



Pulmonary non-tuberculous mycobacterial infections: current state and future management

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Abstract

Currently, there is a trend of increasing incidence in pulmonary non-tuberculous mycobacterial infections (PNTM) together with a decrease in tuberculosis (TB) incidence, particularly in developed countries. The prevalence of PNTM in underdeveloped and developing countries remains unclear as there is still a lack of detection methods that could clearly diagnose PNTM applicable in these low-resource settings. Since non-tuberculous mycobacteria (NTM) are environmental pathogens, the vicinity favouring host-pathogen interactions is known as important predisposing factor for PNTM. The ongoing changes in world population, as well as socio-political and economic factors, are linked to the rise in the incidence of PNTM. Development is an important factor for the improvement of population well-being, but it has also been linked, in general, to detrimental environmental consequences, including the rise of emergent (usually neglected) infectious diseases, such as PNTM. The rise of neglected PNTM infections requires the expansion of the current efforts on the development of diagnostics, therapies and vaccines for mycobacterial diseases, which at present, are mainly focused on TB. This review discuss the current situation of PNTM and its predisposing factors, as well as the efforts and challenges for their control.

Keywords Pulmonary non-tuberculous mycobacterial · Host factors · Virulence factors · Environmental factors · Diagnosis · Treatment · Vaccine

Introduction

Multiple bacterial agents are associated with pulmonary infections [1]; among them, non-tuberculous mycobacteria (NTM) have a rising incidence [2]. NTM are also known as mycobacteria other than tuberculosis, atypical mycobacteria or environmental mycobacteria [3]. NTM are labelled as environmental mycobacteria because they are widely distributed in the environment, such as in soil, marshland, streams, rivers,

estuaries, dust, domestic and wild animals and food [4]. NTM are opportunistic pathogens which rarely cause disease in human unless host defence is impaired [5]. They are associated with disseminated and local infections in lungs, pleura, skin, eye, central nervous system, soft tissue, genitourinary system and lymph nodes, among others [6–16] (Table 1).

Pulmonary infection is the most common disease caused by NTM (PNTM) and it has substantially increased worldwide [28]. Based on the data published by Hoefsloot et al., (2013) from 30 countries across six continents, *M. avium* complex (MAC) (consisting of *M. avium* and *M. intracellulare*) is the most prevalent NTM found in respiratory samples, followed by *M. gordonae* and *M. xenopi* [29]. Among the six continents, the relative contribution of MAC per continent was highest in Australia (71.1%), followed by Asia (53.8%), North America (52.0%), South Africa (50.5%), Europe (36.9%) and South America (31.3%) [29]. In Europe, *M. gordonae* is most prevalent in Germany, while *M. xenopi* is prevalent in Hungary [29]. Rapidly growing *Mycobacterium* (RGM) such as *M. fortuitum* and *M. abscessus* are the major species associated with pulmonary disease in Asia, particularly in Taiwan, South Korea, Saudi Arabia, India, Singapore and Malaysia [29–33] (Table 1).

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Table 1 Some characteristics of the most frequent NTM causing PNMTM

NTM	Phenotypic characteristics [17, 18]							Sequence data [19]		Biofilm components	Pathology				
	Runyon class	M	NaCl	45 °C	Urea	Tween	TR	AS	NR			IU	Median total length (Mb)	Median protein count	Median GC%
<i>Mycobacteroides</i> (“ <i>Abscessus-Chelonae</i> ” clade) [17]															
<i>M. abscessus</i>	RGM/NC	N	P	N	-	N/P	-	P	N	N	5.10513	4991	64.1	GPLs [20], eDNA [21]	Serious lung infection, bloodstream and disseminated infections, rarely skin infection [6, 7]
<i>M. chelonae</i>	RGM/NC	N	N	N	-	N/P	-	P	N	N	5.11552	4915	64	GPLs [22], eDNA [23]	Skin, bone, soft tissue, corneal or disseminated infections [7]
<i>Mycoliticibacterium</i> (“ <i>Fortuitum-Vaccae</i> ” clade) [17]															
<i>M. fortuitum</i>	RGM/NC	N	P	N	-	P	-	P	P	P	6.35543	5984	66.1	GPLs [22], eDNA [23]	Local infection after trauma, skin, lung, lymph node, and joint infections [7, 8]
<i>Mycobacterium</i> (“ <i>Tuberculosis-Simiae</i> ” clade) [17]															
<i>M. avium</i> complex (MAC)	SGM/NC	-	N	N	N	N	P	N	N	-	5.1868	4687	69.1	GPLs [24], eDNA [25]	Pulmonary infection, lymphadenitis, disseminated infections [9]
<i>M. goodii</i>	SGM/SC	-	N	N	N	P	N	N	N	-	7.42292	6308	66.7	-	Lung, soft tissue, peritoneal cavity, cornea and disseminated infections [10]
<i>M. xenopi</i>	SGM/NC	-	N	P	N	N	N	P	N	-	5.25194	4711	65.9	-	Often pulmonary infection and disseminated infection [11]
<i>M. marinum</i>	SGM/PC	-	N	N	P	P	N	P	N	-	6.32439	5248	65.7	LOSs [26]	Skin and soft tissue infections, tenosynovitis, arthritis, osteomyelitis and disseminated infection of lung in immunocompromised patients [12]
<i>M. kansasii</i>	SGM/PC	-	N	N	P	P	N	P	P	-	6.41775	5349	66.1	LOSs [26]	Pulmonary disease, skin, soft tissues, musculoskeletal infections, lymphadenitis, disseminated disease and catheter-associated disease [13]
<i>M. malmoense</i>	SGM/NC	-	N	N	P/N	P	P	N	N	-	5.66547	5135	68.8	-	Often lung infection, skin and tissue infections, lymphadenitis [14]
<i>M. szulgai</i>	SGM/SC	-	N	N	P	P/N	P/N	P/N	P	-	6.67266	5592	65.8	-	Pulmonary, extrapulmonary (skin, joint, intestinal, lymph node) and disseminated infections [15]
<i>M. simiae</i>	SGM/PC	-	N	N	P	N	P	N	N	-	5.78297	4924	65.8	-	Lung infection, osteomyelitis, peritonitis, pyelonephritis and disseminated infection in immunocompromised patients [6]
<i>M. interjectum</i> [27]	SGM/SC	-	N	N	P	P	N	NI	N	-	5.91654	5264	68.1	-	Pulmonary infection, lymphadenitis, disseminated disease [16]

M, manitol; Urea, urease; TR, tellurite; AS, 3-day arylsulfatase activity; NR, nitrate reductase; IU, iron uptake; RGM, rapid growing mycobacterium; SGM, slow growing mycobacterium; NC, non-photochromogen; PC, photochromogen; SC, scotochromogen; GPLs, glycopeptidolipids; LOSs, lipooligosaccharides; eDNA, extracellular DNA; P/N, positive/negative

PNTM is a recognized disease in the developed world as the incidence rate of PNTM is higher than TB in countries such as Japan [34], USA [35] and Australia [36]. Indeed, the inverse trend of the incidence rates of NTM and TB was observed in 75% of 16 geographic areas across four continents [37]. The average annual prevalence of PNTM in the USA ranges from 1.4 to 13.9/100,000 and can reach up to 44/100,000 in Hawaii, with an estimated increment of 2.5–8% annually [38]. In the USA, from year 1999 to 2014, even though the total deaths due to TB are higher compared to PNTM, the number of TB deaths has decreased periodically, while the number of PNTM deaths has increased [39].

The rise of PNTM may be partially associated to the advancement of detection methods of mycobacteria, but its annual augmentation is multifactorial, contributed by the pathogen, host, host-pathogen interactions and the still insufficient management of the disease [40]. The current world dynamic landscape, characterized by a growing population, development associated changes with environmental impact, increase of life expectancy and an increasing pool of immunosuppressed individuals associated with chronic communicable and non-communicable diseases and their interactions, among other factors, configure a context where the increase of PNTM is expected in the foreseeable future [38, 41, 42]. To bridge the gaps in prevention, diagnosis and treatment of PNTM, the National Institute of Allergy and Infectious Diseases (NIAID) and the NTM Research Consortium (NTMRC) established by North American clinicians have organized workshops to gather the experts in discussions for better understanding of the pathogen diversity, host-pathogen interactions and the development of efficient control strategies [43, 44].

This review is divided into two main sections: (1) The disease, which includes the most important factors related to the host, the pathogens and their interactions and (2) the control of the disease, comprising (a) prophylaxis—measures to prevent the disease and (b) management of disease—measures focused in the diagnosis and therapy.

The disease (PNTM)

In this section will be discussed the most important factors involved in PNTM: (1) the host, (2) the pathogens and (3) the host-pathogen interactions (Table 2).

Host

The risk of PNTM development increases due to multiple host-related-factors, such as structural lung defects [327–329], genetic factors [74] and immunodeficiencies [162, 330], among others; all of them are discussed in more detail in the following subsections (Table 2).

Structural lung defects

PNTM are frequently associated with diverse structural lung defects, mainly with chronic obstructive pulmonary disease (COPD) and bronchiectasis, which are linked to different pathologies (Table 2).

Chronic obstructive pulmonary disease Chronic obstructive pulmonary disease (COPD) is a disorder characterized by air-flow limitation and persistent respiratory symptoms, which have been mainly associated with chronic bronchitis, emphysema and chronic obstructive asthma [45, 46]. The association of PNTM and COPD has been reported. It is considered that COPD predispose to PNTM and the infection with NTM can worsen the evolution of COPD and increase the mortality [47–51, 329]. The use of inhaled corticosteroids in COPD and other chronic pulmonary diseases is considered a risk factor for the development of PNTM [52] (Table 2).

Bronchiectasis Bronchiectasis is a syndrome characterized by chronic cough and viscous sputum production, bronchial dilatation and thickening of the bronchial wall, which can be idiopathic or associated with diverse aetiologies and comorbidities such as TB infection, cystic fibrosis (CF), allergic bronchopulmonary aspergillosis (ABPA) and impaired mucociliary clearance, among others [53–56]. Independently of the aetiology, the presence of bronchiectasis predisposes to PNTM [53–56] (Table 2).

(a) Post-TB infection

Retrospective data on patients admitted for bronchiectasis in a large single centre in China for a period of 17 years showed that pulmonary TB was the major predisposing factor (30%), mainly in patients between 30 and 39 and 60–69 years old [57]. Previous history of TB infection is one of the strongest risk factors associated to PNTM [58]. It is estimated that 10 million new cases of TB occurred in 2017 and about one-quarter of the world population has latent TB [59]. In Korea, both TB and PNTM burden have increased, which leads to the speculation that previous history of TB cause structural lung damage and increase the vulnerability to PNTM [60] (Table 2).

(b) Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease, caused by mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene predominantly found in Caucasian populations, is characterized by *CFTR* dysfunction [61]. The CF patients have decreased secretion of chloride and bicarbonate across the *CFTR* channel and increased absorption of sodium through the epithelial sodium channel,

Table 2 Factors associated with PNTM

Related to	Factor	Comments
Host	a) Structural lung defects	<ul style="list-style-type: none"> • COPD [45–52] • Bronchiectasis [53–56] <ul style="list-style-type: none"> • Post TB infection [57–60] • Cystic fibrosis [61–66] • ABPA [67–73] • Impaired mucociliary clearance [74–77]
	b) Genetic defects	<ul style="list-style-type: none"> • Genetic defects in genes related with immune response, CFTR, cilia, and connective tissue [74, 78–83]
	c) Immunodeficiencies	Primary immunodeficiency <ul style="list-style-type: none"> • Gene mutations [84–109] Secondary immunodeficiencies <ul style="list-style-type: none"> • HIV [110–119] • Autoimmune diseases [120] • Cancer [121–123] • Immunosuppressive drugs [124–129] • Surgery [130–133] o Transplantation [134–138] <ul style="list-style-type: none"> • Age over 60 years old/Immunosenescence [139–151] • Malnutrition [152–161] • Vitamin and trace elements deficiencies [162–175] • Addictions: smoking, alcoholism, and drug abuse [176–203] • Lady/Lord Windermere syndrome [204–208]
NTM	a) Virulence factors	<ul style="list-style-type: none"> • Genomic and proteomic analyses identified virulence genes and proteins in NTM similar to Mtb [209–212] • Cell wall components related to virulence, immunogenicity, immunomodulation and drug sensitivity [213–222]
	b) Biofilm	<ul style="list-style-type: none"> • Resistance to physiochemical stress, antimicrobials and immune defence mechanisms [20–26, 223–229]
	Transmission	
	a) Water	<ul style="list-style-type: none"> • Global warming increase water evaporation and aerosolization of NTM on water surface [230–238] • Insufficient treatment of water to avoid NTM colonization [239–241] • Showering, hot bath, sauna and swimming pools increase exposure to PNTM infection [242–244]
	b) Soil and dust particles	<ul style="list-style-type: none"> • High exposure to aerosolized dust/soil in construction, industrial / domestic / recreational activities associated with improper use of personal protective equipment [230, 245–250]
	c) Other sources	<ul style="list-style-type: none"> • Natural disasters, armed conflicts, terrorist attacks and migrations related to poor health conditions [233, 245, 251, 252] • Spread of disease due to ease of transportation [234–236]
Control of PNTM	A. Prophylaxis	
	a) NTM (Blocking the transmission)	<ul style="list-style-type: none"> • Avoid aerosolization [41, 253, 254] • Use of personal protective equipment [255]
	b) Host (Vaccines)	<ul style="list-style-type: none"> • Need to increase research on vaccine development for PNTM [43] • Experimental and clinical results of mycobacterial vaccines support further development in this area [256–278]
	B. Management of the disease	
	a) Diagnosis	<ul style="list-style-type: none"> • Mainly focussed on TB, and little development for NTM [43, 279–290]
	b) Treatment	<ul style="list-style-type: none"> • Need to develop new effective drugs for NTM [43, 44] Immunotherapy <ul style="list-style-type: none"> • Potential use of monoclonal antibodies specific of NTM antigens and/or human IgG or IgA formulations and therapeutic vaccines [256–278, 291–314]
	c) Drug discovery	<ul style="list-style-type: none"> • Multiple challenges in discovery and development of new antibiotics for NTM [315–326]

resulting in increased mucus viscosity, compromised mucociliary clearance and airway obstruction, among other defects [62], predisposing to PNTM (mainly MAC and *M. abscessus*) [63, 64].

As CF patients have high prevalence (20%) of NTM infections, the CF Foundation has recommended an annual screening of NTM in these patients [65] and the need to take precautionary measures to limit the transmission of NTM in CF clinics [66] (Table 2).

(c) Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction to the presence of *Aspergillus fumigatus* associated with asthma and CF [67–69]. Patients with ABPA are at risk of developing PNTM [70, 71] and the infection with MAC and *M. kansasii* is associated with a higher risk of developing chronic pulmonary aspergillosis (CPA) [72], with poor prognosis related to the use of systemic corticosteroid treatment [72]. The probability to develop bronchiectasis decreases if patients with ABPA receive proper treatment [73] (Table 2).

(d) Impaired mucociliary clearance

The mucociliary clearance impairment, with low ciliary beat frequency, low nitric oxide production and impaired toll-like-receptors function, as seen in CF and primary ciliary dyskinesia patients is a critical determinant in PNTM infection [75]. Defect in several genes has been associated with primary ciliary dyskinesia, e.g. *DNAH5*, *DNAI1*, *DNAI2*, *DNAL1*, *CCDC114*, *TXNDC3*, *DNAAF1*, *DNAAF2*, *DNAAF3*, *CCDC103*, *HEATR2*, *LRRC6*, *CCDC39* and *CCDC40* [74].

A study by Matsuyama et al. (2018) showed that in respiratory cells infected with NTM, immune signalling leads to downregulation of ciliary genes, upregulation of the inflammatory cytokine IL-32 and cholesterol biosynthesis [76]. A recent study showed that mutations at *MSTIR* gene were associated with decreased airway ciliary function and interferon- γ (IFN- γ) production [77] (Table 2).

Genetic defects

Multiple genetic alterations have been associated with the susceptibility to PTMN. For example, in the case of structural lung defects, specific gene defects [mentioned in “Cystic fibrosis” and “Impaired mucociliary clearance” subsections] have been described [74]. Specific gene defects associated with immunodeficiencies will be described in the next subsection. Defects on *CHP2* gene have been associated to PNTM due to MAC [78]. Genetic defects in genes related with immune response, CFTR, cilia, and connective tissue have been found with increased frequency in PNTM patients

compared with their unaffected family members and control subjects. Many of the patients had simultaneous defects in various genes, comprising of different categories [79]. Evidence of genetic linkage on chromosome 6q12-q16 with PNTM and the identification of *TTK* as a candidate gene for PNTM have been found in PNTM patients [80]. Also, haplotypic association with PNTM has been reported [81]. Some studies showed association of different HLA antigens and susceptibility to PNTM. In this regard, HLA-A33, HLA-DR6 and the haplotype A33-B44-DR6 were found with higher frequency in PNTM, and the presence of HLA-A26 has been associated with a bad clinical evolution [82, 83]. The studies related with the genetic defects associated with PNTM support the notion that PNTM is a complex, multifactorial disease with the simultaneous presence of several concomitant genetic alterations [79] (Table 2).

Immunodeficiencies

Immunodeficiencies, primary and secondary, are associated with the increase of susceptibility to infectious diseases [84]. It has been documented the increase of NTM infections in immunosuppressed individuals [85, 86]. In the following subsections, examples of association of primary and secondary immunodeficiencies and PNTM will be discussed (Table 2).

Primary immunodeficiency Primary defects of the immune system also known as inborn errors of immunity comprise more than 350 hereditary entities associated to single gene mutations, and their classification has been recently updated by the Primary Immunodeficiency Diseases Committee, under the International Union of Immunological Societies [84].

In the category “Combined immunodeficiencies with associated or syndromic features”, patients affected with “Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)”, in its both variants, EDA-ID due to *NEMO* or EDA-ID due to *IKBA*, produced by genetic defects in *IKBKG* or *IKBA NFKBIA*, respectively, have increased susceptibility to NTM [87–89].

Two diseases included in the category “Congenital defects of phagocyte number or function”, X-linked chronic granulomatous disease and *GATA2* deficiency (MonoMac syndrome), with defects in *CYBB* and *GATA2* genes, respectively, has been reported with increased susceptibility to NTM [84, 90–93].

The diseases from the group known as “Mendelian Susceptibility to Mycobacterial Disease (MSMD)”, included in the category “Defects in intrinsic and innate immunity”, mainly associated with gene defects related with the function of the IL-12/IFN- γ pathway (*IL12RB1*, *IL12B*, *IFNGR1*, *IFNGR2*, *STAT1*, *CYBB*, *IRF8*, *TYK2*, *ISG15*, *RORC* and *JAK1*), are characterized for increased susceptibility to NTM [84, 88, 94–97].

Patients affected by “Adult-onset immunodeficiency with susceptibility to mycobacteria”, belong to the category “Phenocopies of inborn errors of immunity”, produce auto-antibodies against IFN- γ and have increased susceptibility to NTM [84, 98–108].

Also, increased susceptibility to PNTM has been associated to C4 complement deficiency [109].

Secondary immunodeficiency Many different pathological conditions compromise the function of the immune system predisposing to infections, including PNTM. In this subsection will be discussed a group of heterogeneous situations [human immunodeficiency virus (HIV) infection, autoimmune diseases, cancer, Immunosuppressive drugs, surgery, age, malnutrition, vitamin and trace elements deficiencies, addictions and Lady Windermere syndrome] where the presence of malfunction of the immune system increase the susceptibility to PNTM (Table 2).

(a) Human immunodeficiency virus

One of the most demonstrative examples of the impact of immunosuppression on the susceptibility to PNTM is the devastating effect of MAC infection in acquired immunodeficiency syndrome (AIDS) patients [110–115].

Severely immunocompromised patients, such as those with HIV infection, with low CD4+ lymphocyte counts are at high risk of PNTM infection even with the introduction of anti-retroviral therapy (ART) [110, 116]. The infection might not be limited to PNTM, but it may progress into disseminated disease (dNTM) caused by MAC [110, 117]. The mycobacterial infections have caused high morbidity and mortality among HIV-positive individuals [110, 117]. In 1996, the introduction of ART in 1996, together with antibiotic prophylaxis, such as azithromycin or clarithromycin, has successfully reduced the development of disseminated MAC among HIV patients [118].

Even at this ART era, the management of dNTM in HIV patients is difficult as in one study, and 79% of the patients had the immune-reconstitution syndrome, which introduce important therapeutic dilemmas [119].

(b) Autoimmune diseases

In patients with systemic autoimmune rheumatic diseases, PNTM could develop and exacerbate [120].

(c) Cancer

Cancer patients are prone to develop PNTM, which could be favoured by the intrinsic immune suppressive effect of cancer and by inherent additional factors such as malnutrition, immunosuppressive treatment, radiation, stress and surgery [121, 122]. Among cancer patients, PNTM infection is most

common in lung cancer and MAC is the most common causative agent [123].

(d) Immunosuppressive drugs

Immunosuppressive drugs used to treat cancer [124], autoimmune diseases [125], and following transplantation [126], increase the risk of opportunistic infections [127].

The use of immunosuppressive drugs and TNF- α blockers to treat rheumatoid arthritis increases the risk of NTM infections, mostly by *M. avium*, followed by RGM, particularly in the lungs [128, 129].

In the case of patients under immunosuppressive treatment, other factors such as the underlying pathology and surgery, among other concomitant factors, potentiate the immune dysfunction.

(e) Surgery

Any major surgical procedure means a great trauma for the patient with many immunosuppressive associated factors during the pre-operative (pre-operative anxiety), intra-operative (tissue damage, disruption of natural protective barriers, blood loss, transfusion, hypothermia, pain, analgesia, anaesthesia and stress), and post-operative (activation of the hypothalamic-pituitary-adrenal axis, endogenous opioids, prostaglandins, cytokines and their agonists) periods [130–133]. The specific role of surgery per se, in the predisposition of PNTM, is difficult to evaluate, but is a factor that need to be considered in general, particularly in individuals belonging to risk groups of PNTM.

Transplantation Solid organ transplant (SOT) is a special surgical case, because the immunosuppressive effect of surgery and the lifelong immunosuppressive therapy are combined.

The risk of PNTM is high among SOT recipients, especially in lung transplant patients, which have the highest risk of lung infection compared to other organ transplant recipients [134, 135]. The risk of PNTM in haematopoietic cell transplants has also been reported [136–138].

(f) Age

The current world population is estimated to be 7.6 billion [139]. One of the most important characteristics of the current demographic evolution worldwide is the increase of individuals over 60 years of age [140]. The increase in life expectancy is accompanied by multiple challenges for health systems due to the inherent ageing-associated physiological/structural changes and the concomitant increase in associated diseases.

Immunosenescence is one of the processes associated with ageing which is characterized by an increase in predisposition to infection, cancer and autoimmunity and a decrease in response to vaccination [141, 142].

Age is an important risk factor which predisposes to PNTM. Adults older than 60 years old are more prone to PNTM, and their prognosis is commonly unfavourable, which is often complicated by the presence of structural lung defects such as bronchiectasis and COPD [40, 143–150].

This situation may burden health care costs as it is estimated that nearly 1.5 billion people are expected to be over 65 years old by 2050 [151].

(g) Malnutrition

The immune response is affected by the effects related with the undernutrition, low body mass index (BMI), obesity and dietary deficits. Despite the immunological imbalances present in obesity, characterized by inflammation, increase susceptibility to infections and compromise response to vaccination, a clear connection between obesity and PNTM have not been reported, so the discussion will be focussed on undernutrition and dietary deficits [152–157].

In children living in low resource areas such as Mozambique, the prevalence of NTM in pulmonary samples of presumptive TB cases can reach 26.3%, and the most common clinical feature observed was malnutrition [158].

Low BMI was associated with PNTM and was a predictor of dissemination [159]. PNTM has also been associated with low visceral fat and low nutrient intake [160]. Low BMI and cholesterol levels were predictors of bad prognosis in another study [161].

(h) Vitamin and trace elements deficiencies

Vitamin and trace elements are of paramount importance for the normal function of the immune system. Primary and secondary malnutrition have a high impact in the availability of micronutrients with increase susceptibility to infectious diseases. Primary malnutrition is frequently associated to poverty and extreme poverty, wars, natural disasters, migrations, malnutrition following beauty patterns, etc. Secondary malnutrition is associated with diseases such as cancer and parasitism, among others [163, 164].

Vitamin D Deficiency of vitamin D has been observed in adolescent idiopathic scoliosis (AIS) as it affects the regulation of bone mineral density, postural control and fibrosis [165]. Pectus excavatum, a skeletal feature of rickets, is related to hypovitaminosis D, as this vitamin is essential for maintenance of healthy bones [166]. The development of lungs is also affected by the vitamin D level and deficiency of this vitamin may lead to deficits in lung function and volume [167]. In bronchiectasis patients, 50% have vitamin D deficiency and are frequently colonized with bacteria [168]. Generally, the level of vitamin D decreases with increasing age and decreased exposure to sunlight [169]. All the factors

previously mentioned have been linked with PNTM; however, studies related with the link between vitamin D and PNTM are relatively scarce. Association of severe vitamin D deficiency and PNTM has been reported [162]. However, in another study, Fujita et al. (2018) showed association of vitamin D with bone mineral density and antimicrobial peptide levels (hCAP18/LL-37), without a direct link between the serum vitamin D level and PNTM [170].

In PNTM patients due to *M. malmoense*, association of susceptibility with vitamin D receptor gene polymorphisms was found [171].

Vitamins A and E A study by Oh et al. (2019) on serum vitamin levels in PNTM patients showed that they had significant lower vitamin A and vitamin E levels than healthy individuals, without significant changes in vitamin D levels [172]. It has been reported that in TB patients, vitamin A promotes autophagy to reduce bacterial burden in macrophages [173] and vitamin E-selenium increases antioxidant effects to reduce oxidative stress [174], suggesting that low level of these vitamins may inhibit the ability of host immune system to fight mycobacterial infections.

Trace elements deficiencies Decreased levels of selenium and zinc were found in PNTM [175].

(i) Addictions

Addictions such as smoking, alcoholism and drug abuse have a high impact in the normal function of the immune system predisposing to infectious diseases [176]. The link between addictions and PNTM has been reported [177–181].

Smoking It was estimated that over 1/7 of world population (1.1 billion) were smokers in 2016 [182]. Looking at regional smoking prevalence, most Africans and Americans smoke at adolescence [182]. Many people still underestimate the relative risk of smoking [183], and young people perceive smoking as a normal and acceptable behaviour, supported by misconceptions as having stress-relieving effects and social bonding (peer-influence) [184]. Even patients who are diagnosed with COPD do not quit smoking as smoking cessation is difficult due to their lifelong smoking habit [185].

The damages caused by smoking vary significantly depending on the personal smoking practices (frequency of smoking, fraction of smoking, starting age, etc.) and the characteristics of the smoked product (cigarette, tobacco, pipe, chemical concentration, size of the compounds, charged particles formed, etc.) [186].

Cigarette smoke is a mixture of chemical compounds that are free in the gas phase and attached to aerosol particles. It has been estimated that cigarette smoke has 7357 chemical compounds [187], some of them are very toxic and others with great

potential to be respiratory irritants, e.g. 1,3-butadiene, acrolein, acetaldehyde, cyanide, arsenic, cresols, N-nitrosamines and polycyclic aromatic hydrocarbons (PAHs), among others [188].

The antecedent of smoking in patients with PNTM has been reported [32, 86, 189, 190]. Smoking impairs the immune defences at the respiratory level by different mechanisms such as inhibition of bacterial killing due to bacterial phagocytosis defects, modulating CFTR dependent lipid-rafts and autophagy impairment, among others [191–196]. The predisposing role of smoking in PNTM could be mediated by direct effect on the immune response and indirectly, by its association with pathologies that increase the risk of PNTM such as COPD [196, 197].

Alcohol abuse According to WHO, alcohol consumption was related to about 3 million deaths and 132.6 million disabilities in 2016 [198]. Even though several countries have adopted alcohol control policies as suggested by WHO since 1999, including restriction of alcohol marketing, the weak implementation of prevention programmes has not achieved significant impact on human health [199].

Alcohol is another causative agent for airway inflammation and injury as observed in COPD, and prolonged alcohol consumption leads to increased risk of mortality in these patients [200]. The multiple deleterious effects of alcohol in the function of the different arms of the immune system have been documented [179, 180, 201], including disruption of the immune defence mechanisms at the airways [202].

Alcohol abuse has been associated with the risk of PNTM in HIV infected and non-infected individuals [190, 193].

Drug abuse Drug abuse induces important deficits in the immune system, which impacts the susceptibility to infectious diseases [176, 181].

A study on HIV patients with NTM diseases showed that their risk of infections was associated with both alcohol and drug abuse. Depending on the drugs used, the results showed that more SGM were isolated from intravenous and inhalation cocaine users, while RGM were isolated from inhalation crack users [203].

(j) Lady Windermere syndrome

Generally, tall, lean, old Caucasian ladies with MAC lung disease, with an isolated lingular or middle lobe bronchiectasis pattern, are known as LWS. The syndrome is associated with a voluntary suppression of the normal cough reflex due to politeness, which impairs the clearness of airway secretions [330]. Patients affected with this syndrome also tend to have scoliosis, pectus excavatum or mitral valve prolapse even without any apparent immune defects [204, 205].

A study by Chan et al. (2010), showed that NTM infections are more frequent in females even without any overt immune

defects [206]. However, despite of the first perception that this syndrome was not related with immune compromise, defects in *MSTIR* gene, associated with compromised airway ciliary function and reduction on IFN- γ production in response to NTM, have been found in patients with LWS as well as alterations in immune related genes [77].

“Lord” Windermere syndrome Although the alterations associated with LWS have been associated with female gender, similar characteristics to the LWS have been described in men [207, 208].

Pathogens (NTM)

There are more than 180 NTM species that are classified into 4 groups based on growth rate and pigment production, known as Runyon classification. The first 3 groups are slow growers (SGM) which require more than 14 days to growth: (I) photochromogens, which develop pigments in or after being exposed to light, (II) scotochromogens, which become pigmented in light/dark conditions and (III) non-photochromogens, which do not form pigment. The group (IV) RGM require only 2 to 5 days to growth [331]. Some phenotypic [17, 18, 27] and genomic [19] characteristics of the most important NTM associated to PNTM are listed in Table 1.

Recently, based on the results of phylogenomic analysis and identified molecular signatures [Conserved Signature Indels (CSIs) and Conserved Signature Proteins (CSPs)], Gupta et al. (2018) described the division of mycobacterial species in one emended genus: “*Mycobacterium*”; and four novel genera: *Mycolicibacterium*, *Mycolicibacter*, *Mycolicibacillus* and *Mycobacteroides*, which have five clades: “*Tuberculosis-Simiae*”, “*Fortuitum-Vaccae*”, “*Terrae*”, “*Triviale*”, “*Abscessus-Cheloniae*”, respectively. NTM belong to these five clades [17] (Table 1).

“Tuberculosis-Simiae” clade This is the only clade that includes NTM and MTBC species. Some NTM, from this clade, has been reported as pathogenic *Mycobacterium* species including MAC, *M. gordonae*, *M. kansasii*, *M. xenopi*, *M. simiae*, *M. szulgai* and *M. interjectum* causing PNTM [17].

“Fortuitum-Vaccae” clade This clade includes *M. fortuitum* and has been described as causing PNTM [17].

“Terrae” and “Triviale” clades Some members of “*Terrae*” and “*Triviale*” clades have been described as opportunistic pathogens [17].

“Abscessus-Cheloniae” clade This clade has six members and has been described as pathogenic to humans. PNTM has been described caused by *M. abscessus* and *M. cheloniae* [17].

Development in molecular methods, especially DNA sequencing and polymerase chain reaction (PCR) tests, has enabled NTM species-species differentiation and strain typing [332]. Most NTM are considered as non-pathogenic microorganisms which are harmless and unlikely to cause disease but become opportunistic pathogens especially in immunocompromised hosts [333]. On the other hand, those within the *Mycobacterium tuberculosis* complex (MTBC) are regarded as pathogenic microorganisms which cause a specific disease, TB [334].

Virulence factors

Genomic profiling of 41 NTM species showed that MTBC and NTM do share similar virulence factors, e.g. (1) cell surface hypervariable PE/PPE proteins that are important in the evasion of the host immune response, except for PE5, which is only found in NTM; (2) ESX or type VII secretion system (T7SS) for PE/PPE proteins transportation, where ESX-3 is conserved in both groups and ESX-1 which was thought to be specific for Mtb, is also expressed in *M. goodii*, *M. goodii*, *M. goodii* and *M. goodii*; (3) Mce proteins that are involved in host-cell invasion, namely, Mce1, Mce2, Mce3 and Mce4 which are present in Mtb, are also found in many NTM, with Mce5, Mce6, Mce7, Mce8 and Mce9 only present in NTM; (4) Sec export systems, SecA1 and SecA2, that are important to export Mtb lipoproteins are conserved in all species; and (5) Tat export system for Mtb virulence is also conserved in all species [209]. The genes involved in biosynthesis of mycolic acids in NTM are similar to those for Mtb, although genes for dimycoserate esters (DIM) biosynthesis are only found in SGM, particularly in the pathogenic mycobacteria, i.e. MTBC, *M. leprae*, *M. kansasii*, *M. marinum*, *M. ulcerans* and *M. haemophilum* [209].

In terms of immunogenic proteins, previously detected in Mtb, with some role in virulence, a study on 4 NTM species showed that CFP-10 was detected in *M. malmesburii* sp. nov.; GroES was detected in *M. komarii* sp. nov., *M. nonchromogenicum* and *M. fortuitum* ATCC 6841; and DnaK and GroEL were detected in all the 4 NTM [210]. Also, CFP-10 and ESAT-6 of Mtb are detected among *M. kansasii*, *M. szulgai*, *M. marinum* and *M. riyadhense* [211]. The presence of shared antigens between Mtb and NTM has given new insights to consider NTM as potentially pathogenic and could be associated with false positive results with the current interferon gamma release assays (IGRAs) in use [212].

Cell wall components of mycobacteria, including NTM, are important elements related to virulence, immunogenicity, immunomodulation and drug sensitivity [213–216] which have a high impact on the development of diagnostics, therapies and vaccines.

Important cell wall components of NTM are glycopeptidolipids (GPLs) and lipooligosaccharides (LOSs) [213–215]. GPLs, which are absent in Mtb [213] can be species-specific (ssGPLs) or non-specific (nsGPLs) [214]. The addition of an oligosaccharide to nsGPLs confers further immunogenicity producing the ssGPLs, which determine 31 serotypes among MAC members [214]. GPLs are associated with immunopathological responses during infection [214]. The serotypes of MAC are associated with pathological characteristics as in the case of serotype 4 which is linked to disseminated infection in AIDS patients [214, 217]. LOSs are also present in *M. canettii* and some MTBC, but absent in Mtb, such as H37Rv [215, 218]. LOSs are strongly immunogenic and associated with immunomodulation and virulence [218–222].

Biofilm

It is well documented that NTM such as *M. avium* [24], *M. marinum*, *M. kansasii* [26], *M. smegmatis* [223], *M. abscessus* [20], *M. fortuitum* and *M. chelonae* [22] can form biofilms which are important for resisting physicochemical stress, antimicrobials and immune defence mechanisms, favouring their persistence [224].

Besides mycolic acids, the mycobacterial cell wall has extractable lipids such as GPLs [20, 22, 24, 223], LOSs [26], and trehalose dimycolate (TDM) [20] together with extracellular DNA (eDNA) [21, 23, 25] which contribute to the biofilm development. Biofilm development is also partly influenced by the presence of nutrients [225–227] (Table 1).

As mycobacteria lack of pili and fimbriae, GPLs play an essential role in attachment on surfaces for biofilm formation and sliding motility for biofilm spreading [228]. Also, the presence or absence of GPLs determine the morphology and virulence of *M. avium* and *M. abscessus*, i.e. less virulent, non-cord-forming smooth variants has increased GPLs production, and more virulent, cord-forming rough variants lack GPLs [20, 24, 229].

Transmission

Transmission of NTM is similar to TB via aerosolization, but the source of transmission is from the environment, not human or animal, suggesting that PNTM is not contagious [332]. The propensity to PNTM increase due to exposure to environmental factors related to water and soil [230]. Although transmission of NTM from human-to-human is not common, in 2010, a first case of *M. kansasii* isolated from a couple in East London, an area with high TB burden, was reported [231]. The isolates were genetically identical, and the authors were unable to prove a shared domestic exposure [231]. Whole genome sequencing (WGS) has revealed the possibilities of human-to-human transmission, but most probably in an

indirect manner via fomite contamination or inhalation of NTM in airborne water droplets [232]. Contamination of the environment after natural disasters and human mobility might be associated with PNTM transmission [233–236] (Table 2).

(a) Water

NTM are more likely to survive at surface waters than in ground waters [230]. Thus, the risk of PNTM could be potentially associated with the percentage of surface water, temperature, humidity, rain precipitation and potential of evaporation and transpiration, whereby aerolization, favoured by the mycobacterial hydrophobicity and inhalation of water droplets contribute to PNTM [230]. The hydrophobicity promotes bacterial adherence at surfaces and pellicle biofilm formation at the liquid-air interface [224].

A study by Wei et al. 2016 showed that developed and developing countries contributed 53–61% and 39–47%, respectively, to climate changes based on the emissions of carbon dioxide, methane and nitrous oxide [237]. Human activities have changed the atmosphere composition causing accumulation of greenhouse gases leading to global warming [237]. The increase of global air temperature indirectly leads to the increase of evaporation and transpiration that convert surface water, from natural (e.g. sea and river) or artificial (e.g. swimming pools and ponds) sources into atmospheric water vapour [230].

MAC has been reported as an important causative agent for hypersensitivity pneumonitis at hot tub or spa and associated with “hot tub lung”, a diffuse granulomatous lung disease [238].

(b) Soil and dust particles

Activities (hobbies or job-related) associated with long-term contact with soil such as farming, and lawn and landscaping services are more likely to be exposed to NTM infection. Recovery of MAC strains is highly prevalent in the residential soil samples in Japan and the bacteria transmission is associated to duration of soil exposure for more than 2 h per week [245]. Soil properties play an important role in promoting growth and persistence of NTM in nature. The soil of countries with high-risk of infection have higher copper and sodium levels, but lower manganese levels compared to low-risk countries [230].

Trapped, dusty environments promote the aerolization of NTM and cause the development of silicosis and chronic bronchitis in South African gold miners, which may predispose to PNTM, particularly caused by *M. kansasii* and MAC [58]. The exposure of indoor home dust could be a source of PNTM, as *M. avium ssp. hominissuis* is highly found in dust from vacuum cleaner bags in Germany [246].

The presence of NTM such as *M. intracellulare*, *M. abscessus*, *M. szulgai*, *M. fortuitum*, *M. avium*, *M. kansasii*, *M. simiae*, *M. gordonae*, *M. terrae complex*, *M. chelonae* and

M. malmoense has been reported in sand [30]. Dust and sand from deserts, due to storms, can travel long distances even between continents and represent a vehicle for the dispersion of microorganisms, including NTM [247–249]. Also, mycobacterial DNA have been found in cosmic dust [250].

(c) Other sources

Dialyses centres, heater-cooler units, kitchen sinks, household refrigerator taps, home ice machines, tap water filters, retail sold fish, frozen fish, piped surfaces, soil fertilized with chicken droppings, dust from vacuum cleaners, air conditioner and cigarettes have been reported as sources for NTM colonization [335].

Some NTM (MAC) can evade the degradation within free-living *Acanthamoeba polyphaga*, *A. castellanii* and their excysts. Nearly 88% of amoeba (*Acanthamoeba*, *Vermamoeba*, *Echinamoeba*, and *Protacanthamoeba*) from drinking water contains *M. chelonae* [335].

NTM can be transmitted via oral route due to the gastroesophageal reflux [335].

Another important source of transmission are the disasters. Stress, disruption of health care systems, bad hygienic-sanitary conditions, food deprivation and large migratory waves, among others, are the scenarios caused by disasters, whether natural (earthquakes, tsunamis, etc.) or man-made (wars, extreme poverty, ethnic/religious/political conflicts, etc.), which create favourable conditions for the transmission of microorganisms, turning the host susceptible, making them vulnerable to the development of multiple diseases.

War is considered a public health problem [245]. Armed conflicts are classified as one of the biggest disasters that a population can suffer, affecting health directly by the effects of weapons and indirectly breaking the structures of health systems, their supply chains and interrupting health programs as vaccination and paediatric care, among others. These factors together with the destruction of water supply networks, the houses and population overcrowding, among other factors, cause the emergence of epidemics, re-emergence of common vaccine-preventable-infectious diseases in children and diseases associated with severe malnutrition. When this scenario is impregnated with violence and insecurity, it pushes populations to move, with all the terrible consequences that are added. All these factors create optimal conditions for the proliferation of infectious diseases [251, 252].

Armed conflicts are recognized as important factors for the spread of Mtb [252]. The dissemination of NTM and the increase of the incidence of PNTM in war affected populations cannot be excluded, as the presence of the necessary conditions for this to happens is present, but the evaluation of this in the difficult conditions created by war is difficult, in fact, the possibility exists that patients in these populations (initially diagnosed as TB/MDR-TB) could be affected by PTNM.

During some natural disasters, NTM transmission may increase due to several factors. The mixture of the ocean and the fresh waters, together with the mixture of the soil with the water, could produce aerosols that contain NTM, favouring the inhalation. In addition, the free-living amoebas move from their natural niches, providing a “protected” environment for intracellular multiplication of NTM and virulence, which can potentially cause PNTM [233].

Human mobility is another source of transmission. The development of widespread transportation and communication has increased population mobility, which contribute to disease outbreaks and the spread of infections [234]. Nishiuchi et al. (2017) hypothesized that globalization of human activities, mobility and trade may increase the global transmission of MAC via fomites [235]. It is suggested that person-to-person spread is unlikely and the ability of NTM to resist desiccation and detergents might promote their survival during transportation [236] (Table 2).

Host-NTM interaction

The fragile boundary between health and disease could be broken by many associated factors, mainly related with the host and the pathogen, but the resultant of the interactions between them plays the most important role. PNTM is the undesirable resultant of these interactions. The interaction is dynamic and the relative “strength” of “weakness” of each player will depend on continuously evolving factors in each side, given at any moment a “balance”, which will determine the presence or not of the disease. The challenge of disease control lies in the measures that should be implemented to block the NTM transmission and to shift the balance towards the host resistance aimed to prevent the disease, or the recovery once it appears.

Control of PNTM

In this section, prophylactic measures and the management of the disease will be discussed.

Prophylaxis

The prevention of infectious diseases is one of the most important objectives of the health systems, which are mainly achieved through (1) pathogen-related prophylactic measures (blocking the transmission), and (2) host-related prophylactic measures (vaccines) (Table 2).

- (a) Pathogen-related prophylactic measures: blocking the transmission

In the case of PNTM, some measures could be implemented to decrease the transmission mainly through water and soil.

Despite better public health measures, i.e. improvement in water supply via centralized water supply systems, which help to minimize most pathogenic water-borne bacteria, unfortunately, it has promoted NTM colonization [239]. In centralized water supply systems, water travels long distances, which eventually leads to degradation of the disinfectants, i.e. decrease in chlorine concentrations due to heat inactivation [239]. Also, a study showed that despite addition of ozonation and filtration treatments, NTM can still persist in water systems [240]. NTM can be recovered in water with free and total chlorine levels of 2.5 and 2.8 mg/l, respectively, suggesting that chlorination is unable to efficiently kill mycobacteria [241]. One of the main reasons that mycobacteria can survive in this harsh environment is their ability to form a protective shield, biofilm [229]. In potable water, slow growing MAC form a highly culturable biofilm compared to RGM, suggesting that the former has better adaptation to growth in low-nutrient environments [229]. Also, *M. avium* is able to survive and grow in free-living amoeba, particularly *Acanthamoeba lenticulata* as parasites or endosymbionts, and the encystment protect *M. avium* from the disinfection processes [336]. Water treatment has always been focused on eliminating water-borne gastrointestinal bacteria such as *Campylobacter*, *Salmonella*, *Shigella* and *Escherichia coli* but not in the elimination of mycobacteria [337]. Considering the ability of mycobacteria to survive in these harsh environments even after treatment, a more appropriate water treatment plan is needed as the consequences of NTM infection should not be overlooked. A study by Inkinen et al. (2016) suggested that copper pipelines might be effective in preventing NTM colonization compared to polyethylene pipelines [338].

Many studies have showed that inhalation of aerosols generated from shower-heads, therapy pools, hot-tubs and swimming pools may promote PNTM [242–244]. A study reported by Feazel et al. (2009) showed that among the 16 microorganism genera present in shower-heads, mycobacterial biofilms had the highest prevalence, mainly composed by *M. gordonae* and *M. avium*, which were more than 100-fold than in their background water composition [339].

Preventive measures such as cleaning shower-heads by soaking in vinegar or water, replacing shower-heads periodically, removing shower-heads completely, taking baths instead of showers, and avoiding steam rooms and hot tubs have been recommended to the public [340]. In general, the recommended preventive advices are not incorporated in our daily routine and most people still prefer showers compared to baths, partly due to convenience. Also, in line with water conservation drives and to achieve a more eco-friendly environment, a quick shower is definitely better than a bath as an average shower of 10 min uses 10 to 25 gal of water, while a bath needs at least 70 gal [341].

Inhalation of water during swimming also exposes the respiratory system to NTM. A study by Prevots et al. (2014) showed that swimming in indoor pools is associated with PNTM, which may be attributed to the formation of bacterial biofilms in closed environments which facilitates higher exposure to aerolized biofilms [41]. The lack of ventilation in closed areas facilitate inhalation of water aerosols. Also, the use of pressure washers during cleaning has indirectly increased water aerosolization and this exposure increases the risk of occupational hazard [253]. Thus, to prevent this environmental colonization, it has been suggested that such closed environments be kept dry and have proper ventilation [254].

It is recommended that workers with occupational risk should wear personal protective equipment such as masks and gloves while doing soil-related works. The World Health Organization (WHO) recommended the use of respiratory protective equipment in airborne contaminated working environments, but frequently, the workers remove the masks after wearing it for long periods of time in hot and cramped environments [255]. The use of respiratory protective equipment should be recommended also for domestic or recreational activities associated to soil and dust exposure.

(b) Host-related prophylactic measures: “arming” the host by vaccination

Prophylaxis by vaccination is one of the most potent health measures to control infectious diseases, which allow the prevention of the disease, even when the measures for pathogen control are not fully effective.

Currently, there is no vaccine recommended for PNTM. Bacillus Calmette-Guerin (BCG), the only vaccine currently available for TB, has shown protective effects in extrapulmonary NTM infections, but there is no report for PNTM [43]. A review by Zimmermann et al. (2018) based on ten studies involving 12 million participants showed that BCG vaccination is protective against NTM lymphadenitis caused by MAC and Buruli ulcer caused by *M. ulcerans* [342]. However, the cross-reactivity between these *Mycobacterium* may lead to low efficacy of BCG vaccine, especially in high NTM exposure areas [343].

There are several mouse models which demonstrated the protective effects of subunit vaccines against PNTM infections. A study by Fattorini et al. (2002) using intranasal immunization of mice with *M. avium* GroES recombinant protein, co-administered with CpG oligodeoxynucleotides, was protective against intranasal *M. avium* challenge [256].

A plasmid DNA encoding *M. abscessus* phospholipase C formulated with copolymer 704, and administered intramuscularly in mice protected against aerosolised challenge with *M. abscessus* [257]. Immunization of mice with genetic

constructions containing the *M. abscessus* MgtC gene induced protection against challenge with *M. abscessus* and the production of specific antibodies in mice [258].

A dewaxed whole-cell vaccine of *M. ulcerans* devoid of its mycolactones (cytotoxic macrolide exotoxin) and waxy cell walls, protected against *M. ulcerans* infection and prevented Buruli ulcer development in mice [259]. Priming with recombinant BCG expressing the Ag85A antigen of *M. ulcerans*, followed by a booster with recombinant *M. smegmatis* expressing Ag85A of *M. ulcerans* induced murine CD4+ T cell responses which reduced tissue damage and bacterial loads [260]. However, recombinant surface proteins MUL_2232 and MUL_3720 of *M. ulcerans* induced strong TH1 immune response but without protective effect [261].

An NTM vaccine commercially used in veterinary, Gudair®, containing the inactivated *M. avium paratuberculosis* strain 316F, is effective in decreasing the prevalence of the infection and reducing the bacteria faecal shedding in sheep [262].

The antigenic similarity and immune cross-reactivity between mycobacteria have been exploited in the development of vaccines and immunotherapy of TB [17–19, 27, 203–211, 331–334]. Proteoliposomes [263] and lipid-based preparations of the cell envelope, obtained from *M. smegmatis* [264], were protective against Mtb intratracheal challenge in mice, and induced cross-reactive humoral immune responses against Mtb antigens [87, 265, 266].

DAR-901, a heat-inactivated whole-cell *M. obuense* SRL172 strain, has been recommended as a vaccine booster for TB in adults primed with BCG as it is safe and is able to induce both cellular and humoral immune responses [267]. A murine model further demonstrated that DAR-901 conferred protection against Mtb [268].

M. habana TMC5135, a species synonymous to *M. simiae* serotype I, isolated from Cuba, showed protective effects against Mtb using animal models as live vaccine [269].

M. manresensis, a new species under the *M. fortuitum* complex, which is commonly found in drinking water, was heat-killed and used as oral vaccine to stop the progression of active TB and as adjuvant for TB treatment in a mouse model [270]. It has been developed into a galenic preparation food supplement known as Nyaditum resae® and used in clinical trials, which seemed to be effective in reducing the risk of developing active TB [271, 272].

Immunotherapy with killed *M. vaccae* has been used in the treatment of patients with TB, multidrug resistant TB, HIV-TB and leprosy with significant effects [273, 274].

M. indicus pranii as a booster to BCG via the aerosol route showed protective effect in a mice model of TB, inducing pro-inflammatory cytokines like IFN- γ , IL-12 and IL-17, and increased frequency of multifunctional T-cells [275]. In vitro studies showed that *M. indicus pranii* modulates pro-

inflammatory responses via the TLR-4 pathway, activate the innate immunity [276] and induced autophagy in TB infected macrophages [277]. Clinical trials as adjunct therapy showed that it is safe with no significant side effects and able to clear the pathogens in TB relapse patients [278].

Overall, these encouraging results on NTM based vaccine candidates for the prevention of experimental NTM infections, its use as veterinary vaccines and their evaluation for the prevention and therapy of TB support the possibility to develop vaccines for the prevention of PNTM as well as immunotherapeutic tools to help in the management of these infections.

Management of the disease

When prophylactic measures fail, the disease appears in susceptible individuals; beyond this point, its control is only possible with a fast and appropriate diagnosis and therapy.

(a) Diagnosis

The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) recommend that in case of suspicion of PNTM, chest radiographic studies, three or more sputum microbiological analysis and clinical exclusion of other disorders are needed to confirm a diagnosis of PNTM should be indicated [332]. Such criteria are needed because NTM exists naturally in the environment, and isolation of NTM from non-sterile respiratory specimens does not confirm that the organism is the causative agent for lung disease [344]. High-TB burden countries are normally those of the low to middle income countries (LMIC), where resources for microbiological culture using the traditional diagnostic TB gold standard either on solid Löwenstein–Jensen medium or liquid culture [Mycobacteria Growth Indicator Tube (MGIT)], are limited. Thus, sputum smear microscopy is the most important test used for TB diagnosis [345]. With the current rise of PNTM infections, the non-specific microscopic testing, which detects all acid-fast bacilli, cannot differentiate between PNTM or TB infection. The application of chest X-ray screening to predict the presence of TB or PNTM remains subjective. As recommended by ATS/IDSA, PNTM can be diagnosed based on nodular or cavitary opacities on chest radiography [332]. Gommans et al. (2015) studied 83 PNTM patients showing that cavities were observed most frequently, while consolidations were a predictor for risk of mortality [346]. A radiographic study on 108 TB and 25 PNTM patients showed that the presence of honeycomb appearance (characteristic appearance of variably sized cysts in a background of densely scarred lung tissue) is significant in PNTM patients; consolidation,

miliary nodules, cavities, atelectasis, fibrothorax and mediastinal widening are more common in TB patients; and pleural effusion, pleural lesions, and reticulonodular infiltration are observed in both TB and PNTM patients [347]. Therefore, the confirmation of PNTM in LMIC remains a diagnostic challenge for microbiologists and clinicians.

Many studies have been focused on the development of diagnostics for active, latent and drug-resistant TB [279]. Genotypic characterization tests such as Xpert MTB/RIF, loop-mediated amplification tests, and line-probe assays (LPA) which are more sensitive, easier and faster compared to phenotypic microbiological characterization for Mtb have been endorsed by WHO [279]. According to ATS/IDSA, besides Runyon classification, genotypic identification of NTM can be done using acridium ester-labelled DNA probes targeting 16S rRNA, DNA sequencing of 16S rDNA, and PCR restriction endonuclease activity targeting *hsp65* [332]. Also, WHO has recommended one nucleic acid amplification test (NAAT), NTM + MDR-TB Detection Kit 2 (Nipro Co., Japan) using LPA [280]. Other NAATs commercially available to detect NTM and drug resistance are included in Table 2 [281–290]. Detecting drug resistance in the early phase of diagnosis can help determine better treatment options for patients with the possibility to eradicate the infection in shorter time (Table 3).

The current available diagnostic tests using single gene-target sequencing are unable to differentiate all the NTM species, and higher subspecies discrimination require multiple genes sequencing [344]. Species characterization is important because different species have different pathogenicity and drug susceptibility patterns [348]. The type of NTM isolated from the lungs determines the risk or likelihood of lung disease. Hence, the probability of lung disease is high if *M. kansasii* is detected; intermediate if MAC, *M. abscessus* complex, *M. chelonae*, *M. malmoense*, *M. szulgai* and *M. xenopi* are detected; low if *M. simiae*, *M. fortuitum*, and *M. terrae* are detected and very low if *M. gordonae* is detected [236, 348]. A retrospective study on PNTM patients' survival rate and type of mycobacterium infection showed that the median survival rate due to *M. xenopi* infection is the shortest (7 months), followed by *M. malmoense* (10 months), *M. kansasii* (39 months), MAC (41 months) and RGM (78 months), suggesting that *M. xenopi* is highly virulent [346].

Advancement in high-throughput technologies has revolutionised the detection of infection causing organisms. Comparison of detection of NTM using PCR and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) showed that the later have higher accuracy (97.4%) with faster and cost-effective performance [349]. The development of WGS has enabled identification of diverse bacteria up to the strain level [350]. For example, *M. abscessus* is the most drug resistant species with a wide

Table 3 NAATs available for the detection of NTM

NAAT kits	MTBC	NTM (identified by numbers in legend)	Drug resistance	Accuracy
NTM + MDRTB Detection Kit 2 (Nipro Co., Japan)	Yes	6, 25, 26,	For MTBC: - RIF (<i>rpoB</i> gene) - INH (<i>katG</i> and <i>inhA</i> genes)	• Commonly used to detect MDR-TB [280]
GenoType Mycobacterium Common Mycobacteria (CM) (Hain Lifescience, Germany)	Yes	2, 6, 9, 13, 20, 23, 25, 26, 28, 30, 34, 36, 40, 46.	No	• GenoType CM/AS was 96% (211/219) concordance with 16S rDNA sequencing. GenoType CM alone identified 88% (192/219) isolates [281]
GenoType Mycobacterium Additional Species (AS) (Hain Lifescience, Germany)	No	3, 8, 15, 16, 19, 21, 22, 24, 26, 27, 32, 35, 37, 38, 39, 40, 44		• GenoType CM/AS was 99.3% sensitive and 98.3% specific for rapid differentiation of MTBC and NTM [282] • GenoType CM/AS successfully identified 75 NTM isolates except for one due to unavailability of specific probe for the target [283] • Genotype CM correctly identified 74/76 strains (97.4%) except for <i>M. intracellulare</i> serovar 7 and <i>M. kansasii</i> sequevar VI [284] • Genotype AS correctly identified 26/28 (92.9%) except for two <i>M. celatum</i> II strains [284]
Real-Q NTM-ID kit (BioSewoom Inc., South Korea)	No	1, 6, 9, 13, 20, 25, 26, 31.	No	• Identified NTM: 97% (223/230) concordance with multi-gene sequence-based typing [285]
INNO-LiPA MYCOBACTERIA (Innogenetics, Belgium)	Yes	6, 7, 8, 11, 14, 16, 20, 21, 25, 26, 28, 30, 36, 38, 39, 46.	No	• 100% sensitive and specific for genus-specific probes [286] • 100% sensitive and 94.4% specific for species-specific probes—probes for <i>M. fortuitum</i> complex, MAIS and <i>M. intracellulare</i> type 2 cross-react with other mycobacteria [286]
GenoType NTM-DR (Hain Lifescience, Germany)	No	2, 6, 9, 12, 25	For NTM: - macrolides [<i>rrl</i> and <i>erm</i> (41) genes] - aminoglycosides (<i>rrs</i> gene)	• Identified NTM: 98% (100/102) concordance with Sanger sequencing and 94.1% (96/102) concordance with phenotypic susceptibility testing for drug resistance [287]
DR. TBDR/NTM IVD kit (DR. Chip Corporation, Taiwan)	Yes	1, 3, 6, 9, 13, 20, 25, 26, 27, 28, 29, 36, 37, 40, 46.	For MTBC: - RIF (<i>rpoB</i> gene)	• Identified Mtb: 89.5% (17/19) [288] • Correctly identified <i>M. abscessus</i> , <i>M. fortuitum</i> , <i>M. gordonae</i> , and <i>M. kansasii</i> isolates, but misidentified two <i>M. chelonae</i> and one MAC isolates [288] • Failed to differentiate between <i>M. abscessus</i> (sensu stricto), <i>M. massiliense</i> , and <i>M. bolletii</i> [288]
CapitalBio Mycobacteria Real-Time PCR Detection Kit (CapitalBio Corporation, China)	Yes	5, 6, 10, 13, 18, 20, 25, 26, 30, 33, 35, 36, 39, 41, 42, 46	No	• Identified MTBC: 100% (358/358) • Identified NTM: 98.4% (126/128) [289]
REBA Myco ID (YD Diagnostics, South Korea)	Yes	1, 4, 6, 8, 9, 14, 17, 20, 25, 26, 31, 33, 36, 40, 43, 45	No	• Identified MTBC: 100% (358/358) • Identified NTM: 98.4% (126/128) [290]

(*Mycobacterial species*) 1. *abscessus*, 2. *abscessus* complex, 3. *asciaticum*, 4. *aubagnense*, 5. *aurum*, 6. *avium*, 7. *avium-intracellulare-scrofulaceum*-(MAIS), 8. *celatum*, 9. *chelonae*, 10. *chelonae/abscessus*, 11. *chelonae-complex*, 12. *chimaera*, 13. *fortuitum*, 14. *fortuitum* complex, 15. *gastri*, 16. *genavense*, 17. *genavense/simiae*, 18. *gilvum*, 19. *goodie*, 20. *gordonae*, 21. *haemophilum*, 22. *heckeshornense*, 23. *interjectum*, 24. *intermedium*, 25. *intracellulare*, 26. *kansasii*, 27. *lentiflavum*, 28. *malmoense*, 29. *marinum*, 30. *marinum/ulcerans*, 31. *massiliense*, 32. *mucogenicum*, 33. *nonchromogenicum*, 34. *peregrinum*, 35. *phlei*, 36. *scrofulaceum*, 37. *shimoidei*, 38. *simiae*, 39. *smegmatis*, 40. *szulgai*, 41. *szulgai/malmoense*, 42. *terrae*, 43. *terrae/nonchromogenicum*, 44. *ulcerans*, 45. *ulcerans/marinum*, 46. *xenopi*

variety of drug resistance profiles, which render treatment challenging [350]. The application of WGS helps to detect these variants for proper management of the patients [350] and it is also able to detect the potential mode of transmission either from individuals or environment [232].

(b) Treatment

PNTM is a chronic disease which requires a long treatment (18 to 24 months) with multiple antibiotics, which is associated with serious side effects and frequent resumption of

treatment due to relapses [44]. Based on the Patient-Centered Research Priorities suggested by NTMRC, experts should be consulted for prescription of antibiotics and drugs to implement the more suitable treatment [44]. The effectiveness of the treatment is assessed based on the patient's quality of life [66]. Other adjunctive treatments such as airway clearance, exercise and probiotics which seems to ameliorate patients' outcomes require more clinical testing [44].

Differentiation of PNTM and TB is important because the first-line antibiotics used to treat TB are less effective against NTM [351]. A study of 12 SGM and 12 RGM with 15 antimicrobial drugs showed that 24, 16 and 8 strains were resistant to isoniazid (INH), rifampicin (RIF) and streptomycin (STR), respectively [351]. The authors concluded that STR, amikacin (AMK), the fluoroquinolones (FQs), and the tetracyclines (TET) are the most effective antimicrobial agents against the 24 strains [351]. A study of 95 NTM strains with ten drugs showed that ethambutol (EMB) is the most useful agent against NTM, but its resistance rate among the tested strains was around 42% [352]. The emergence of multidrug resistant NTM (which can be resistant to five or more antimicrobial drugs) has also complicated the treatment [353]. Thus, according to the British Thoracic Society guidelines, different drugs or combination of drugs should be used to treat different species [236]. For example, treatment of MAC lung disease with RIF, EMB and macrolides [clarithromycin (CLR) or azithromycin (AZM)]; treatment of *M. kansasii* lung disease with RIF, EMB and macrolides; treatment of *M. xenopi* lung disease with RIF, EMB, macrolides and FQs/INH; and treatment *M. abscessus* lung disease with AMK, tigecycline (TGC), imipenem (IPM) and macrolide is recommended [236].

However, one of the most complex situations in the treatment of NTM is represented by the infections with *M. abscessus* complex, which comprise *M. abscessus* ssp. *abscessus*, *M. abscessus* ssp. *massiliense* and *M. abscessus* ssp. *bolletii* [354] due to the high degree of antibiotic resistance and the poor outcome of the treatment [355]. Special therapeutic problems are associated with the resistance to macrolides linked to the presence of the macrolide inducible *erm(41)* gene, which is active in *M. abscessus* ssp. *abscessus* and *M. abscessus* ssp. *bolletii* and inactive in *M. abscessus* ssp. *massiliense*, which have a high impact in the response to the treatment [356]. Using Mtb treatment as reference, it is considered that in patients with *M. abscessus* ssp. *abscessus* infections, the results of the treatments are worse than in the case of multidrug resistant TB (MDR-TB), and equivalent to the outcome of the treatment of extensively drug resistant TB (XDR-TB); in the case of *M. abscessus* ssp. *massiliense*, the results are close to that obtained in MDR-TB [355]. *M. abscessus* ssp. *bolletii* is considered to have similar patterns of resistance to macrolides than *M. abscessus* ssp. *abscessus* [357].

Considering the different profile of antibiotic resistance and evolution of the different *M. abscessus* complex members, it is of great importance the strain identification to implement the more suitable therapeutic strategy [358]. “The antibiotic nightmare” [357] represented by *M. abscessus* complex infections, which has been also implicated in transmission associated to surgical procedures [359, 360], has stimulated the search for new therapeutic alternatives, such as the use of phage therapy, which opens a window of hope not only for *M. abscessus* complex but for treatment of mycobacterial diseases in general [361].

Besides the existing drugs, several approaches have been conducted using novel drugs/compounds, modified drugs, medicinal plant extracts, animal venom-derived antimicrobial products and synergistic and combination effects with other antimicrobials to combat the antibiotic resistant NTM with promising results [362]. However, the translation of these studies from in vitro to in vivo remains challenging. The drug delivery mechanism via the inhalation route has been studied to ensure that a high concentration of antibiotics can be delivered directly to the lung without cytotoxic effects to the host [362]. Screening libraries have been used to identify potential antimicrobial compounds for NTM [362].

The ability of NTM to form biofilms has enabled them to survive under environmental stress and confers protection against antibiotics causing bacterial colonization and onset of disease and invasion [228, 333]. A study by Ortíz-Pérez et al. (2011) on biofilm-producing RGM treated with antibiotics showed that biofilms are resistant to AMK, CLR and ciprofloxacin (CIP) [363]. Among these three antibiotics, CIP is the most active drug affecting the thickness of the biofilms and its combination with anti-biofilm agents such as N-acetylcysteine (NAC) and Tween 80 have resulted in higher bacterial death [364].

Besides the identification of the bacteria itself to confirm the presence of the disease, detection of the risk factors would be beneficial to reduce exacerbation of the disease [365]. Adults presenting with NTM infections should be initially screened for HIV, systemic illness and medication history which may lead to immunosuppression. If no risk factors are identified, individuals with pulmonary disease should undergo chest imaging, pulmonary function test and vitamin D level test to detect any structural lung abnormalities. If the disease is not due to pulmonary defects, then subsequent tests are needed to detect primary immunodeficiency and CF. If no risks are identified, tests to detect autoimmunity or pro-inflammatory cytokines should be taken into account to explore the presence of autoimmune diseases [365].

Patients who are diagnosed with PNTM need to be studied for the presence of underlying TB infection because the prescription of treatment only for PNTM could have risk to develop MDR-TB [366]. In addition, for elderly patients infected with PNTM who need to be treated with macrolides,

rifamycin and FQs, comorbidities and associated concomitant therapies should be determined since these drugs may interact with those that interact with P-450 and disturb the metabolism of drugs [367].

Hong et al. (2015) suggested that serum carbohydrate antigen (CA) 19-9 can be a useful marker to monitor the therapeutic responses in PNTM as it is higher in PNTM than in TB, and its concentration is reduced after successful PNTM treatment but not in TB [368].

One aspect that should be considered in the treatment of PNTM is the use of immunotherapy, which could represent an important co-adjuvant of the drug treatment; in this regard, the use of *M. vaccae* together with antibiotic treatment was not associated with improved response in pulmonary MAC infections [291]; however, the indirect and direct evidences of the potential of vaccination in PNTM support further evaluation of this aspect. Encouraging results have been reported with the

use of IFN- γ and IFN- α in the immunotherapy of PNTM [292, 293].

The growing consensus about the protective role of antibodies in mycobacterial infections [294–298] suggests the potential use of antibody formulations for the treatment of PNTM. Previous studies have demonstrated the role of humoral immune responses in the defence against mycobacteria in humans [299–301].

Monoclonal antibodies against Mtb antigens have demonstrated protective effect upon Mtb challenge after the administration by mucosal or parenteral routes to mice [302–305].

The combination of the administration of mucosal IgA monoclonal antibodies with IFN- γ demonstrated therapeutic effect in mice challenged with Mtb [302]. Commercial human gamma-globulin formulations have demonstrated prophylactic and therapeutic effect in challenge models with Mtb and BCG [306, 307].

Table 4 Main factors that affect the NTM drug development

Challenges	Comments	Ref
Hydrophobicity and innate resistance	<ul style="list-style-type: none"> • Hydrophobic, lipid-rich double membrane cell envelope (major permeability barrier) • Non-polar cell surface (prevents adherence or binding of antibiotics charged positive or negative) • Reversible colony morphology switch (variability in drug resistance) • Efflux pumps (prevent intracellular accumulation of drugs) • Polymorphism in the target gene (natural resistance to drugs—i.e. preventing drug binding) • Modification of the target binding site (bacterial gene expression upon drug exposure) • Enzymes (metabolizes drugs to a less active form) 	[315–317, 319]
Acquired drug resistance	<ul style="list-style-type: none"> • Genomic mutations (mutations in the target or other related genes to confer high-level resistance after long-course treatment) • Lateral gene transfer of drug resistance genes (less frequent but possible) 	[315, 321, 323]
Lack of bactericidal activity	<ul style="list-style-type: none"> • Current drugs-base regimens are bacteriostatic or weakly bactericidal at high concentration: <ul style="list-style-type: none"> ◦ High metabolic rate and slow division of bacteria 	[315, 325]
Poor correlation between in vitro MIC determination and clinical outcomes	<ul style="list-style-type: none"> • Mycobacteria growth conditions for MIC are very different from NTM pulmonary disease: <ul style="list-style-type: none"> ◦ MIC <ul style="list-style-type: none"> - Exponential growth - Suspension in aerated nutrient-rich broth ◦ Lung <ul style="list-style-type: none"> - Different type of complex and dynamic lesions - Stress appearance - Drug tolerance or “phenotypic drug resistance” - Growth in airways mucus and as biofilms - Effect of local microenvironments on drug penetration 	[315, 318]
Intracellular growth and residence in phagocytic cells	<ul style="list-style-type: none"> • NTM can grow, survive and persist extra and intracellularly: <ul style="list-style-type: none"> ◦ Escape macrophage apoptosis mechanism (possibility to spread and infect other cells) ◦ Restriction of intra-phagosomal acidification ◦ Decrease apoptosis and block autophagy flux • Found within phagocytic cells and in granulomas in infected organs (lung and spleen) 	[315, 316, 319, 322]
Caseum, mucus and biofilm growth	<ul style="list-style-type: none"> • Capability of maintaining long-term viability: <ul style="list-style-type: none"> ◦ Mycobacteria change to a non-replicative state under nutrient starvation or oxygen deprivation) • Drug resistance: <ul style="list-style-type: none"> ◦ Antibiotics do not actively destroy cell components • High drug-tolerance under non-replicative conditions: <ul style="list-style-type: none"> ◦ Molecular mechanisms—“phenotypic drug resistance” • High production of mucus in NTM pulmonary disease (bacteria evasion of the immune system and affected drug susceptibility) 	[315, 316, 324, 326]

Human IgA formulations obtained from colostrum administered by the mucosal route produced protective effects in a model of progressive TB in mice [306].

Considering these antecedents, the use of monoclonal antibodies specific of NTM antigens or human IgG or IgA formulations by the systemic or mucosal route in PNTM patients could be a new approach in combination with antibiotic treatment, or a valid alternative in cases of treatment failure [308–314].

(c) Drug discovery

Efforts to develop new drugs for the treatment of NTM infections are continuously being made. The search for new NTM drugs is focussed on reducing the long treatment time which is accompanied by the toxicity of the drugs.

Patients with NTM infections urgently need more safe and effective treatments, preferably orally administered and capable of covering a broad spectrum of microorganisms. Different strategies have been proposed to address the drug discovery lines, i.e. de novo drug discovery and repurposing/repositioning of existing antibiotics. However, there are multiple challenges that affect the discovery and development of new antibiotics for NTM [315–326] (Table 4).

These factors have been recently summarized from different points of view. Wu et al. (2018) described them from a bacteriology and disease pathology standpoint [315], while Falkinham (2018) grouped the factors in accordance with the innate genetic defects and physiologic traits of NTM as well as the difficulties in measuring anti-NTM antibiotic activity in the laboratory [316]. In general, these challenges facilitate the survival of mycobacteria under different environments.

Conclusion

PNTM infection is multifactorial, related to the host, the microorganisms involved, the environment, the socio-economic aspects and human behaviour. Emphasis should be put on recommendations related to human activities, aimed to reduce the risk of exposure to NTM, which are being neglected. The priority to the development of new diagnostics, treatments and vaccines for TB should be expanded to PNTM, as sensitive and specific diagnostic tests, vaccines and immunotherapies for these infections are still lacking.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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