REVIEW

21(86), July - August, 2017

ISSN
2321–7359
EISSN
2321–7367

Medical Science

Combating the obstinate killer, Tuberculosis: a literature review

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Publication History
Received: 16 May 2017
Accepted: 25 June 2017
Published: July-August 2017

Citation
Singh Z. Combating the obstinate killer, Tuberculosis: a literature review. *Medical Science*, 2017, 21(86), 207-213

ABSTRACT

Tuberculosis (TB) is a highly prevalent disease and a leading global killer, making it an important public health issue. It's significance as a public health issue stems from the difficulty in its elimination and thus its inherent widespread effects as a disease. This literature review seeks to evaluate various aspects of the disease such as, the transmission methods, bovine tuberculosis, co-morbidities, and issues with compliance to treatments and drug-resistant strains of TB in order to better understand why the prevalence of this disease is still very high, and why it is so challenging to eliminate. The methodology will discuss the steps taken in selecting the specific sources of literature used in this review, while the results section will describe the contents of the literature. The discussion section will then propose some solutions for how to combat this disease, in relation to the findings presented.

Keywords: Tuberculosis, transmission, bovine, co-morbidities, compliance, drug-resistance and prevention

1. INTRODUCTION

Background

Tb is a contagious, airborne disease caused by Mycobacterium tuberculosis. The disease predominantly attacks the lungs; however it can also attack other parts of the body, such as the brain, spine and kidneys. Interestingly, not everyone infected with the bacteria becomes unwell, as presented in the case of latent TB infection (LTBI). LTBI represents a case in which an individual is in a state of

consistent immune response, resulting in the absence of clinical manifestations of the disease, (1). The bacteria can remain inactive permanently; however can also be made active due to certain conditions such as co-morbidities that weaken the host's immune system. Due to the absence of symptoms, LTBI proves to be a more challenging diagnosis, however the bacteria can still be detected through TB blood tests. Other diagnostic tests include the skin test, which is cheap and easy to administer, thus making it highly accessible, (2). This is beneficial considering the diverse range of groups that suffer from TB. Some of these high risk groups include individuals that work in high-risk settings, such as hospitals, prisons and homeless shelters, as well as substance abusers, individuals with weakened immune systems, those who were not treated properly for the disease in the past and people of lower economic status, (3).

Public Health Significance

TB is the second leading cause of death from an infectious agent after HIV, and is ranked as one of the leading causes of death globally. It affects approximately one third of the world's population, (4), and in 2014, there were 9.6 million cases of TB, with 1.5 million deaths, (5).These figures demonstrate the high prevalence of the disease, and as such show it to be a significant public health issue. It is also one of the oldest killers of humans and has prevailed throughout the ages since ancient times,(6), as shown by its presence in the spines of Egyptian Mummies dating back to 5000 B.C. This highlights both the difficulty in its elimination, and its obstinate nature, thus making it an important target for eradication and control efforts. In fact, a major facilitator of TB's prevalence is drug-resistance. There are not only drug-resistant strains present; however there are now also multi-drug-resistant (MDR-TB) and even extensively drug-resistant (XDR-TB) strains present in 105 countries, (5). This is alarming, as it highlights how adaptable the bacteria are, how prevalent the disease is, and how challenging it will be to eradicate it, due to the vast number of strains present today.

2. METHODOLOGY

For the identification of relevant and usable literature for the review on TB, the database MEDLINE was used, as well as google scholar. The restrictions and inclusion criteria for literature remained the same for both search tools. On the MEDLINE database, the basic search tool was used as the search option and the results were limited to those accessible with the full-text, so that a complete and in-depth analysis of the publication could take place. A further restriction to the results was the date of publication, with publications no older than five years being used, in order to look for the most recent data and information regarding the disease. To ensure that relevant literature was not excluded from the search, broad search terms were used, such as "tuberculosis" plus "comorbidities" or "disease-resistance". The specific literature could then be included in the study if it talked about TB in relation to the second search term, such as those mentioned above: "comorbidities" and "disease-resistance". This same method was used to search for studies relating to the other factors assessed in this literature review.

Following this, an in-depth analysis of the selected studies occurred. Those studies in which the relevant variable was not sufficiently described were excluded at this stage. Only those studies with a sufficient level of information regarding the factor at hand where then selected for use in this literature review. This analysis entailed the reading of the studies at hand and then comparing them to other studies that had investigated the same factor, such as compliance to medications. However, certain limitations to consider regarding the methods used in this literature review include the aspect of subjectivity when selecting and comparing studies via the method of reading. Although the restrictions applied in the search for the articles provides a sufficient and relevant sample to review, the vast quantity of literature available and limited resources in terms of time and manpower in conducting the review itself, are limitations that could perhaps have resulted in the exclusion of more appropriate literature that should have been used.

3. RESULTS

Transmission Methods

TB is an airborne, droplet infection that can be transmitted through methods such as coughing, sneezing, speaking and even laughing. The bacteria infect the lungs via aerosol droplets from an infected individual with pulmonary TB. Other forms of the disease, which can be present in the brain, spine and kidneys are generally not transmissible, with bacteria in the lungs and throat being the most likely to be transmitted to other individuals. The risk of infection is dependent upon several factors, such as the quantity of bacteria inhaled, the immune competency of future hosts, the degree of infectiousness of the bacteria and the distance between individuals, (7). Due to the transmission method, high risk groups tend to be in locations with large numbers of individuals in confined areas, such as in prisons, hospitals or even in certain housing conditions. TB can also undergo congenital transmission and although this is rare, with TB being relatively common in pregnant women, it poses a serious threat with high mortality rates of

50% untreated infants, and 22 % in treated infants, (8). Congenital transmission can also cause a problem when the mother has LTBI, as this will generally go undetected, thus leaving the infant highly vulnerable to the active disease, given that their immune systems may not be strong enough to prevent the rapid replication of the bacteria. In contrast, individuals with strong immune systems will generally be able to combat the infection from two to eight weeks of being infected, (7), as the immune system will stop the replication of the bacteria.

Nonetheless, TB is a pandemic that affects almost a third of the global population and its success as a disease it perhaps in part, thanks to the method of transmission. Since this droplet infection can be transmitted through infected aerosol droplets, this means that all individuals are susceptible to the disease and with the recent phenomenon of globalization, this has provided a vector for the spreading of the disease more frequently, successfully and to all locations around the world.

Bovine Tuberculosis

Bovine tuberculosis (bTB) is caused by Mycobacterium bovis and is a zoonotic infectious disease. This form of TB is found most commonly in wildlife such as cattle, as well as elk, deer and bison and has the ability to cause TB disease in humans. This form of the disease generally affects the lungs and lymph nodes, as well as other parts of the body, while it can also result in LTBI. Some of these individuals with the latent infection may then go on to develop TB disease. Importantly, bTB is fairly rare and causes approximately two percent of the cases of TB in the United States (9). This low prevalence is predominantly due to the successful implementation of control methods, not only in the US, but in several countries around the world. In fact, the transmission of bTB from cattle to humans decreased significantly due to these control efforts, which include procedures such as the routine pasteurization of cow milk. Given that the most common method of transmission to humans from cattle is through the drinking or eating of dairy products that are contaminated and unpasteurized, the process of pasteurization played a significant role in decreasing the transmission of bTB to humans, (9). Other methods of transmission to humans include inhalation, although this is rare from animals to humans, it is common between people, regardless of the type of bacterium. Direct contact with wounds is another method for transmission, although this mainly affects individuals in specific high-risk groups, such as those which work in slaughter houses, hunt or work with the infected animals or their products, (9). Individuals in high-risk groups should actively undertake prevention methods, such as through regular screenings for the infection, which include the tuberculin skin test and the blood test. In fact, bTB presents with similar symptoms to TB that is caused by Mycobacterium tuberculosis, and is also treated in a similar manner. However, it is common for bTB to be resistant to the antibiotic: pyrazinamide, however successful treatment is still achievable through the use of a different combination of antibiotics, (9).

The zoonotic element of bTB makes it a public health threat, especially due to its contribution to the number of TB cases globally. As such, control of this disease is paramount in the fight against TB. A critical aspect of controlling bTB is the identification of the source of the disease, however due to certain characteristics of the disease including its long duration of infection, long incubation period and low levels of infectiousness; it is difficult to identify the source, (10). In fact, a major challenge for control methods and policies for bTB, along with issues with the epidemiological aspect of the disease, is the ethical aspect of the disease control. It is imperative to consider the public perception and attitudes regarding the proposed control methods, (11), as several methods may be unethical and harmful to animal welfare. Moreover, given that another significant reason for bTB eradication and control is to mitigate the negative consequences of the disease on animal welfare and productivity, the omission of the ethical aspect of control does not achieve all of the desired goals. Unethical practices that were observed between the years 1971 and 1997 in Great Britain include: snaring, gassing, shooting and trapping being utilised as methods for population reduction, (11). These were eventually discontinued, with the view that these methods were not the most effective strategy. More recently, control methods are based around the testing of animals for bTB and their subsequent slaughter if they test positive. The most commonly used test is the tuberculin skin test, which although has limited sensitivity, is adequate for use as the herd level, (11). This newer method of testing is more humane than previous approaches, however is not optimal due to the degree of uncertainty that comes with the testing method.

The public health significance of zoonotic diseases is based around the fact that these diseases can be most challenging to control or eradicate, due to their characteristic of being transferable between different species. As such, the integration of knowledge from veterinary fields and medical fields is imperative in the fight against zoonotic diseases. Due to this, it is important to remember that the animals must be considered as patients that are afflicted with these diseases and so should undergo ethical control and treatment regimens, in a similar fashion to our species.

Comorbidities

Weak immune systems due to co-infections are a leading cause in the development of TB disease and the progression of LTBI to active TB disease. Given that the immune system is a major barrier in the development of the disease, other diseases and infections that weaken the immune system inherently increase the risk of developing clinical manifestations of the disease, transmitting the disease and becoming infected with it. Currently, the most prominent example of comorbidity is the HIV/TB comorbidity, with 1.2 million individuals out of the 9.6 million that were infected with TB in 2014, also having HIV, (5). It has been described as the perfect syndemic, due to the fact that HIV specifically attacks the immune system, and the virus-associated immune deficiency increases an individual's vulnerability to TB. This is made evident by the fact that the incidence rate ratio of TB in individuals with HIV was as high as 36.7 in low-level epidemic regions, when compared to individual's without HIV, (12). Other factors that have resulted in the high prevalence of this comorbidity are due to the overlap of several sociographic factors between both of the diseases, (12). These factors include poverty, low education levels and poor working conditions, as they all facilitate the transmission of these diseases.

Another prominent co-morbidity involves diabetes mellitus and TB. Diabetes is another highly prevalent disease and it significantly increases the risk of obtaining TB disease. The increased likelihood of obtaining TB when an individual already has diabetes is shown by the fact that the relative risk of TB in diabetic patients was 3.1, relative to the patients in the study who did not have diabetes, (13). The theory behind this hypothesises that the increased risk is due to the fact that immune response changes are associated with hyperglycaemia, which commonly occurs in those suffering from diabetes mellitus. These immune response changes result in an inconsistency that provides a route for TB disease to manifest and LTBI to progress to active TB disease. Due to this, control programs for diabetics include proper glycaemic control, as this can reduce the frequency and severity of symptoms, thus keeping the bacteria under control and inherently resulting in a reduced risk of transmission. Moreover, individuals who are suffering from this comorbidity, as well as the HIV/TB comorbidity, are more likely to have unfavourable treatment outcomes, as the combined exacerbating effects of both diseases acting together prove to be incredibly difficult to treat and as such, are associated with high mortality rates.

Compliance to Medications

A patient is said to be non-compliant to medications if they miss over 25 percent of their treatment in a month, do not collet their medication for more than one week, or if they miss a daily or intermittent injection for more than one week, (4). When a patient is not compliant with regard to not collecting their medication, they are referred to as defaulters and if a patient then defaults for more than a month, the treatment is then considered abandoned. Many epidemiologists regard obtaining high levels of compliance as an even more important factor than the identification of new cases, (4), due to the fact that non-compliance is one of the major causes of poor treatment outcomes, prolonged duration of the disease and the emergence of drug-resistance strains. This indicates how important compliance to medications and the treatment regimen is, when it comes to controlling the spread of the disease.

Some of the major reasons for non-compliance include socioeconomic issues, a prolonged duration of the treatment, drug toxicity, the need for several drugs, a lack of social support and a lack of counselling, (14). The issue of a prolonged duration of treatment compounds the issues regarding a lack of social support and counselling. Given that the recommended minimum duration for treatment is 6 months, (4), and prevention strategies involve isolation from others, this treatment regimen can place a large psychological burden on a patient and even their family and friends. In fact, in a survey, 30.94 percent of participants listed the main reason for non-compliance to be a lack of social support, highlighting how important this factor is in creating a successful treatment process.

Moreover, socioeconomic issues and the number of drugs a patient may be required to take also tie in together, as medications can be expensive and may even be difficult to access, (15). This results in several people taking certain medications and not others, or simply abandoning their treatments all together once they start to feel better. Of course these results in an incomplete treatment, thus potentially causing them further health issues in the future, such as a resurgence of the TB disease. The medications can also be fairly toxic, resulting in negative side effects. This can dramatically reduce the quality of life for patients, with the issues being exacerbated by the long duration of their treatment. Due to this, they are likely to stop taking their medications when their symptoms start to clear, which of course results in non-compliance, and the development of drug-resistant strains. This is perhaps the major consequence of non-compliance, unfortunately implying that multi-drug-resistant TB is perhaps a man-made phenomenon.

Drug-resistant TB

Drug-resistance is the phenomenon, whereby a drug is made ineffective due to gene mutations in the bacteria, (16), which result in the development of the resistant strain. Drug-resistance is perhaps the main threat that is preventing the achievement of TB control,

and is progressively getting worse, with a 14 percent increase from 2013 to 2014, (5). In fact, in 2014, there were 480,000 cases of MDR-TB with 190,000 deaths, and this form of TB only has a 50% survival rate, (5), highlighting the gravity of its threat on a global scale. MDR-TB is defined as being resistant to isoniazid, rifampin and at least two of the most powerful first-line drugs, while XDR-TB is defined as being resistant to all of these drugs, along with any fluoroquinolone and at least one of the second-line drugs, (17). Any type of drug-resistance occurs if the individual is initially infected with a resistant strain, or if resistance is acquired in an individual who is already infected, (18).

The predominant risk factor for the development of resistant strains is inadequate treatment, as this can result in the development of resistant mutants, which can then become the dominant strain in the infected individual. Issues that can lead to inadequate treatment include non-compliance, clinical errors such as an erroneous diagnosis and treatment regarding the specific strain of TB and even organizational errors from disease control planners, (14). Other social factors include the individual's level of education, socioeconomic status and social security, (16), as these can facilitate the transmission of the disease due to a lack of awareness of transmission methods and treatment practices, as well as being subject to high-risk settings, such as poorly ventilated housing. Moreover, negative treatment outcomes are much more likely in patients with acquired resistance, than those without it. The main reason for this is the use of second-line drugs (SLD) in the treatment process, which are not effective enough, require a long treatment duration, are costly and are also poorly tolerated, (17). In fact, treatment with SLDs can increase the risk for the development of further resistance, which is a major issue due to the fact that there would be very few effective drugs left for treatment and thus may also result in the development of XDR-TB, (17).

This phenomenon of drug-resistance poses a major obstacle to any chance of disease eradication, and is reflective of the flaws in disease control and treatment programs for TB, (16). The prevalence of TB has made a significant decrease in the past few decades, however the increasing burden of disease-resistance and the current lack of medical, social and pharmaceutical resources, provide a bleak outlook for the future with regard to TB control.

4. DISCUSSION

TB represents over a quarter of the preventable death world-wide, (16), and to date, no other disease compares to TB, in relation to the magnitude of morbidity and mortality it has inflicted upon the human race, (6). This makes a strong case for greater efforts towards control and eradication, as despite great knowledge of this disease for several decades, it is still a leading killer on a global scale.

A major contributor to a recent resurgence of the disease is drug-resistance, with the WHO stating that control-efforts are off-track with regard to disease management, (17). A potential reason for this is the fact that risk factors, rates and patient outcomes are not well defined for acquired resistance, (17), thus providing a large hurdle to research regarding new drugs. As such, funds should be allocated to research programs in order to identify issues such as risk factors, so that advances can be made in finding treatments and policies can be set on societal, community and organizational levels to control the issue, (16). In addition, further research to target factors that facilitate the development of resistance, such as long treatment regimens should be promoted, as by decreasing drug-exposure times, the likelihood of resistance developing decreases, (19).

Moreover, TB is primarily a poverty-related disease, as demonstrated by its uneven distribution among populations. It is highly prevalent in areas of low socioeconomic status and confined areas, such as prisons and low income housing. The poorly ventilated and confined areas provide easy transmission routes for the bacteria, creating disease reservoirs. Due to this, high-risk groups in populations should be identified and intervention programs should be targeted at these groups, as they may be the source of the epidemic in certain regions, (20). Strategies for these intervention programs should include increased screening, the provision of more accessible health care and education regarding disease prevention strategies.The education regarding prevention strategies is imperative, as due to the method of transmission of TB, it is easily spread between individuals. Educating individuals on prevention, will thus reduce morbidity and mortality rates in the population, as they could protect themselves better in high-risk settings. In fact, education can also facilitate a decrease in patient non-compliance rates, (20). This is due to the fact that providing further information and following the ethical principle of patient autonomy, allows the patient to make a more educated decision with regard to treatment compliance, thus improving treatment outcomes and reducing the risk of disease-resistance.

Other factors that increase the prevalence of TB are comorbidities. A major factor resulting in increasing prevalence of comorbidities, is that traditional approaches, which are disease-specific, do not generally recognise common features of management between different diseases and there is not enough knowledge on the combined effects of the diseases, (21).Due to this, it is imperative to further research these combined effects and how they affect treatment outcomes, as this could provide alternative treatment methods, as well as identifying potential risk factors that could then be controlled.

A further factor contributing to the increased prevalence of TB disease is bovine tuberculosis. This zoonotic disease adds another dimension to the disease by increasing the transmissibility of this disease by providing another source of infection: animals. In order to effectively combat bTB, there is a need for an integrated approach involving both the veterinary and medical fields, in order to ensure that the most efficient strategy is employed in the effort to control and eradicate this specific disease and then achieve the ultimate goal of eradicating TB disease altogether. Moreover, the traditional methods of control that are centred around epidemiological research, must also incorporate social science, (11), as public perception and ethical considerations are critical to the process of elimination of any disease. In fact, alternative methods for disease control should be implemented. These should include more sustainable solutions that are centred around the philosophy of prevention, such as the creation of a vaccine for cattle, (11), which could significantly decrease the prevalence of the disease. In addition, funding should be increased for more targeted research into detection methods for the source of the disease. Currently, whole-genome sequencing is a tool that is being utilised and is transforming the field of forensic epidemiology for several diseases and has the ability to be utilised for bTB investigations, (10). However, the mutation rate of bTB is highly variable relative to other RVA viruses, on which most of the success of whole-genome sequencing is based in epidemiology, (10). Given its optimal performance with other diseases, it would be prudent to invest in further research and data collection in order to enable the success of this method with bTB as well.

5. CONCLUSION

Tuberculosis is a leading killer globally and is one of the most challenging diseases to eliminate. Its success as a disease is multifaceted, with its high mutability and survivability resulting in the development and high prevalence of multi-drug resistant and extreme-drug-resistant strains. Compounding this, the method of transmission facilitates its development as a pandemic and is exacerbated by comorbidities, which further increase mortality. Thus, factors that facilitate the worsening of this pandemic such as compliance to medications must be addressed. Research should focus on alternative drugs, risk factors and high-risk groups, with an ultimate goal of policy changes to establish control. Through these policy changes, regulations regarding treatment methods and drug prescribing can be monitored to ensure the maintenance of proper clinical procedure, therefore minimizing the risk for drug-resistance. Moreover, protocols must be put into place to reduce the risk of transmission in high-risk settings, such as prisons and hospitals, with the aim of restricting and eventually eliminating reservoirs for the disease. One of the most challenging issues however, is patient non-compliance. The best solution to combat this issue is the integration of education into the treatment process, in order to enable patients to fully understand the potential consequences due to non-compliance. This concept of integration should be extrapolated to the zoonotic element of TB, as although bTB presents in only a small number of TB cases, it still poses a threat to both humans and certain animals, while also preventing the complete eradication of this disease. An integration of veterinary and medical fields will enable a fully educated and more comprehensive approach to controlling and eliminating the disease. By tackling each issue directly, through methods that are educated by intensive research, the establishment of greater control over TB disease may be achievable.

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