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Bovine Tuberculosis: A Re-emerging Zoonotic Infection

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ABSTRACT

Bovine tuberculosis is caused by *Mycobacterium bovis (M. bovis)*, which infects both humans and cattle. In 2018, a dairy farm in Wisconsin was affected by *M. bovis*, including a farmworker with exposure to the affected herd. Largely eradicated by effective public health strategies in the United States, most cases are now associated with risk factors including occupational hazards, food consumption, and iatrogenic infections. *M. bovis* continues to cause disease worldwide affecting certain at-risk populations in the United States. Infections more often result in extra-pulmonary sequelae and resistance to pyrazinamide is universal. Thus, successful treatment depends on early and correct identification of the mycobacterium species. A One Health approach to control this re-emerging disease is crucial.

KEYWORDS

bovine tuberculosis; dairy farmworker; Mycobacterium bovis; One Health; zoonotic disease

Introduction

Tuberculosis was a leading cause of death in people in the United States only 100 years ago with an estimated 10% of all cases of tuberculosis in humans resulting from exposure to cattle or products from cattle.[1] Zoonotic transmission (defined as an infection or disease spread from animals to humans) of *M. bovis* is the causative agent of bovine tuberculosis (TB). Previously, one of the most common infections affecting cattle, leading to more losses of U.S. farm animals in the early 20th century than all other infectious diseases combined, bovine TB is now a rare cattle disease within the United States due to the success of the National Tuberculosis Eradication Program.[2,3] Federal and state slaughter facilities are required to undergo carcass inspection in addition to antemortem inspection prior to slaughter.[3] Other means of detecting disease include testing animals prior to movement, during investigations, and at the time of accreditation for TB-free herd status.[3] Together, the United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) eradication program and the widespread practice of pasteurization of dairy products have led to the dramatic decline of *M. bovis* in humans. Although the program has been highly successful, sporadic cases of *M. bovis* continue to appear in U.S. livestock herds and some wildlife populations.[3]

Case study

In October 2018, bovine tuberculosis was identified in a Wisconsin dairy cow, the first reported case in 38 years.[4] Inspectors identified pulmonary tubercles in the affected animal during routine public health slaughter inspection.[5] The Wisconsin Department of Agriculture, Trade, and Consumer Protection determined the source of infection as an infected worker, based on the specific strain matching the strain isolated from an individual who worked on that farm 3 years prior.[5] The direction of transmission is uncertain, as it is possible that either the farmworker or the dairy cow may have been the primary source of infection. Nonetheless, the presence of bovine tuberculosis presents a public health and agricultural challenge. Risk factors for *M. bovis* (Table 1) should be considered when evaluating suspect patients or persons at risk presenting with signs and symptoms consistent with TB. Most commonly, *M. bovis* is transmitted through contaminated milk, but respiratory transmission is possible between cervids and people, including transmission person-to-person.[6,7] In this report, we

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Table 1. Risk factors for infection with *M. bovis*.

Risk Factor	Exposure	Transmission
Occupational	• Livestock farmworker • Veterinary worker • Abattoir/slaughter-house worker • Meatpacker • Zookeeper • Dairy milker	• Respiratory, particularly in non-ventilated spaces • Cutaneous • Contaminated secretions • Contaminated milk, particularly on dairy farms
Iatrogenic	• Superficial bladder cancer treatment • Urology staff	• BCG chemotherapy
Hobby and special populations	• Taxidermy • Raw milk consumption • Hunting • Visiting Friends and Relatives (VFR) travel • Recent immigrants and refugees	• Cutaneous • Gastrointestinal • Respiratory
Zoonotic	• Cattle • Elk • Deer • Bison • Goats • Swine	• Slaughtering • Puncture wounds

summarize the epidemiology of specific populations influenced by *M. bovis* infection in the United States and worldwide.

Populations at risk in the United States

Certain subgroups of the human population are still at risk for bovine TB. Worldwide, *M. bovis* causes nearly 143,000 infections and 12,300 deaths yearly.[8] Of all U.S. tuberculosis cases between 2006 and 2013, 1.3%-1.6% of cases were attributed to *M. bovis* (n = 59,273).[9] High-risk groups included infants (ages 0–4), children (ages 5–14), foreign-born individuals, Hispanic individuals, females, and those who resided in United States–Mexico border counties.[9] Dairy farmworkers, by nature of their daily activities, are in close contact with zoonotic reservoirs of *M. bovis*. Dairy farmers and farmworkers, in general, are disparately more susceptible to infection based on an established increased risk of bovine TB amongst dairy cattle due to environmental factors alone.[10] Latent TB infection (LTBI) prevalence among Mexican dairy farmworkers in California during an outbreak of bovine TB was reportedly 45%.[11] A study in Mexico found a high prevalence of latent tuberculosis by both TST and IGRA, 76.2% and 58.5%, respectively, in dairy farmworkers exposed to cattle with confirmed *M. bovis* infection, particularly those with occupational exposures to non-ventilated spaces.[12] One retrospective analysis of TB case surveillance data in San Diego, California between 1994 and 2005 identified *M. bovis* as the causative agent in 45% of all culture-positive TB cases in children and 6% of adult cases.[13] Notably, infected individuals with *M. bovis* were 2.55 times more likely to die during treatment than those with *M. tuberculosis*.[13]

Migrant and seasonal farmworkers have a significantly higher rate of TB infection compared to the general population with a lifetime risk of 10% for developing active TB.[14] Farmworkers' demographics, immigration status, and access to health care all contribute to their increased morbidity and delayed diagnoses.[13–16] There are approximately 3 million migrant farmworkers in the United States.[15] This group is overwhelmingly foreign born (76%), largely male (68%), and typically young (44% less than age 35).[15] Only 47% of this population reported having health insurance and 34% reported receiving health care from a community health center or migrant health clinic.[15]

Global impact of M. bovis zoonotic disease

The World Health Organization (WHO) recognizes *M. bovis* transmission as an important intersection between animal and human health in creating a roadmap for zoonotic TB. Worldwide, the prevalence of bovine TB is higher than in the United States, attributed to the relative absence of standardized public health policy aimed at eradication of *M. bovis* in animals.[17] "The Paradigm Shift" highlights the population at risk for zoonotic diseases as a neglected population deserving greater attention.[17] Bovine TB directly affects this population's health and the health of their livestock, which in turn indirectly affects their livelihood.[17] Seventy percent of the world's 1.4 billion people living in poverty are dependent

on livestock for dietary protein consumption of meat and milk, as a source of material goods like wool and leather for income generation, and as a labor source for agriculture activities.[17] Loss of affected livestock could have a dramatic effect on their livelihood, as it would for a farm owner's affected herd in the United States.

In a globalized world, U.S. clinicians must recognize the disparately increased burden of bovine TB disease in the developing world. Recent immigrants and those who travel internationally, especially those in the category of Visiting Friends and Relatives (VFR) travelers,[18] may be at increased risk of zoonotic transmission and subsequent presentation of clinical disease when in the United States. There is a lack of surveillance data from humans and animals in most developing countries where bovine TB is endemic.[17] The prevalence of bovine TB in cattle from certain regions was as high as 24.7% in Adama, Ethiopia[19] as identified by meat inspection and 16% in high milk production regions of Mexico identified by bovine carcass bacterial isolates.[20] The reported global prevalence is between 0.3% and 7.2%,[17] but the absence of appropriate surveillance and diagnostics may suggest underestimation of global prevalence.[17] In a meta-analysis of zoonotic *M. bovis* infection, areas of Africa, particularly those areas lacking regular dairy pasteurization and high rates of HIV are particularly at high risk for developing bovine TB, and the presence of these exposure factors may be important signals for enhanced surveillance for zoonotic transmission of *M. bovis*.[21]

The WHO summarized its priorities for zoonotic infections in its call to action in 2017 to bring further awareness to the general population and clinicians with an aim to decrease the global burden of bovine TB disease. These WHO mitigation priorities include increased data collection on bovine TB cases in both humans and animals to accurately assess the global burden of disease, increased laboratory capacity for correct *M. bovis* identification through polymerase chain reaction testing, improved commercial and household food safety practices, focused veterinary efforts in reducing *M. bovis* infection in livestock and disruption of risk pathways for zoonotic transmission to humans through safer food consumption practices like pasteurization.[22]

Discussion

Though occupational risks and food consumption risks predominate globally, iatrogenic modes of *M. bovis* transmission to patients must also be explored. Bacille Calmette-Guerin (BCG) is a live, attenuated microbe derived from *M. bovis*, with the rare potential for disseminated infection.[23–26] Globally, BCG vaccine has been used as immunoprophylaxis against tuberculosis since 1921.[27] Lotte et al. retrospectively reviewed >1000 reports of BCG vaccine complications from 1921 to 1982 and identified 60 cases of disseminated BCG with a mortality rate of 50% in the affected population.[28] In a prospective survey of BCG vaccine complications for infants between 1979 and 1981 in six European countries, the estimated incidence of disseminated disease was 2 cases per 1 million children with a mortality rate of 80%.[29] A literature review of >5,000 reports identified 27 cases of disseminated BCG between 1980 and 1995 with the majority of patients noted to have immunocompromised status. Interestingly, in this study, 50% of cases were vaccinated in a developing nation but 85% of cases were reported from a developed nation.[30] In another report, 38 children with osteomyelitis or osteitis were identified from Taiwan's vaccine injury compensation program between 1982 and 2012.[31] Clinicians in the United States should inquire about BCG vaccine status in cases of suspected tuberculosis. Individuals with primary immunodeficiencies are at highest risk for disseminated or severe BCG infections.

Another means of iatrogenic transmission of *M. bovis* is intravesical BCG instillation, which has been used as a treatment for transitional cell bladder carcinoma since 1976.[32] The reported incidence of systemic BCG infection as an adverse event related to intravesical BCG adjuvant therapy ranges from 3% to 7%.[33] One report describes two cases of hematogenous dissemination of *M. bovis* identified by bone marrow aspirates after BCG intravesical therapy for bladder cancer.[34] Case studies also raise the possibility of transmission from contaminated equipment. One report noted biopsy-proven *M. bovis* infection in a patient who received alternate intravesical treatment, not with BCG chemotherapy.[33] Another report described two cases of children with leukemia found to have BCG-associated meningitis in the absence of BCG vaccination history, speculated source from

accidental inoculation during intrathecal therapy.[27] Intravesical BCG therapy is a risk factor for patients receiving treatment for bladder cancer and other cancer patients through contaminated equipment for therapy.

Conclusion

Patients who present with symptoms consistent with tuberculosis should be interviewed for a thorough occupational and social history to determine their level of risk (Table 1). Individuals with direct contact with infected livestock have the highest risk of transmission.[12] In a suspected tuberculosis case with the above risk factors, clinicians should consider *M. bovis* on the differential. First-line treatment of *M. tuberculosis* includes isoniazid, rifamycin, ethambutol, and pyrazinamide. Clinically, correct identification of the pathogen is needed for appropriate treatment as *M. bovis* is intrinsically resistant to pyrazinamide.[35] Inappropriate therapy with a typical regimen for *M. tuberculosis* could contribute to the further development of resistant strains of *M. bovis*, especially if the strain is additionally resistant to isoniazid or rifampin.[36,37] As a result, current CDC recommendations suggest 9 months of treatment duration for *M. bovis*.[38] A missed diagnosis of *M. bovis* could lead to poorer outcomes as it is more likely to cause extrapulmonary infections.[36,37,39,40]

Although certainly not a novel idea, but one that is gaining momentum, is that of "One Health" when approaching these multisectoral diseases. As the interface between humans, animals, and the environment grows ever closer, it is important to start thinking and problem-solving via an interdisciplinary approach and *M. bovis* is a great example of One Health in practice. In order for prevention strategies to be effective, public health, medical, and veterinary professionals collaborated to create programs such as the National Tuberculosis Eradication Program aiming to eliminate *M. bovis* in domestic cattle and ultimately preventing clinical cases of *M. bovis* in people. Without this interdisciplinary action, the control and resultant eradication of zoonotic *M. bovis* would pose significant challenges. The transmission of *M. bovis* involves multiple domestic and wildlife reservoirs with zoonotic disease spread to humans through foodborne, respiratory, and cutaneous routes as noted in Table 1. Multisectoral response at federal, state, and local levels is essential in prevention and eradication efforts. It is important to engage and harness these collaborations for *M. bovis* to ultimately minimize its impact on human and animal health and prevent re-emergence of zoonotic diseases.

Disclosure statement

No potential conflict of interest was reported by the authors.

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