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Bovine tuberculosis and its public health significance/bovine tuberculosis and its public health significance: A review

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Abstract
Tuberculosis has been declared as global emergency by WHO as about 85 per cent of all tuberculosis cases occur in WHO region of South East Asia (34%), Africa (31%) and western pacific (20%). The disease is accountable for more deaths throughout the world than any other bacterial disease ever today and about 8 million new cases occur each year of which 3 million die. The most important causes of bovine TB in cattle is *M. bovis* which infects other domesticated and wild mammals. The zoonotic transmission of *M. bovis* is responsible for 10-15 per cent of new human TB cases in developing countries and about 1-2 per cent of the cases in developed countries and prior to pasteurization 25 per cent of all TB cases of children are due to bovine TB and the condition is aggravated in immunocompromised patients. Worldwide loss due to bovine TB is 3 billion US$ is due to loss of production (30%), trade barrier and long therapy (9 months) due to extrapulmonary form of disease. It is estimated that about 90 per cent of human population lives in countries where cattle and dairy animals receive partial or no protection against bovine tuberculosis. Bovine TB is endemic in India, the overall prevalence of bovine TB in animal is 7.3 per cent. Lack of National TB control policy, poor lab facility, wild life and domestic animal reservoir are the hindrance to achieve the goal of elimination of TB by 2025.

Keywords: *Mycobacterium*, public health implication, zoonotic tuberculosis, re-emerging, extrapulmonary form

Introduction
Tuberculosis (TB) is a chronic insidious contagious disease of man and animal caused by pathogenic organisms of the genus mycobacterium characterized by development of tubercles with resultant caseation and calcification. The name tuberculosis comes from the nodules, called 'tubercles', which are frequently located in lung and lymph nodes but, they may be found in the liver, spleen, intestine, peritoneum, meninges and long bone. Excepting skeletal muscle, tubercles may be seen in almost all the tissue and organ of the body. According to location of the tubercle in body, it is known by different name that are Pearl's disease (tuberculosis of serous membranes that is characterized by small rounded grayish elevated lesions and occurs chiefly in cattle), Scrofula (Granulomatous cervical lymphadenitis), Acinitis (TB of acinus of gland), Scrofuloderma/Lupus vulgaris (Chronic dermatitis of skin), Pott's disease (TB of spine). Other synonym of disease are Consumption disease (common term for wasting away of body, particularly from pulmonary TB), Pthisis (Greek word meaning 'a dwinding or wasting away'), King's evil (because of myth that it could be cured by the touch of a reigning monarch) or Great white plague, Great white scourge, Rajayakshman (The king of diseases), Tuberculous caseous pneumonia.
The most important causes of bovine TB in cattle are *M. bovis* and *M. caprae* both of which infects other domesticated and wild mammals [24]. *M. bovis* is a member of the *M. tuberculosis* complex, which also include *M. tuberculosis*, *M. cannettii*, *M. microti*, *M. africanum* and *M. caprae* [4]. Clinically, *M. bovis* shows a high degree of virulence for both humans and cattle, in contrast to *M. tuberculosis* which is virulent for human and not for cattle. The zoonotic importance of *M. bovis* has been increased because of high incidence of TB in human population in the countries, mostly the developing ones that are currently being plagued by HIV/AIDS infection [30]. It has been estimated that zoonotic transmission of *M. bovis* is responsible for 10-15 per cent of new human TB cases in developing countries and in about 1-2 per cent of the cases in developed countries [1]. Prior to mandatory pasteurization of milk in

many countries, *M. bovis* accounted for 25 per cent of all TB cases in children [26]. In addition to being a threat to public health, bovine TB is also a major economic concern, costing an estimated USD 3 billion worldwide annually due to losses from reduced cattle productivity, culling and movement and trade restrictions [35].

Tuberculosis has been declared as global emergency by WHO as about 85 per cent of all tuberculosis cases occur in WHO region of South East Asia (34%), Africa (31%) and western pacific (20%) [37]. The disease affects all age groups of susceptible hosts and is accountable for more deaths throughout the world than any other bacterial disease ever today [27] and about 8 million new cases occur each year of which 3 million die. Six Asian countries account for about 4.5 million cases of the 8.0 million new cases, these are Bangladesh, China, India, Indonesia, Pakistan and Philippines. Every second adult in India is infected with TB and every minute one Indian dies (5.0 lakh every year) of this disease [21]. An estimated 12 to 13.0 million TB cases are in India, of which 3.5 million are sputum positive, 2.2 million new active cases of TB reported every year and only half seek medical help [21]. The World Health Organization (WHO) considers tuberculosis a re-emerging disease.

Childhood deaths from *M. tuberculosis* are usually caused by meningitis or disseminated disease [37]. Young children infected with *M. bovis* typically have abdominal infections and older patients suffer from swollen and sometimes ulcerated lymph glands in the neck [32]. Cases of tuberculosis in children usually represent between 10 to 20 per cent of all tuberculosis. Because of less-developed immune system, children under 5 years of age are more prone to develop (up to 20%) the disease mostly within 2 years following infection [37]. The commonest age of childhood TB is 1 to 4 year.

History

It is one of the most ancient diseases of the mankind and animals. Aristotle was first to say that tuberculosis is an airborne disease. In 1865 Jean Villemin, put out the idea that TB was genetically inherited. While, in 1882 Robert Koch proved it wrong by discovering the tubercle bacillus as the cause of tuberculosis, during this time; TB killed one out of every seven people living in the United States and Europe. Avian bacillus was recognized by Nocard in 1885 and in 1898 *M. bovis* was identified [22] and in the same year differentiation of bovine and human tubercle bacilli was done by Theobalt Smith. Diagnosis of tuberculosis was aided by discovery of the acid fast nature by Ehrlich in 1882, development of tuberculin test by Von pirquet and Mantoux in 1907-1908 and preparation of purified protein derivative (PPD) of tuberculin by Seibert in 1931. For prevention of TB in 1921, Calmette and Guerin developed an attenuated strain of *M. bovis* [5]. Griffith isolated *M. bovis* from the sputum of a butcher suffering from pulmonary tuberculosis in 1909. In 1911, it was clearly shown that *M. bovis* was able to cause all forms of tuberculosis in man and good number of children got infection through milk.

Epidemiology

M. tuberculosis complex (Group1) includes seven species namely *M. tuberculosis, M. bovis, M. africanum, M. microti, M. canettii, M. caprae* and *M. pinnipedii.* The bacilli are long, slender, strait or slightly curved rods (1-10 µm x 0.2-0.6 µm) and are facultative intracellular microbe, non-capsular, non-spore forming, non- motile and obligate aerobic. Its cell wall is rich in lipids, *i.e*. mycolic acid which is responsible for acid fastness. *M. bovis* lacks an outer cell membrane that is known as *M. tuberculosis var* [10]. *M. bovis* is a member of *M. tuberculosis* complex based on 16S ribosomal RNA sequence studies it shared more than 99.95 per cent of identity with other members of *M. tuberculosis complex.* Zoonotic tuberculosis is caused by *M. bovis, M. caprae, M. orygis, M. pinnipedii* and *M. microti,* all cause tuberculosis in humans [18].

Host Range

Maintenance host

Cattle (most susceptible), sheep, goat, buffalo, dog, cat, horse, pig, deer, monkey, chimpanzee, bison, elephant, marsupials, mink, moles, badgers, opossum, cockattoo, ferret, fox, hare parrot and [8]. Rabbit and cats are susceptible to *M. bovis* and are quite resistant to *M. tuberculosis* [19].

Reservoir host

Free-ranging populations of white-tailed deer (*Odocoileus virginianus*) in the US, brushtail possum in New Zealand, badger in the Republic of Ireland and the United Kingdom and wild boar in Spain and Iberian Peninsula [21].

Resistant host

White races seem to have an inherent resistance or herd immunity to TB. Other peoples, such as the eskimos and negroes had no previous contact with either human or bovine TB and were therefore much more susceptible [17].

The most important causes of bovine TB in cattle are *M. bovis*. Bovine tuberculosis in wildlife was first reported in 1929 in greater kudu (*Tragelaphus strepsiceros*) and common duiker (*Sylvicapra grimmi*) in South Africa and by the 1940s, the disease was found to be endemic in greater kudu [2].

Table 1: Susceptibility of animals to the mycobacteria that cause tuberculosis

	Mycobacterium tuberculosis	***Mycobacterium bovis***	***Mycobacterium avium subsp avium***
Primates	+	+	-
Cattle	(+)	+	(+)
Sheep and goat	-	+	(+)
Pig	(+)	+	(+)
Horse	-	+	+ (intestine)
Dog	+	+	-
Cat	+	-	-
Poultry	-	-	+
+ = susceptible, (+) = slightly susceptible or become sensitized, - = resistance to infection			

Global distribution of disease

Distribution of *M. bovis* and *M. tuberculosis* is worldwide**.** Today it remains a major disease of cattle and wildlife**.** Zoonotic TB is distributed globally and is more prevalent in most of Africa, part of Asia and of the America except Antarctica, Caribbean islands, parts of South America, Australia, Iceland, Denmark, Sweden, Norway, Finland, Austria, Switzerland, Luxembourg, Latvia, Slovakia, Lithuania, Estonia, the Czech Republic, Canada, Singapore, Jamaica, Barbados and Israel. Although most of the developed countries have reduced or eliminated bovine TB from their cattle population. However, the disease is still present in the wildlife of United Kingdom, United States and New Zealand [32].

Distribution of disease in India

TB is widely prevalent among cattle, buffaloes and pigs. The infection has been detected in 20 per cent dairy herd of Bangaluru in 1973, reported from Haryana (1970-1979), Meghalaya (1982), Uttarpradesh (1985), Punjab (1994) and Orissa (1997). Analysis revealed a pooled prevalence estimate of 7.3 per cent, indicating that there may be an estimated 21.8 million infected cattle in India. No reports were found from Arunachal Pradesh, Assam, Chhattisgarh, Goa, Jharkhand, Manipur, Mizoram, Nagaland, Sikkim, Telangana, Tripura, Andaman and Nicobar Islands, Chandigarh, Dadra and Nagar Haveli, Daman and Diu, Delhi and Lakshadweep, comprising a total of 11 states and six union territories [31]. These data suggest that India being the world's largest producer of milk (156 MMT) and the world's largest red meat exporter (1.9 MMT), there is an urgent and as yet unmet need for control of bovine TB for both economic and public health reasons [7]. The prevalence of bovine TB in cows (6.3%) was marginally higher than the prevalence in buffaloes (4.3%) and amongst cows, prevalence by breed did not vary greatly as crossbred cows were found to have the highest prevalence with 8.1 per cent, followed by indigenous cows (7.4%) and exotic cows (7.0%). Unlike cattle breed, larger differences were seen amongst production systems as cattle housed in gaushalas had a higher prevalence (19.1%) as there are over 5,100 of these "old age homes" for cows in India [7], than those kept in organized farms (5.1%) and rural conditions (4.4%). The time period 1941–1960, was found to have the highest prevalence (13.8%), while 1961–1980 was found to have the lowest (3.6%). The time period between 1981 and 2000 showed a prevalence of 7.0 per cent and the prevalence of the most recent time period between 2001 and 2016 were determined to be 6.8 per cent.

Transmission in animal

Animal to animal transmission

- Direct contact – Transmission of *M. bovis* from infected animal to the healthy animal via direct physical contact with their discharge (blood and body fluid) or contact with contaminated utensils.
- Inhalation – Transmission of *M. bovis* is mainly occurring through aerosol. It is demonstrated that <10 viable bacilli are sufficient to cause established tuberculosis pathology [9]. In 75-90 per cent of animals the primary focus is found in the lungs. The animal and man expels tubercle bacilli in small droplet of secretion, which shrink a droplet nucleus less than 5 µm in diameter. This droplet nucleus is small enough to remain suspended indefinitely in the air, and to be deposited in the respiratory tract, well beyond the ciliated epithelium [9].
- Ingestion of infected material along with food and water. Ingestion of milk from infected dams in case of new borns or through umbilical vein as a result of uterine infection. 10 mg of bovine tubercle bacilli are necessary to cause alimentary infection in calves whereas 0.01 mg of bovine tubercle bacilli are required to cause pulmonary infection [15].
- Bite of infected hard tick (in guinea pigs and rabbits) and of infected badgers (in badgers). The hard ticks which have been found to act as a reservoir of *M. bovis* to deer, cattle, guinea pigs and rabbits, respectively.
- The infected bull semen may transmit diseases through artificial insemination [32].

Man to animal transmission

- Urination by farm workers with renal tuberculosis in cowsheds [38].
- Direct exposure of animals to infected farm worker [23].

Transmission in human

Issue of human infection with *M. bovis* has risen because of its significance and prevalence of human to human transmission. The transmission of *M. bovis* from animal-to-man takes place due to:

- Direct exposure to infected animal/carcass during work at farm/abattoir/clinics (occupational exposure). An estimated annual average of 10-15 persons contract the infection from one case of infectious pulmonary TB.
- Ingestion of unpasteurized milk or raw or inadequately cooked meat from infected animal, contact with contaminated dust.

Factors favours transmission and distribution of *M. bovis*

1. Survivability outside the host

M. bovis can survive in the environment for various months especially in cold, dark and moist conditions. The survival period varies from 18 to 332 days at 12-24^{0}C which is dependent on sunlight exposure. It is found that *M. bovis* best survives in frozen tissue and there are adverse effects of tissue preservatives, that is, sodium tetraborate on viability [33]. Faeces of infected cattle are major source of infection as faeces remain infective for 6-8 weeks in slurry [29]. *M. bovis* survives in stagnant water for 18 days and it is highly resistant organism surviving in cow faeces for at least 5 months in winter, 4 months in autumn, 2 months in summer, up to 2 years in soil, 4 months in liquid manure stored underground and 1-2 months in soil during the summer months[38]and one week on pasture in dry conditions thus facilitating the spread of infection. It can survive in guinea pig carcasses - 49 days, carpet - up to 70 days, dust - 90 to 120 days, cockroaches - 40 days, paper book - 105 days, sputum (cool, dark location) - 6 to 8 months, clothing - 45 days [20]. Milk products such as yoghurt and cream cheese made from unpasteurized milk have been found to contain TB bacilli 14 days after manufacture and butter as long as 100 days after manufacture [17].

2. Susceptibility to disinfection

Bacilli can survive in Droplet for 8-10 days. *M. bovis* survives in 5 per cent phenol, 15 per cent sulphuric acid, 3 per cent nitric acid, 5 per cent oxalic acid, 4 per cent sodium hypoxide and are susceptible to disinfectant having high concentration of iodine, glutaraldehyde, formaldehyde [20].

3. Physical inactivation

Sensitive to moist heat (121^{0}C for at least 15 min) and light [20].

The incidence appears to be affected by many factors, such as

1. General health care- Poor/inadequate health care favours disease
2. Standard of living- Poor living/socioeconomic conditions favours disease
3. Nutrition- Poor diet favour, malnourished animals readily contact the infection rather than well nourished group. Vitamin A, D (it has key role in activation of macrophages in early stage) and C deficiency predispose

the infection.

4. Age – Younger age group of animal are less susceptible where as younger age group of human population are more susceptible to tuberculosis. Eight out of 10 of all those struck by tuberculosis are in economically productive age group of 15-49 years. Congenital infection in calves has been reported infrequently. The disease is more prevalent in buffaloes having around 5-6 years of age as body mass less than 550 kg [12, 13]. Cattles are more prone to infection with increased age. Bull calves are less susceptible [16]. In India, from an average of 2 per cent in "0-14 years age group" childrens are affected. In the developed countries, the disease is now more common in the elderly. Adult animals are more often diagnosed and they are more commonly symptomatic.
5. Breed- *Bos taurus* is usually more affected than *Bos indicus* [34].
6. Population density- Higher density favour the occurrence.
7. Occupation- Necessitating exposure to metallic and stone dust and congregation, laboratory/post-mortem room workers
8. Sex- More male than female because of opportunity of congregations
9. Contact with tuberculosis patient- 3 aspect are important; (a) The duration of infectious stage (open/sputum positive), (b) The bacterial concentration in the air, and (c) Degree of contact. In a tuberculosis ward, one case contributed one infectious particle per 200 cubic feet of air.
10. Personal hygiene- Poor personal hygienic habit, over-crowding and inadequate ventilation favour spread of tuberculosis. Overcrowded house, premises and common drinking and feeding troughs are the important source. Thus, disease is more prevalent in dairy cattle rather than range cattle.
11. Innate resistance- Gurkhas had five times more incidence of tuberculosis than Marathas in Indian army suggested that innate resistance influenced the transmission.
12. Condition of the individual- Immune-compromised state due to drug or infection like AIDS/HIV, diabetes mellitus, alcoholism is predisposing condition for the disease.

Pathogenesis

Pathogenicity of Mycobacterium is due to its ability to escape killing by macrophages and induce delayed type hypersensitivity. This is an account of several components in its wall.

a. Cord factor, a surface glycolipid present in the cell wall (trehalose-6, 6' dimycorate, sulphur containing glycolipids). Virulent strain of *M. tuberculosis* have cord factor on their surface, whereas avirulent strains do not. It causes formation of characteristic granuloma, IL17 is an important cytokine in the induction of optimal Th1 response and protective immunity against Mycobacterial infection [28].
b. Lipoarabinomannam (LAM), a heteropolysaccharide similar in structure to the endotoxin of gram negative bacteria. It inhibits macrophage activation by interferon-gamma. LAM also induces macrophages to secrete tumor necrosis factor alpha and IL-10 which causes fever, weight loss, tissue damage and interleukin-10 that suppresses mycobacteria induced T cell proliferation.
c. Complement, when activated on the surface of mycobacteria, it opsonize the organism and facilitates its uptake by the macrophage complement receptor (CR3). However, this occurs without triggering the respiratory burst necessary to kill the organism.
d. Highly immunogenic *M. tuberculosis* heat shock protein. This has a role in autoimmune reaction induced by *M. tuberculosis*.
e. The primary phase of *M. tuberculosis* begins with inhalation of the mycobacteria and ends with a T cell-mediated immune response which produces hypersensitivity to the organisms. In this phase inhaled mycobacteria is first phagocytosed by alveolar macrophages and transported by these cells to lymph nodes. Normal macrophages are unable to kill the mycobacteria, which multiply, destroy the host cell, infect other macrophages and sometimes spread through the blood to other part of lung and elsewhere in the body. After a few weeks, T cell-mediated immunity develops. Mycobacterium- activated T cell interact with macrophages in three ways:
    - CD4+ helper T cells secrete interferon- gamma, which activates macrophages to kill intracellular mycobacteria through nitrogen intermediates, such as NO (nitric oxide), NO2 and HNO3 (nitric acid). This is associated with the formation of epitheloid cell granulomas and clearance of mycobacteria.
    - CD8+ suppressor T cells lyse macrophages infected with mycobacteria contribute to the necrotic caseous centers.
    - CD4- CD8- (double negative) T cells lyse macrophages, without killing mycobacteria. Lysis of macrophages results in formation of caseating granulomas.

Cord factor induce the swelling and disruption of liver mitochondria as well as disintegration of endoplasmic reticulum and detachment of ribosomes in liver cells.

Clinical Sign

Incubation period is 3-6 weeks and may extend upto years. It is said that young children infected with *M. bovis* typically have abdominal infections and older patients have swollen and sometimes ulcerated lymph glands in the neck. *M. bovis* is the commonest cause of cervical lymphadenitis and other forms of extrapulmonary TB that occur in infancy and childhood [11]. Some 5-17 per cent of TB is extrapulmonary and 18-25 per cent affects bones and joints.

Cattle

Usually superficial lymph node will be swollen. If udder is affected, it will show a progressive hardening and swelling. Milk becomes thin and watery with yellow flakes in it. The generalized TB cases of year standing show emaciation (hide bound condition), cough, dry and harsh body coat, dull and sunken eyes and sometimes diarrhea with capricious appetite, fluctuating body temperature and at times, snoring due to involvement of retropharyngeal lymph node. In cutaneous TB, lumpy swelling, sometimes indicated by cording, occurs on the lower part of the front legs and rarely on hind legs.

Dogs and Cats

Marked emaciation, constant discharge from nose, cough, pleurisy (pleural cavity may get filled with fluid) causing

difficulty in breathing and swelling on chest and abdomen are seen [17].

Species wise variation of clinical sign in different species

- Abdominal organs are affected more often than the respiratory tract in equids and some other hosts, while elephants tend to have few signs until the lesions are extensive.
- Subclinical infections seem to be prevalent in pigs, but disseminated disease can also be seen, especially in young animals. Osteomyelitis and meningeal involvement are reported to be relatively common in this species.
- Respiratory disease is a common form of tuberculosis in both badgers and brush-tailed opossums, but it tends to be chronic in badgers, which may survive for years, while opossums often die within a few months [17].

Humans

In humans, clinical tuberculosis occurs in 3 stages

i. **Primary tuberculosis-** The lung infection results in the information of the tubercle which consists of a central core containing bacilli and enlarged macrophages, and an outer wall made up of fibroblasts, lymphocytes and neutrophils. The centers may break down into necrotic, caseous lesion and gradually heal by calcification.
ii. **Secondary tuberculosis-** The dormant bacilli from primary case can become reactivated. In chronic tuberculosis the bacilli drain into the bronchial tubes and upper respiratory tract. The patient shows violent coughing, greening or bloody sputum, fever, anorexia, weight loss, extreme fatigue, night sweats and chest pain.
iii. **Extra pulmonary tuberculosis-** During course of secondary tuberculosis the bacilli disseminate rapidly to other organs, as regional lymph nodes, kidney, long bones, genital tract, brain and meninges. Renal TB results in necrosis and scarring of renal medulla, pelvis, ureters and bladder. Genital TB affects reproductive function of both sexes. TB of bones and joints (vertebral column) results in paralysis and sensory loss. Tuberculous meningitis can result into mental deterioration, permanent retardation, blindness and deafness.

Macroscopic examination

Firm and hard nodule or tubercle in lungs which are either grey, grayish white or yellowish in appearance and are caseous, caseo-calcareous in consistency in cattle, small ruminants, pigs and a number of other species. However, tubercles in some species of cervids are often poorly encapsulated, tend to resemble abscesses and may have purulent centers. In some hosts such as cats, dogs and horses the lesions tend to appear as diffuse granulomatous infiltration, which can resemble neoplasia or multiple small uncalcified nodules or caseous foci. Smooth, gray infiltrative lesions in the spleen and liver, are characteristic of primary tuberculosis lesions in horses [3].

Microscopic examination

Typical granulomatous nodule consist of central area of caseous necrosis with or without calcification (calcification is prominent in cattle) surrounded by macrophages, epitheloid cells and multinucleated giant cells and presence of acid fast bacilli, zone of lymphocytes then presence of fibrous connective tissue encapsulating the lesions. Tuberculous lung lesions are enriched in Fox P3 Tregs and IgG secreting B cells and express lower level of cathelicidin [25].

The Economic and Social burden of disease

Animals

The disease hampers the economic aspects. There is condemnation or poor product (10%), loss of milk production (22%), reduction in reproduction performance (6.5%), loss of meat production (7.1%) and loss of body weight (11.1%) [14]. According to WHO about 5 per cent cattle are affected with tuberculosis and 30 per cent cattle lose their power of productivity. It is estimated that about 90 per cent of human population live in countries where cattle and dairy animals receive partial or no protection against bovine tuberculosis.

Humans

Besides the disease burden, TB also causes an enormous socioeconomic burden to India. TB primarily affects people in their most reproductive years of life. Almost 70 per cent of TB patient are between 15 and 54 years of age. While 2/3rd of the cases are male, TB takes disproportionately larger toll among young female, with more than 50 per cent of female cases occurring before the age of 34 year. Nearly 1/3rd of female infertility in India is caused by tuberculosis. In India, tuberculosis is mainly a disease of the poor.

Public health significance

Bovine TB is most important food borne disease as organism is resistant to one of the commonly used first line anti-TB drug that is pyrazinamide. Extrapulmonary form is most common form of *M. bovis* that is why the death rate are higher with *M. bovis* than *M. tuberculosis*, although due to boiling of milk and introduction of pasteurization in most of the developed countries only 1-2 per cent of person are affected as compare to developing countries where 10-15 per cent are infected annually. Further, most of the developing countries lack National Bovine TB control programme and efficient lab facility for diagnosis. Close proximity of wild animal, domestic animal and humans are also help in spillover the disease.

Conclusion

Bovine tuberculosis is a complex and difficult disease to control, both in humans and animals. In designing a strategy to control bovine TB in India and progress towards elimination, it is important to be flexible and set up systems that ensure new insights from surveillance and research, which efficiently incorporated into policy and implementa0074ion. Bovine TB incidences in India, definitely in cattle and possibly in wild animals like lions, monkey, badgers are at best roughly stable. This cannot be allowed to continue.

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