infected animals to be shipped across state and, more importantly, national borders. In 2012, 54% of MAP infected/diseased animals imported into Japan came from the United States [16].

Discussion

Historically, the therapy for Crohn's disease had been addressed through manipulations of diet. The demonstration that almost any drug therapy that disrupted the body's pro-inflammatory response could induce beneficial results initiated a competition to develop a patentable drug. In 2003, a disruptor of the body's proinflammatory cytokine, tumor necrosis factor alpha, received FDA approval. Its FDA filing identified adalimumab's ability to induce temporary clinical remissions in 40% of study individuals versus 17% for subjects receiving a placebo. At 56 weeks post-drug therapy termination, 36% remained in remission compared with 12% of individuals receiving the placebo [17]. When remissions were induced, they were of time-limited duration.

Through marketing of product, adalimumab attained drug-of-choice status. In its 2018 Clinical Guideline for CD, the American College of Gastroenterologists states "Despite the recent advances in the treatment of patients with CD, there still remains a large group of patients who do not respond adequately to our current medication armamentarium. ……. We will certainly expand our medical treatment war chest and uncover effective biologics with different mechanism of action to treat our patients. If the initial biologic drug fails, the patient will be able to be switch to another agent and even combination biologics may become a reality". …… [18]. In 2023, the therapy of choice for most gastroenterologists remains the administration of biologics.

The ability to induce temporary remission through pharmaceutical disruption of the immune system's pro-inflammatory response re-routed the explanation of CD to a single postulate of causation: autoimmunity. Over the next two decades, autoimmunity and its therapeutic application to CD left unanswered, not just identification of the target antigen, but all the questions embedded in CD's epidemiological profile:

- Its global spread, but one restricted to industrialized nations,
- The relative protection afforded by breastfeeding,
- Initial involvement of only a small area of the small bowel,
- The need for one or more operations to remove diseased bowel in 25% of the cases, and
- The failure of Th1 disruption to ever cure CD [19].

The absence of answers could have moved governmental agencies to ponder whether the linear growth of disease constituted a threat to the public welfare.

The documented pathogenesis of CD

The initial governmental response to allegations of a possible relationship between MAP and CD had been mediated by USDA. Through its effective warehousing of its MAP dilemma in its Volunteer Bovine Johne's Disease Control Program and a five-year long Johne's Disease Prevention Dairy Herd Demonstration Program, USDA unintentionally documented that MAP was a poor potential pathogen for individuals with intact immunity. Individual probability of having ingested viable MAP is a function of time and diet. What was unaddressed was MAP's pathogenic potential for individuals with compromised immunity.

As early as 2005, Hruska., *et al*. at the Veterinary Research Institute in the Czech Republic had identified that 49% of 51 brands of infant formula manufactured by 10 different producers in seven different countries contained MAP DNA [8].

In 2015, the Hruska Postulate was finally released [1]. What it stated was that CD is an immune-mediated disease caused by MAP acting through two divergent mechanisms of action: first as an infectious disease agent and subsequently as an antigen.

Lacking acquired immunity during a significant portion of the neonatal period, a newborn infant is an immune-compromised being. Acquired immunity is central to the immune governance of viruses and mycobacteria. The Hruska Postulate stated that if a newborn infant's MAP infection occurs within its period of immune system compromise, its inherent immune system can become so stressed to abort continued MAP replication that its anti-MAP proinflammatory response can become fixed within immunological memory. Every time preprogrammed mononuclear cells encountered the antigen of MAP; they again respond by elaborating directed cytotoxic cytokines. Confirmation of this postulate was readily attainable, but not in a form that would meet FDA standards. The alternate avenue for confirmation resided in demonstrating how the Hruska Postulate's statement of occurrence addressed every single fact within the natural history of CD. To circumvent effective counter marketing, the explanation of how and why were released in piece-meal fashion:

- Why breast-feeding protected against an infant's future development of CD: avoidance of MAP infection occurring within its period of vulnerability [20].
- Why CD progressed from a rare disease entity to a global pandemic: the widespread presence of MAP in infant formula and powdered milk coupled with the aggressive marketing of infant formula [8,20,22].
- Why is the initial site of disease in the ileocecum: the need for both prolonged and intense cytotoxic occurrence to overcome the regenerative capacity of the gastrointestinal mucosa [22].
- Why the occurrence of bowel perforations, loop-to-loop anastomosis, fistula, strictures: the failure of treating physicians to treat or effectively treat submucosal polymicrobial infection by the gastrointestinal microbiota with proper antibiotic coverage [21-23].
- Why is intense utilization of vegetarian-like diet superior therapy to biologics: avoidance of potential adulterated milk-based foods and meat from herbivores that had been MAP adulterated [24-26].
- Why the failure of FDA to require that biologics be tested against only placebo? Sigell-Boneh., *et al*. achieved clinical and sustained remissions in 70% of children and adults who had failed biological therapy [24]. Chiba., *et al*. demonstrated that 94% of Crohn's afflicted individuals who had achieved remissions on a semi-vegetarian diet remained in clinical remission if dietary guidelines were adhered to [26].

In contrast to zoonotic organisms that cross species boundaries, MAP's pathogenicity for humans was muted until the sheer number of adverse constituted a global pandemic.

Crohn's disease illustrates how an embedded zoonotic potential pathogen, if under- or unaddressed by government agencies, can have adverse global consequences.

USDA's reluctance to prevent widespread MAP dissemination among milking herds set into motion the process by which MAP, first as an infectious disease, and secondarily as an antigen creates the global pandemic of Crohn's disease.

With the pathogenesis of Crohn's disease confirm and unchallenged, aborting the CD pandemic has condensed down

to a single intervention point, avoidance of MAP presence in any form of infant nutrition administered in the first few weeks of a newborn's life.

The FDA's avoidance of principles of both the Rio Declaration and WHO's Precautionary Principle puts into question the ability of governmental agencies to act in the public interest when the need for regulatory action threatens an economic norm. It is IDI's firm contention that strongly advocating breast feeding and the limiting aggressive marketing of infant formula until a newborn attains reasonable degree of acquired immunity stand to significantly impact on future CD recruitment.

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