IBOM MEDICAL JOURNAL
Vol.13 No.2 May - Aug., 2020. Pages 66 - 72
www.ibommedicaljournal.org

Tuberculosis: A review

Airauhi, OA[1]MBBS, FMCPH[1]*; Airauhi UL. Ph.D.[2]; Yusuf EO MBBS, FMCPath[2]

[1]*Department of Community Medicine, School of Medicine, Lagos state University Teaching Hospital, Ikeja, Lagos State.*
[2]*Department of Medical Microbiology, School of Medicine, College of Medical Sciences, University of Benin, Benin city Nigeria.*

Summary

Tuberculosis (TB) is an infectious disease of bacterial origin caused by *Mycobacterium tuberculosis* (MTB), which is a member of the *Mycobacterium tuberculosis* complex (MTBC). *Mycobacterium tuberculosis* (MTB) is also known as Koch bacillus or tubercle bacillus. The burden of TB has remained a problem due to factors that have promoted and fostered transmission, including increasing resistance of the disease to the most effective first-line anti-TB drugs. There is the need for cases to be diagnosed early and managed appropriately by skilled and knowledgeable health care workers (HCWs). Reports of low level of knowledge concerning TB among some HCWs during the 2016 hajj prompted this review which was prepared using articles on TB searched on various websites of international institutions like the world health organization (WHO), the United States center for disease control and prevention (CDC) and PubMed. Here we provide a brief history of tuberculosis and an overview of the current literature on, basic classification of, immunology, public health concerns and treatment guidelines of TB. The information provided will be a useful guide for HCWs and the general public.

Keywords: *M. tuberculosis*, Koch bacillus, infectious disease, immunology, treatment guidelines.

Introduction

Tuberculosis (TB) is a chronic communicable disease characterized by spherical lesions (granuloma or tubercle with caseous necrosis). It is contracted mostly by inhalation of droplet nuclei; it could also be via ingestion of the bacillus in unpasteurized milk and by transdermal transmission[1]. The etiologic agent is the bacillus *Mycobacterium tuberculosis* (MTB); it is a member of the *Mycobacterium tuberculosis* complex (MTBC). Together with other species which include: *M. bovis*, *M. africanum*, *M. microti*, *M. caprae*, *M. pinnipedii*, *M. canetti* and *M. mungi*, MTB constitute the MTBC[2; 3]. The synonyms for *Mycobacterium tuberculosis* (MTB) include: Koch bacillus and tubercle bacillus. Recognized as the world's leading bacterial cause of death,[4] TB remains a threat to the health of people worldwide. [1]

Corresponding Author: Dr. Airauhi, OA

Department of Community Medicine, School of Medicine, Lagos state University Teaching Hospital, Ikeja, Lagos State Nigeria.
E-mail: sega_11@yahoo.com

Brief history of TB

In a brief narrative of the history of TB, Daniel in 2006[5] provided the following that, 'work on the pathogenesis of tuberculosis began with Rene-Theophile-Hyacinthe Laennec, a French physician at the beginning of the 19th Century. In 1821 Laennec described what is now called caseous necrosis as 'the tuberculous matter which begins as a grey, semitransparent matter that little by little becomes yellow, opaque and dense. Then it softens and, slowly acquires liquid-like pus and when expelled through the airways, leaves cavities commonly called ulcers of the lungs that we will designate as tuberculous excavations.[6] He also established that pathologically similar lesions are seen in different parts of the body, although he could not and, did not state the cause of the illness. Therefore Laennec's

work, apart from clearly expounding the pathology of tuberculosis it also provided a description of the pulmonary disease introducing terms to describe findings that are still in use today. The modern understanding of tuberculosis began with Laennec's treatise. [5] In continuation of the narrative, it was also reported that, another French physician Jean-Antoine Villemin established the infectious nature of tuberculosis, and that it was transmissible. Later on, the etiologic agent of the disease previously described by Laennec and Villemin was identified by Robert Koch as *Mycobacterium tuberculosis* when he announced his brilliant achievement on March 24th 1882. The paper describing Robert Koch's work which is 'Der Aetiologie der Tuberculose' was published in Berliner Klinische Wochenschrift on April 10th 1882.[7, 8]

During his presentation, Koch also posited his famous postulate that remains the standard till date for the demonstration of infectious disease etiology[5]. This revolutionary finding, along with the later discoveries of tuberculin in 1890 and the Bacillus-Chalmette Guerin (BCG) vaccine in 1908 and, tuberculosis drugs starting in 1943, offered hope for the eradication of a disease deadlier than the plague.[9]

Transmission of *M. tuberculosis*

Person to person transmission occurs when aerosolized *M. tuberculosis* bacillus in droplet nuclei which is small in size (1-5um in diameter) is inhaled by exposed individuals and, penetrates into the terminal alveoli avoiding the defenses of the bronchi to initiate infection.[3] The inhaled *M. tuberculosis* bacilli are engulfed by phagocytic immune cells (macrophages and dendritic cells) and, can also infect non-phagocytic cells of the alveolar space including M-cells, alveolar endothelial and type 1 and type 2 epithelial cells which are the pneumocytes.[10] An estimated 30% of those exposed will have evidence of infection by tuberculin skin test.[11] The outcome following the transmission of the bacillus in the lung can lead to a few possible outcomes including: 1) The immediate clearance of the organism from the body. 2) Primary disease: the immediate onset of active disease in the individual. 3) Latent infection. 4) Reactivation (secondary) disease: the onset of active disease many years after a period of latent infection).[1, 2] In order to perpetrate itself in nature, the tubercle bacillus must be transmitted from one host to another host. Humans are the main reservoirs of *Mycobacterium tuberculosis* which means that the infection and disease are essential for the transmission and survival of the organism. Therefore, the granuloma undergoes necrosis, forming a necrotic core which favors bacterial growth and transmission to a new host; this occurs when the infected individual releases droplet nuclei containing the infectious bacteria which aerosolize. Latently infected persons represent an enormous reservoir of potential reactivation TB, which can spread to other people, and they are estimated to be about 2 billion in the world.[1]

Humans that are immunologically competent are sometimes unable to clear infections with *M. tuberculosis* which is quite remarkable and represents the hallmark of the pathogen. The tubercle bacillus has evolved multiple strategies to manipulate infected host cells in order to evade or modify the ensuing immune response so as to avoid elimination and thus persist in the host.[3]

Primary Pulmonary Tuberculosis

Following inhalation, tubercle bacillus reaches the alveolar spaces where it is engulfed by alveolar macrophages. The organism continues to proliferate, eventually the macrophage is destroyed releasing cytokines and chemokines which attract other phagocytic cells, but the proliferation of the bacillus continues eventually forming a nodular granulomatous structure called the tubercle. Individuals who fail to eliminate the organism at the first contact develop primary pulmonary tuberculosis which is an infection located in the sub pleural portion of the lungs and it is referred to as Ghon focus. The lesion was first described as the initial tuberculous granuloma by **Anton Ghon,** an Austrian pathologist, who described it as formed during primary infection that is not radiologically visible unless it is calcified. **He** spent his life researching tuberculosis and meningitis.[12] The proliferating bacteria enlarge the granuloma and the contained bacteria continue to multiply. The bacterial organisms spread involving adjacent lymph nodes and lymphatics when it is known as Ghon's complex or primary complex.[13] The Ghon focus usually enters a state of latency in most

individuals known as latent tuberculosis.

Latent tuberculosis infection (LTBI)

Latent infection is the demonstration of the presence *M. tuberculosis* by the tuberculin skin test (TST) or IFN-y release assay (IGRA) without clinical sign or symptoms of disease and a normal chest radiograph[1]. It can take 2 to 8 weeks after the initial TB infection for the body's immune system to be able to react to tuberculin and for the infection to be detected by the TST or IGRA. The formation of granuloma walls off the bacilli from the rest of the lung tissue, but within the granuloma, cells of the immune system continue with efforts to clear the bacteria but some resistant bacteria escape killing and enter a state of dormancy and persist by avoiding elimination by the immune system.[4,14,15] During latent tuberculosis infection (LTBI) there is persistent immune response to stimulation by *Mycobacterium tuberculosis* antigen without clinical manifestations of active TB and it can be maintained for a life time. Those with LTBI do not constitute a source of infection and cannot spread the infection to other people. However, reactivation of latent infection occurs in about 10% of infected individuals leading to active tuberculosis which is contagious.[14] Encapsulation may prevent bacterial escape or limit immune intrusion.[16]

However, at some point, even after many years of latency, exogenous factors like the secreted protein resembling Resuscitation-promoting factor (Rpf), can be activated,[17] when the bacteria are reverted from a suppressed state to an active state and can resume cell division.[18,19] Some individuals who are exposed to *M. tuberculosis* may or may not develop LTBI but in the event of a challenge to the immune system in the host, latent tuberculosis is capable of being reactivated.

Active Secondary Pulmonary Tuberculosis TB

A latent TB infection may be reactivated in 5-10% cases when a primary disease develops.[14,20] There is continuous proliferation of bacteria inside the granuloma which causes it to enlarge and when the pathogen enters the local draining lymph node, this causes the lymph nodes to enlarge which is the manifestation of primary tuberculosis (TB). Individuals who have active secondary pulmonary TB disease may spread the bacteria to other people. Miliary tuberculosis refers to clinical disease resulting from hematogenous dissemination of *Mycobacterium tuberculosis*. Miliary TB can arise as a result of progressive primary infection or via reactivation of a latent focus with subsequent spread via the bloodstream.

Host immune response to TB

The immune response in the lung following inhalation of droplet nuclei containing *M. tuberculosis* is a complex cellular event dominated by macrophages and lymphocytes.[21] *Mycobacteria* can change the expression of their genes and therefore their surface antigens to evade T-cell recognition.[18] Following engulfment by alveolar macrophages, the *M. tuberculosis* infected macrophages release inflammatory cytokine and chemokines which serve as signal for infection. Other cells of the immune system (monocytes, neutrophils and lymphocytes migrate to the site of infection. This response is mediated by pattern recognition receptors (PRRs)[18,22] expressed by macrophages and dendritic cells that recognize pathogen-associated molecular patterns (PAMPS) expressed on MTB.[22]

Toll-like receptors (TLRs) help uptake MTB, which induces an intracellular signaling cascade to produce the cytokines. However, the combined efforts of these cells fail to clear the bacteria and so the organisms continue to proliferate resulting in the necrosis of the macrophage.[23] This is followed by rupture of infected macrophage, releasing the contained bacteria which continue to multiply extracellularly attracting more macrophages which also fail to arrest bacterial growth and proliferation. Dendritic cells containing engulfed bacteria mature and migrate to the regional lymph node to prime T-cells against the bacterial antigen[24]. This specific immune response produces primed T-cells which migrate back to the focus of infection guided by chemokines produced by infected macrophage. The accumulation of macrophages, T-cells and other host cells (dendritic cells, fibroblasts, endothelial cells and stromal cells) lead to the formation of granuloma (tubercle) at the site of infection.[21] If the bacterial replication inside the granuloma is not inhibited, the granuloma enlarges and could spread to enter the local draining lymph nodes which cause lymphadenopathy that is the characteristic

manifestation of primary tuberculosis. A Ghon complex can develop if the lesion produced by extension of the tubercle spreads into the lung parenchyma and lymph node.[12]

Much of the pathology to tuberculosis results from the host immune response to tubercle bacilli which usually proliferate until an effective cell-mediated immune response develops. This usually takes about 2-10 weeks following initial infection in more than 90% of infected individuals[13]. In the lungs, failure to mount an effective cell mediated immune response and tissue repair could lead to extensive damage. Tumor necrosis factor-alpha, nitrogen intermediates, reactive oxygen and the constituents of cytotoxic cells (perforin, granzymes) whose function it is to eliminate *M. tuberculosis* could contribute to collateral damage of the host and the development of caseous necrosis.[13]

Public Health Concerns about TB

The complex immunological response, chronicity and need for long term treatment makes tuberculosis (TB) a major public health burden and, it is one of the most prevalent infections of human beings that shows little sign of abating.[3] It is a chronic infectious disease and, it is one of the leading causes of mortality due to infectious disease worldwide. [25]

There appears not to be any encouraging result despite efforts being made to control the disease because of the morbidity and mortality still being recorded worldwide due to the disease. Tuberculosis in developing countries like Pakistan, the Philippines, China, South Africa, Indonesia and Nigeria experience the highest morbidity and mortality rates and when combined, these countries accounted for 64% of all tuberculosis related deaths in 2016 according to the WHO.[26, 27] Another report from developing countries shows that about 7% of all deaths are attributed to TB which is the most common cause of death from a single source of infection among adults.[28]

The current TB epidemic is being sustained and fuelled by two important factors: the human immunodeficiency virus (HIV) infection and its association with active TB disease and increasing resistance of *Mycobacterium tuberculosis* to the most effective (first-line) anti TB drugs.[29]

Other factors that are associated the spread of TB include poverty,[30] and overcrowding.[31,32] Early diagnosis and appropriate management of TB cases by knowledgeable and skilled health care workers (HCWs) are key to addressing its global health issue. A study was conducted to understand the knowledge, attitudes and practices (KAP) concerning tuberculosis among 540 health care workers (HCWs) from 17 countries working in 13 hospitals during the 2016 hajj.[33] Of the 540 study participants who are HCWs, 21% thought that TB is caused by a virus, and 18% indicated that surgical masks are appropriate personal protective equipment (PPE) to use when dealing with patients with active TB. Also, 17- 42% thought that TB is transmitted via contaminated surface, sharing food or drinks, kissing or shaking hands. Only 25% of HCWs knew the definition of multidrug-resistant (MDR) TB and even fewer13% knew extreme drug-resistant TB (XDR-TB). Inadequate or poor knowledge was also recorded for questions relating to the length of standard treatment for drug-sensitive TB, infectiousness of people with latent tuberculosis infection (LTBI), the result of smear microscopy, whether BCG vaccination offered protection against TB, and whether MDR-TB was curable.[33] Only 25% of HCWs (mostly nurses) reported attending lecture/seminar/workshop on TB in the previous 12 months prior to the study.[33]

The need for knowledgeable and skilled HCWs was emphasized as pivotal to addressing global health issues.[34] Bacille Calmette-Guerin (BCG) is the only vaccine available to date in use for the prevention of TB in humans and, has been in use for more than 90 years.[35] Concerning infection control and practices on TB, a study in Addis Ababa among 261 HCWs, revealed that only 12% of the study participants regularly wore masks when caring for TB patients[36], also in Ebonyi state in Nigeria, KAP about TB among 52 HCWs revealed that only 14 (27%) of the respondents had a good knowledge score on TB.[37] In Delta state, Nigeria, although poor knowledge was found among HCWs with a lower educational level, a high knowledge grade was found among those with higher education level.[38]

A review of the national tuberculosis and leprosy control Programme (NTLCP) in Nigeria revealed challenges to TB control to include the shortage of TB health workers at primary health care (PHC) level and, shortfall in TB laboratories and quality

assurance services.[39]

Treatment and Management of Tuberculosis

Treatment of an active tuberculosis infection requires a combination of drugs. Monotherapy should never be used for the active disease to reduce the risk of *Mycobacterium* developing drug resistance.[1] First-line medications are the most used regimens for active tuberculosis: Isoniazid, Rifampin, Ethambutol and Pyrazinamide: Patients should have periodic liver function tests, chest X-rays, serum uric acids, and sputum microscopy done 2 to 3 months and at the completion of treatment[1]. The four- medication combination (isoniazid, rifampin, ethambutol and pyrazinamide) is administered for 2 months, followed by a combination of isoniazid and rifampin for 4 months. Second-line medications include: Injectable Aminoglycoside: Streptomycin, amikacin, and kanamycin. Injectable polypeptides: Viomycin and capreomycin Fluoroquinolones: levofloxacin, gatifloxacin and moxifloxacin. Third-line anti-tuberculosis medications are drugs with viable but unproven efficacy against the disease. They are the last resort for total drug-resistant tuberculosis infections and include: Amoxicillin/clavulanic acid, Clarithromycin, Clofazimine, Linezolid, Imipenem/cilastatin. Drug-resistant TB is caused by *M. tuberculosis* organisms that are resistant to the drugs used to treat the disease.[1] In Multidrug-resistant TB (MDR TB), *Mycobacterium tuberculosis* is resistant anti-TB first-line drugs which are used to treat most TB cases. In extensively drug-resistant TB (XDR TB) *Mycobacterium tuberculosis* is resistant to isoniazid and rifampin, in combination with any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)[1].

Effective treatment is achieved through Directly Observed Treatment (DOT), this ensures that the TB patient takes the right drugs, in the right doses at the right times. The treatment supervisor watches the patient swallow the tablets throughout the whole course of treatment. Supervisors could be either a health worker or "treatment supporter" (which could be a trained; volunteer, member of the family or the community or guardians).[40]

Tuberculosis (TB) contacts are persons who interact closely with those infected and as such are at high risk of contracting infection. They should be investigated systematically and actively for TB infection and disease. Such interventions are called 'tuberculosis contact investigations.[41] These contacts contribute to early identification of active TB, and latent TB infection (LTBI), which allows for preventive measures to be put in place.

Such preventive measures include; immunization with the BCG vaccine, chemoprophylaxis for patients with LTBI, general health promotion measures like good housing with adequate ventilation, avoidance of overcrowding, good nutrition and health education on personal habits like coughing and spitting.[42]

Conclusion

Some of the key steps to addressing global health issues include early diagnosis and appropriate management of TB cases by knowledgeable and skilled HCWs.[34] Due to reports which reveal low level of knowledge concerning TB among 540 HCWs from 17 countries during the 2016 hajj[30] and also the report of shortage of skilled TB health workers at the primary health care (PHC) level in Delta and Cross Rivers states, Nigeria.[38,39] This review provides some useful information on TB for HCWs and the public in general. More people are thought to have died of TB than of any other infectious disease throughout history.[43] Most infected individuals usually contain or clear the infection successfully.[44]

This review provides the outcome of host-pathogen interaction, showing how the host can suppress the infection or clear it at the first site of infection, in the innate granuloma, or later, when the granuloma is further re-enforced by adaptive immunity.[45,46] Suppression of infection results in a clinical latency during which the bacteria persist indefinitely in the host and can produce active disease even decades later when the individual is a source of infection to others.[17] A study which revealed HCWs reporting that surgical masks are an appropriate personal protective equipment to use while dealing with patients with active TB is quite worrisome. Therefore, there is an urgent need for collaborative efforts among all stakeholders to ensure regular training for HCWs. This no doubt will serve to remove some of the obstacles which promote public

health burden of the disease.

References:

1. Lin PL, Flynn JL. Understanding latent tuberculosis: A moving target. J Immunol 2010; 185(1):15-22.
2. Van Sooligen D, Hoogenboezem T, de Haas PE, Hermans PW, Koedam MA, Teppema KS, Brennan PJ, Besra GS, Portaels F. Top J, Schouls LM van Embden JD. A novel Pathogenic Taxon of the Mycobacterium tuberculosis complex canetti: characterization of an exceptional isolate from Africa. Int. J. Syst Bacteriol 1997;47(4):1236-45
3. Ahmad S. Pathogenesis, Immunology and Diagnosis of latent Mycobacterium tuberculosis Infection. Clinical Developmental Immunology 2011 http: dx.doi.org/10.1155/2011/814943.
4. Flynn JL and Chan J. Immune Evasion by Mycobacterium tuberculosis: 'Living with the Enemy 'Current Opinion in Immunology 2003; 15(4):450-455.
5. Daniel TM. The History of Tuberculosis. Respr Med 2006; 100:1862-1870.
6. Laennec R. A treatise on Diseases of the Chest. London: T and G Underwood 1821 In: Schulger NW. The Pathogenesis of Tuberculosis. The First One Hundred (and Twenty-Three years). Am. J. Respr. Cell. Mol. Biol 2005; 32:251-256.
7. Schulger NW. The Pathogenesis of Tuberculosis. The First One Hundred (and Twenty-Three years). Am. J. Respr. Cell. Mol. Biol 2005; 32:251-256.
8. Keshavjee S, Farmer P. Tuberculosis, drug, resistance, and the history of modern medicine. N Engl J Med 2012; 367(10):931-6.
9. Fogel, N Tuberculosis: A disease without boundaries. Tuberculosis 2015(95):527-531.
10. Bermudez LE and Goodman J. Mycobacterium tuberculosis invades and replicates within typeII alveolar Cells. Infect. Immun 1996; 64(4):1400-6.
11. Jereb J, Etkind SC, Joglar OT, Moore M, Taylor Z. Tuberculosis contact investigations: outcomes in selected areas of the United States, 1999. Int J. Tuberc. Lung Dis2003; 7(12 Suppl 3):384-390.
12. Ober WB. Ghon but not forgotten: Anton Ghon and his complex. Pathology annual. 1983 18(2): 79-85.
13. Jilani TN, Sidduqui AH. Active Tuberculosis [Updated 2019 mar 23]. In: Stat pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2011.
14. Tufariello JM, Chan J, Flynn TL. 'Latent tuberculosis: mechanisms of host and bacillus that contribute to persistent infection'. The lancet infectious Diseases 2003; 3(9):578-590.
15. Flynn JL and Chan J. 'What's good for the host is good for the bug' Trends in Microbiology 2005; 13(3):98-102.
16. Shaler CR, Horvath CN, Jeyanathan M, Xing Z. Within the Enemy's camp: contribution of the granuloma to the dissemination, persistence and transmission of Mycobacterium tuberculosis. Front Immunol 2013; 4(30):1-8.
17. Chao MC and Rubin EJ. Letting sleeping dogs lie: does dormancy play a role in tuberculosis? Annu Rev Microbiol 2010; 64:293-311.
18. De Martino M, Galli L, Chiappini E. Reflections on the immunology of tuberculosis: Will we ever unravel the skein? BMC Infect Dis 2014; 14(Suppl. 1): S1 [Internet] [cited Available from: http://www.ncbi.nlm.nih.gov/
19. Ernst JD. The immunological life cycle of tuberculosis. Nat Rev Immunol 2012; 12(8):581-591.
20. Comstoc GW. Epidemiology of tuberculosis. Am. Rev. Respir Dis 1982; 125:8-15.
21. Gonzalez-Juanero M, Turner OC, Turner J, Marietta P, Brooks JV, Orme IM. 'Temporal and Spatial Arrangement of Lymphocytes within lung granuloma induced by aerosol infection with Mycobacterium tuberculosis'. Infection and immunity 2001; 69(3):1722-1728.
22. Hossain MM, Norazmi MN. Pattern recognition receptors and cytokines in Mycobacterium tuberculosis infection-the double-edged sword? Biomed Res Int 2013; 2013: 179174.doi:10. 1155/2013/179174.
23. Chen M, Gan, H and Remold HG. 'A mechanism of Virulence: Virulent Mycobacterium tuberculosis strain H37Rv, but not attenuated H37Ra, causes significant mitochondrial inner membrane disruption in macrophages leading to necrosis. The journal of immunology; 2006 176(6):3707-3716.
24. Bodnar KA, Serbina NV and Flynn JL. 'Fate of Mycobacterium tuberculosis within murine

dendritic cells'. Infection and immunity 2001 69(2):800-809.
25. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C. The Growing Burden of Tuberculosis: global trends and interactions with the HIV Epidemic. Arch Intern Med 2003; 163(9):1009-21.
26. Schaller MA, Wicke F, Foerch C, Weidauer S. Central and Neuroradiological Features. Cli. Neuroradiol 2019; 29(1):3-18 In: Jilani TN, Sidduqui AH. Active Tuberculosis 2019.
27. Morton B, Stolbrin M, Kagima W, Raylance J, Mortimer K. The early Recognition and Management of Sepsis in sub-Saharan African Adults. A Systemic Review and Meta-Analysis. Int. J. Envirion. Res. Public Health 2018, 15(9): doi 10.3390/ijerph 15092017.
28. Kaye K and Frieden TR. Tuberculosis Control: The Relevance of Classic Principles in an Area of Immunodeficiency Syndrome and Multidrug Resistance. Epidemiol Rev.1996; 18(1):52-63.
29. World Health Organization. Global Tuberculosis Control 2009: Epidemiology, Strategy, Financing: WHO Report 2009 Geneva: World Health Organization 2009.P.303 (WHO/HTM/TB/2009.441).
30. Pang PT, Leung CC, Lee SS. Neighbourhood Risk Factors for Tuberculosis in Hong Kong. Int. J Tuberc Lung Dis,2010;14:585-592.
31. Prasad A, Ross AA, Rosenberg P, Dye CA. World of Cities and the End of TB. Trans R. Soc Trop. Med. Hyg.2016;110:151-152
32. Shetty P. Health Care for Urban Poor falls Through the Gap. The Lancet 2011; 377:627-629.
33. Alotaibi B, Yassin Y, Mushi A, Maashi F, Thomas A, Mohammed G, Hassan A and Yezli S. Tuberculosis knowledge, Attitude and Practice Among health Care Workers During the 2016 Hajj. PLoS ONE 14(1); e0210913://doi.org/10.1371/journal.pone.0210913.
34. World Health Organization. Global Tuberculosis Report 2017. Geneva 2017.
35. Luca S and Mihaesca T. History of BCG Vaccine. Medica (Burchar) 2013; 8(1):53-58.
36. Tenna A, Stenehjem EA, Margoles L, Kacha E. Infection Control Knowledge, Attitude and Practices Among Health Care Workers in Addis Ababa Ethiopia. Doi: https//doi.org/10.1086/673979.
37. Ukwaja KN, Alobu I and Onu EM. Frontline Health Care Workers' Knowledge of Tuberculosis in Rural South-east Nigeria. African Journal of Respiratory Medicine,2013 9(1):7-10
38. Isara AR, Akpodiete A Concerns about the Knowledge and Attitude of Multidrug-resistant Tuberculosis Among Health Care Workers and Patients in Delta State, Nigeria. Nigeria Journal of Clinical Practice. 2013;18(5):664-669.
39. Otu AA. A Review of the National Tuberculosis and leprosy Control Programme (NTBLCP) of Nigeria: challenges and Prospects. Annals of Tropical medicine and Public Health 2013; 6(5):491-500.
40. Nwobi .B (ed). National Tuberculosis and Leprosy Control Programme (NTBLCP). Federal Ministry of Health Nigeria. Workers' Manual – revised 5th edition, 2015.
41. Lucas A.O, Gilles H.M. *Short textbook of Public Health Medicine for the tropics*. Fourth edition: Hodder headline group; 2003.
42. https://www.who.int/tb/areas-of-work/laboratory/contact-investigation/en/. [Accessed 7th of December 2019].
43. Lawn, S.D., and Zumla, A.I. Tuberculosis. Lancet 2011; 378, 57–72.
44. Zumla, A., Raviglione, M., Hafner, R., and von Reyn, C.F. Tuberculosis. N. Engl. J. Med. 2013; 368, 745–755.
45. Cambier, C.J., Takaki, K.K., Larson, R.P., Hernandez, R.E., Tobin, D.M., Urdahl, K.B., Cosma, C.L., and Ramakrishnan, L. *Mycobacteria* manipulate macrophage recruitment through coordinated use of membrane lipids. Nature 2014; 505, 218–222.
46. Zmudowski, J.D., Adams, K.N., Edelstein, P.H., and Ramakrishnan, L. (2013). Antimicrobial efflux pumps and Mycobacterium tuberculosis drug tolerance: evolutionary considerations. Curr. Top. Microbiol. Immunol. 374, 81–108.