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Cases of Paratuberculosis in Nigeria's Livestock Industry

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Abstract

The bacterial illness known as paratuberculosis, or Johne's (Yo'-ness) disease, is caused by the Mycobacterium avium subspecies paratuberculosis (MAP) and is a major problem in both big and small ruminants, as well as other animals. The illness is recognized and documented in industrialized countries as a serious disease of livestock concern due to its effect on animal health and substantial economic loss. The purpose of this study is to summarize the state of knowledge regarding paratuberculosis in Nigeria. Johne's disease, paratuberculosis, Africa, prevalence, Nigeria, report, occurrence, and Mycobacterium avium subspecies paratuberculosis were used to retrieve a total of 95 articles from databases like Scopus, Google Scholar, Research Gate, PubMed, and CABI abstracts. This review paper drew on 60 research articles and the reading of organization databases. The World Organization for Animal Health (OIE) only received a small number of reports of paraTB in Nigeria. Lack of awareness and reporting about this significant illness in farmed animals lead to the conclusion that Johne's disease is underreported in Nigeria, despite rising worldwide concerns. Research is needed to fill in the blanks before the illness becomes widespread and poses a serious threat to the economy and public health in Nigeria and, by extension, Sub-Saharan Africa.

Keywords: Paratuberculosis; *Mycobacterium avium* subspecies *paratuberculosis* (MAP); Johne's disease.

1. Introduction

Johne's disease (JD) or paratuberculosis (paraTB) is a chronic granulomatous gastroenteritis due to infection with the bacterium *Mycobacterium avium* subspecies *paratuber- culosis* (Garvey, 2018). In 1895, the condition was charac- terized by Frothington and Johne (Olsen et al., 2002; Bakkeret al., 2000; Okuni, 2013). MAP is a slow-growing, acid-fastbacillus (Olsen et al., 2002; Agrawal et al., 2021; Izhar ul Haque et al., 2022) that can only reproduce as an obligate intracellular bacteria within a host cell (macrophages) of a susceptible species (Grant, 2005; Garvey 2018). The diseasecommences as a localized infection that may become gener- alized and leads to chronic granulomatous enteritis charac- terized by weight loss, diarrhea, reduction in milk, meat or wool production, emaciation, submandibular edema, and death (Whittington et al., 2019; Okuni et al., 2020). ParaTB is endemic worldwide, frequently occurring in cattle, sheep, goats, and farmed deer (Kennedy & Benedictus, 2001; Grant, 2005; Pal et al., 2015; Idris et al., 2022), and has beenreported in camel (Alluwaimi, 2015). The disease has also been reported in non- ruminants, wild rabbits, foxes, stoats (Whittington & Sergeant 2001; Adhikari, 2020), and pri- mates such as mandrills and macaques (Uzoigwe et al., 2007).

JD is considered by the World Organization for Animal Health (WOAH) as a disease of global importance; the dis- ease is also regarded to be of socio-economic or publichealth significance, and in the trade of animals and animal products, it has also been categorized as a reportable disease (OIE, 2008). Paratuberculosis (PTB) is categorized in the Terrestrial Animal Health Code as one of the List B diseases(OIE, 2019). It has been estimated that for every clinicalcase of JD, four (4) to eight (8) other animals on the farm may be found positive (subclinical or asymptomatic) carries (Pal et al., 2015). In Africa and Asia, sheep/goat contributes significantly to mitigating poverty in low-income societies through the provision of milk, skin, meat, and for animal exports. These sources of income can be significantly af- fected by paraTB infection (Idris et al., 2022). Although the occurrence of paraTB has been reported in some African countries, African countries are among the nations with a paucity of data associated with the prevalence, epidemiolog- ical pattern, and disease control. This is due to the absenceof case reporting, limited research, and a need for more awareness and policies about the disease (Okuni et al., 2020). This study aims to survey the cases reported and identify the knowledge gap about Johne's disease in Nigeria:a disease of economic and public health significance. The article will also arouse interest in research on Johne's dis- ease and the need for complete awareness of livestock farm- ers by every critical stakeholder.

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Indo-American Journal of Agricultural and Veterinary Sciences
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2. Materials and methods

About 95 research articles were downloaded from onlinejournal databases such as Google Scholar, Scopus, Research Gate, PubMed, and CABI abstracts. Articles were selected and downloaded based on proximity to the search keywords:Johne's disease, paratuberculosis, Nigeria, report, Africa,prevalence, occurrence, and *Mycobacterium avium* subspe- cies *paratuberculosis.* A perusal of the following organiza- tion databases (World Animal Health Information Database (WAHID), World Organization for Animal Health (OIE)Handistatus II (1994–2004), Food and Agricultural Organi- zation (FAO), and Johne's information center was also car- ried out.

3. Results and discussion

After a proper and careful reading of the downloaded re- search article and various organization databases, about 60 articles were used in writing the review article. A few cases and suspected cases of paraTB were reported in Nigeria by the World Organization for Animal Health (OIE).

Report of Paratuberculosis in Nigeria

Lobry (1963) first reviewed the occurrence of paraTB in Africa and reported the incidence of the disease in Nigeria and some other countries. The first case of paraTB in Nige- ria was reported in the northern part of the country in an enclosed farm rearing white Fulani zebu cattle with occa- sional Friesian half-breeds in 1958 as two (2) cattle tested positive twice for avian tuberculin (Johnson et al., 1962). Clinical cases were suspected to have been due to two (2) cattle from a nomadic herd bought about seven (7) years earlier (Johnson et al., 1962). World Organization for Ani- mal Health (WOAH) database (Prior to 2005) reported that "No Information" was available regarding the occurrence of paraTB in Nigeria (OIE, 2012). A perusal of the OIE World Animal Health Information System (OIE-WAHIS) database from 2005 to 2021 indicates that seven (7) cases of paraTB (Report ID: 141933 and 142242) in cattle were reported with twenty-six (26) susceptible cattle in 2013, in OsunState, South West Nigeria. The disease was reported as "Present" in both domestic and wild animals from 2014– 2019, although no case was reported. Between the year 2020and the first semester of 2021, paraTB was reported to be "Absent" in Nigeria (Report ID: SMR_150808, SMR_152723, and SMR_152529) (OIE-WAHIS 2022). To the best of our knowledge and based on the articles re-viewed, there is no research study on the occurrence orprevalence of paraTB in Nigeria, despite the disease being reported in three (3) northern regions of Cameroon, which are bordering Nigeria, Chad, and the Central African Repub-lic (Policap et al., 2009). These may be attributed to the following reasons:

Lack of adequate public awareness: Despite the knowledge about the disease in developed and some devel- oping countries, there needs to be more public awareness about paraTB in Nigeria. Livestock farmers need to be in- formed by critical stakeholders about the disease and its economic/public health implications.

Poor livestock disease surveillance: With the disease being reported in Nigeria in 2013 and neighboring Came- roon, there is a need for a proper disease surveillance plan inNigeria, especially in border states and the livestock market, which needs to be improved.

Lack of adequate diagnostic facilities: In Nigeria, thereare limited veterinary diagnostic laboratories, while the few equipped laboratory might be miles away from a farm or grazing reserve, which could affect the laboratory outcome.

Poverty: Most livestock farmers in Nigeria are low- income earners; some cannot afford the consultation fee to invite a veterinarian for a proper diagnosis of sick animals. This often leads to animals being attended to by quacks.

Research Gap: Studies on the effect or prevalence of paraTB in Nigeria received little or no attention; this may bebecause the disease is not considered a disease of public health or socio-economic importance (Whittington et al.,2019).

With an estimated cattle population of about 25.7 millionheads by 2050 (FAO, 2019) and due to the open grazing system of pastoralists, MAP survival for extended periods insoil or water and the effect of severe rain and flood, which could lead to the circulation of the infectious agent in the environment (Grant, 2005; Okuni et al., 2020), there is a need for studies to be conducted on paraTB in Nigeria. Stud-ies should concentrate on herd-level prevalence, within-herdprevalence, molecular epidemiology of different strains, dynamics of transmission, host factors that could lead to susceptibility or tolerance among breeds in Nigeria, factors that contribute to the survival of MAP in the environment, and public health and economic impact of the disease. Studyobjectives should also include farmers' attitudes and knowledge about Johne's disease, evaluating different con- trol and prevention programs, and assessing different diag- nostic tests.

Indo-American Journal of Agricultural and Veterinary Sciences
ISSN 2321–9602 www.iajavs.com

Pathogen Biology

Mycobacterium avium subspecies *paratuberculosis* (*M. a. ptb*) is among the *M. avium* complex belonging to the genus *Mycobacterium*, the only genus in the family Myco- bacteriacea (Olsen et al., 2002). The genus is differentiated based on its ability to secrete mycolic acid (Adhikari, 2020).The organism was first documented as *Mycobacterium en- teritidis chronicae pseudotuberculosis bovis johne* (Olsen et al., 2002) but has been renamed *Mycobacterium johei*, *My- cobacterium paratuberculosis* and recently *Mycobacterium avium* subspecies *paratuberculosis* (Thorel et al., 1990) as a result of its genetic relationship to *M. avium* subspecies *avium* (*M. a. avium*) (Valentin-Weigand & Goethe 1999).

M. a. ptb is a gram-positive, aerobic, short-slender rod of about 1–2 mm long and 0.5 mm in width, slow-growing, non-motile, and acid-fast bacillus (Cocito et al., 1994; Olsenet al., 2002; Agrawal et al., 2021; Izhar ul Haque et al., 2022). *M. a. ptb*, like other Mycobacteria, has a dense, waxycell wall of about 60 % lipid. This confers the properties of acid fastness, hydrophobicity, resistance to chemicals suchas chlorine, and physical process (pasteurization) to the bacteria (Cocito et al., 1994; Okuni et al., 2020; Corneli et al., 2021).

Due to its fastidious nature, colonies take at least eight (8) weeks to appear when isolated on a media (Pal et al., 2015; Okuni et al., 2020). Colony growth can be observedon Herrold's egg yolk medium (HEYM) (Pal et al., 2015; Okuni et al., 2020; OIE, 2021; Idris et al., 2022), modified Lowenstein-Jensen media (Valentin-Weigand & Goethe 1999; Singh et al., 2018; Idris et al., 2022), Middlebrook agar; 7H9, 7H10, 7H11, 7H12 Bactec (Ristow et al., 2006; Okuni et al., 2020; OIE, 2021; Ssekitoleko et al., 2021), Watson-Reid agar (Cocito et al., 1994; Valentin-Weigand and Goethe 1999), modified Dubos's medium (OIE, 2021). Due to the failure of MAP to synthesize mycobactin (iron chelating compound), most of these growth media are en- riched externally with mycobactin (Manning & Collins, 2001; Grant, 2005; Radostits et al., 2006; Idris et al., 2022) needed for MAP growth, a distinctive feature that differenti-ates it from other Mycobacteria (Grant, 2005; Okuni et al., 2020). Mycobactin and exochelin are two types of sidero- phores that aid in chelating iron from an organic source (Cocito et al., 1994). In addition to fecal and tissue culture being considered as "gold standard" for the diagnosis of paratuberculosis (Olsen et al., 2002; Pal et al., 2015; Guptaet al., 2019), a direct stain of fecal and tissue impression slides have been used in identifying the agent. However, neither method is sensitive and specific for *M. a. ptb* as distinguishing it from non-pathogenic mycobacteria can be challenging (Bakker et al., 2000; Manning & Collins, 2001; OIE, 2021; Idris et al., 2022). Isolates from fecal and tissue culture are identified using: phenotypic identification; this method is based upon the fact that *M. a. ptb* is the only fami-ly member of acid-fast mycobacterial that require mycobac- tin, a siderophore needed for obtaining iron from the envi- ronment (Manning & Collins 2001; Rastogi et al., 2001), genotypic identification; this assay been 100 % sensitive andspecific focuses on the insertion sequence IS900 and IS1311considered unique to MAP (Izhar ul (Cocito et al., 1994; Cousins et al., 1999; Bakker et al., 2000; Olsen et al., 2002; Tiwari et al., 2006; Garcia & Shalloo 2015; Singh et al., 2018; OIE, 2021; Izhar ul Haque et al., 2022). However, the IS900 sequence has been isolated from *Mycobacterium cookii* with 94 % similarity; there is a need to identify genes other than the IS900 sequence for genotypic identification of *M. a. ptb* (Adhikari, 2020). Antigen 85-monoclonal antibodyimmunoassay: this assay is based on detecting a secretory product (antigen 85) of actively replicating mycobacteria (Manning & Collins 2001).

Wu et al. (2007) reported the diagnosis of paraTB using purified protein derivatives (PPD) skin test. Paratuberculosiscan also be diagnosed with the aid of immunological tests such as enzyme-linked immunosorbent assay (ELISA), complement fixation test, agar gel-immunodiffusion test, delayed-type hypersensitivity test (DTH), gamma-interferon test, lymphocyte proliferation test (LPT), and flow cytome- try (Pal et al., 2015; Garcia & Shalloo, 2015; Singh et al., 2018; Whittington et al., 2019; Corneli et al., 2021).Based on pigmentation and growth rate, two strains of *M. a. ptb* have been identified (Figure 1); Type I/III (sheep type or type S) and Type II (cattle type or type C) (Bryant et al., 2016; Ssekitoleko et al., 2021). Ovine hosts are mainly affected by Type I strains, while cattle, deer, goats, sheep, and other ruminants are affected by Type II strains. The Type III strain, a subgroup of sheep type, was isolated from small ruminants, cattle, and camels (Idris et al., 2022). MAP, first isolated from bison in Montana, United States of America (USA), has been classified based on single nucleo- tide polymorphism (SNP) analysis of IS1311 as Type B (India bison type) isolated from animals in India was found to differ from those isolated from USA base on molecular analysis. Type B stains are a sub-lineage of Type C (Stevenson, 2015; Ssekitoleko et al., 2021).

Indo-American Journal of Agricultural and Veterinary Sciences
ISSN 2321–9602 www.iajavs.com

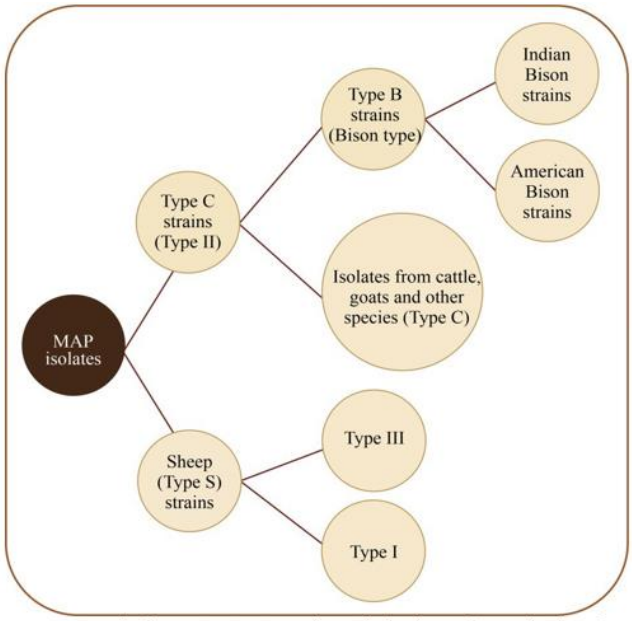

Fig. 1. Whole genome SNP-based phylogenic analysis of *M. a. ptb* strain (Ssekitoleko et al., 2021)

Pathophysiology

M. a. ptb is transmitted primarily through the fecal-oral route with young calves mostly infected (Ssekitoleko et al., 2021; Corneli et al., 2021) through ingestion of contaminat- ed water, feces, milk/colostrum, or oral contact with con- taminated udders, soil, or surfaces. Transmission via body fluids such as semen, uterine fluid, and saliva has been re- ported (Grant, 2005; Arsenault et al., 2014; Maroudam etal., 2015; Corneli et al., 2021; Field et al., 2022). Calves can also acquire the infection in-utero (Manning & Collins, 2001; Maroudam et al., 2015; Corneli et al., 2021). The quantity of the infectious agent and the age of the animal during the time of exposure determines the degree and the rate of progression of the disease. Only a tiny dose of the infectious agent is needed in a newborn calf to establish infection (Maroudam et al., 2015). Infected animals primari-ly shed *M. a. ptb* in their feces, and most infectious animals in a herd are categorized as intermittent and low shedders (Field et al., 2022).

Following ingestion, the organism invades the wall ofthe intestine via the intestinal mucosa of the ileum facilitatedby specialized absorptive mucosal microfold cells (M cells) residing in the peyer's patches and enterocytes through fibronectin-dependent mechanisms. The organism also lo-calizes in the associated lymph nodes of the small intestine, the tonsils, and supra-pharyngeal lymph nodes (Tiwari et al.,2006; Arsenault et al., 2014; Pal et al., 2015; Mallikarjunap- pa et al., 2021). Multiplication of *M. a. ptb* starts a few weeks after infection in the wall of the intestine, and the animal eliminates or remains infected as a healthy carrier based on the resistance ability of the animal (Maroudam et al., 2015). Macrophage receptors such as complement recep-tors (CR1, CR3, and CR4), immunoglobulin receptors (FCR), mannose receptors, and scavenger receptors aid in MAP uptake by sub-epithelial macrophages (Tessema et al., 2001; Arsenault et al., 2014; Ssekitoleko et al., 2021; Mallikarjunappa et al., 2021). Other receptors include fi- bronectin receptors (FnRs), vitronectin receptors (VnR), transferrin receptors (TfR), and surfactant protein receptors (SpRs) (Tessema et al., 2001). Plasma membrane molecule that includes cholesterol and sialophorin plays a vital role in mycobacteria's binding, entry, and intracellular survival (Tessema et al., 2001). The specific receptors used and the molecular mechanism of uptake of *M. a. ptb* into macro-phages need to be better understood (Tessema et al., 2001). The organism survives and multiplies in the macrophages, the target cells, until the cell ruptures and releases the path ogen into nearby tissues (Tessema et al., 2001) or organs such as the uterus, fetus, testes, and mammary gland after being transported via macrophages (Maroudam et al., 2015; Pal et al., 2015). The organism also can persist within the macrophages through the secretion of superoxide dismutase, which neutralizes superoxide radicals (Arsenault et al., 2014; Ssekitoleko et al., 2021), possessing the ability to disable reactive oxygen anion intermediates such as hydro- gen peroxide, hydroxyl radicals, and superoxide anions(Ssekitoleko et al., 2021), hindrance of phagosome acidifi- cation and phagolysosome fusion, improving macrophage secretion of IL-10 and obstructing the capability of

Indo-American Journal of Agricultural and Veterinary Sciences
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infected macrophages to be activated by gamma interferon for intra- cellular pathogen removal (Ssekitoleko et al., 2021; Field et al., 2022). These mechanisms aid the infectious agent in evading the host immunological response resulting in latent infection (Ssekitoleko et al., 2021; Field et al., 2022) after uptake of MAP by macrophages which, once activated, stimulate T cell activation and clonal expansion (Manning &Collins, 2001). TH1 and TH2 T helper cell subpopulations initiate different host immune responses. MAP infection appears to follow patterns identified with infections by *M. leprae*, *M. bovis*, or *M. tuberculosis* (Manning & Collins,2001). At different stages of the infection, the clinical signs of paraTB vary and are not frequent until two (2) or more years post-infection. Clinical cases are primarily seen in 2 – 6-year-old animals, although animals of any age can be affected (Maroudam et al., 2015).

Public Health Significance of Paratuberculosis

Crohn's disease (CD), a severe granulomatous intestine infection, has been suggested to be caused by MAP (Olsenet al., 2002; Uzoigwe et al., 2007). The clinical manifesta- tion of the disease includes abdominal pain, general malaise,weight loss, bloating fever, malnutrition, and diarrhea (Grant, 2005; Pal et al., 2015; Garvey, 2018). The role of MAP in causing CD has been studied by researchers with opposing results (Graham et al., 1987; Olsen et al., 2002; Bull et al., 2003; Scanu et al., 2007). A study by (Uzoigweet al., 2007) supports the hypothesis that CD is caused by MAP based on the strength of association, consistency of effect, temporality, and biological plausibility of the six (6) epidemiological causal criteria for the causation of CD (Okuni et al., 2020). The zoonotic potential of MAP should be noticed due to the clinical similarity (Table 1) of JD toCD (Garvey, 2018). Based on immune dysfunction, MAP has also been hypothesized to be causally associated with Type 1 Diabetes (T1D), multiple sclerosis, Hashimoto's thyroiditis, sarcoidosis, human immunodeficiency virus, Blau syndrome, rheumatoid arthritis, and Parkinson's dis- ease (Garvey 2018; Adhikari, 2020; Ozana et al., 2022; Ekundayo et al., 2022a) and possibly, Sjogren's syndrome (Dow & Alvarez, 2022). These hypotheses are based on the fact that MAP can cause infection in non-ruminants, includ- ing non-human primates, immune system dysregulation, andenvironmental exposure to the infectious agent through contaminated milk, beef, and feces; via fecal-oral route as MAP can survive up to one hundred and twenty (120) weeksin the environment, dairy products; as pasteurization only reduces MAP load (Waddell et al., 2015; Dow & Alvarez 2022).

Table 1
Clinical manifestations of Crohn's disease and Johne's (Yo'-ness) disease (Maroudam et al., 2015)

Clinical sign	Crohn's disease (CD)	Johne's (Yo'-ness) disease
Diarrhea	Present	Present
Intermissive diarrhea	Present	Present
Abdominal pain	Present	--
Weight loss	Present	Present
Blood in stool	Present	Rare
Vomiting	Present	Absent
Quiescent periods	Present	Present
Obstruction	Present	Absent

In 2022, a study conducted by Ekundayo *et al.* indicated a strong association between MAP and multiple sclerosis (MS) based on the meta-analytic synthesis of MAP-related multiple sclerosis data. This finding supports the hypothesis that MAP is a significant environmental trigger of multiple sclerosis (Ekundayo et al., 2022a). MAP was also found to trigger multiple sclerosis in individuals genetically suscepti- ble to *Mycobacterium* (Cossu et al., 2016). T1D is a severe autoimmune condition associated with infant exposure to dietary cow milk (Dow & Alvarez, 2022; Ozana et al., 2022), with the disease high in children worldwide (Ozanaet al., 2022). An investigation using meta-analysis found that anti-MAP antibodies and MAP deoxyribonucleic acid (DNA) have a significant link with T1D (Ekundayo et al., 2022b). Association between MAP and T1D has been con- firmed using polymerase chain reaction (PCR); by detecting MAP-specific IS900 signature (Sechi et al., 2008; Rosu et al., 2009; Rani et al., 2010; Shariati et al., 2016), immune assay (ELISA); by detecting antibodies against MAP 3865c and ZnT8 homologous epitopes, and the detection of the cell

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envelope protein (MptD) and immune response to MptD peptide. These findings support the hypothesis that MAP could be a trigger for T1D. A study by (Bitti et al., 2012; Masala et al., 2013) reported that MAP was found in T1D children. Of the numerous studies implicating MAP as a trigger for T1D, only one study failed to do so. In the study conducted in India, MAP was not isolated from the blood of T1D patients, and one of the reasons includes; the thought of cross-protection of BCG vaccine against paraTB as it does with leprosy (Reni et al., 2014).

The ability to influence lipid metabolism in the host and assemble cholesterol within macrophages to improve infec- tion is a feature of MAP. Tyrosine phosphate A (PtpA) and kinase G (PknG) MAP virulence factors are essential for the survival of MAP in macrophages. The theory of MAP being implicated in the pathogenesis of rheumatoid arthritis has received support because PtpA and PknG are observed in rheumatoid arthritis (Dow & Alvarez, 2022).

4. Conclusions

Johne's disease is a menace to the livestock industry glob-ally and of public health and economic importance. In Nige-ria, research studies, prevention and control programs, and policies on the disease need to be included. This has led to a significant information gap on this significant disease's true prevalence and occurrence in livestock animals. Due to the open grazing system mostly practiced by pastoralists in Nige-ria, it is paramount that studies are carried out to investigate the occurrence, epidemiological patterns, and prevalence of paraTB. In addition, the following strategies and approaches are recommended to address the challenge effectively:

Public enlightenment: There is a need for comprehen- sive public awareness, primarily targeting livestock farmers and other stakeholders about the disease and its effect on livestock production.

Routine surveillance: Surveillance strategies should be implemented, especially in border states, livestock markets, grazing reserves, and the northern part of Nigeria due to the open grazing system practiced in the region. This will help in understanding the epidemiological pattern of the disease and also give essential guidance in the design of national or regional policies and prevention and control programs. Fi- nally, government and other funding agencies should pro- vide adequate funds for research on paratuberculosis and adequate diagnostic tools to diagnose the disease in gov- ernment veterinary hospitals effectively.

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Indo-American Journal of Agricultural and Veterinary Sciences

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