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Review

Epidemiology of rare bacterial, parasitic, and fungal pathogens in India

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ABSTRACT

Rare human pathogens are infrequently observed clinically but can lead to undiagnosed infections, delays in treatment, severe complications, including death. Traditional diagnostic tools cannot routinely detect rare infections in public health settings. This study focuses on the incidence and outcomes of rare pathogenic microorganisms over 13 years (2010-2022) using PubMed database to obtain epidemiological data on rare bacterial, parasitic, and fungal infections in hospitals throughout India. A total of 974 articles were screened using case studies, datasets, comments, classical articles, letters, editorials, observational studies, and meta-analyses. Our analysis identified 28 rare bacteria, six parasites, and five fungal species infections in India. Fatal cases were associated with rare bacterial and fungal infections, including two from pan-drug–resistant bacteria (both from the *Myroides* genus). A total of 10 bacterial species displayed multi-drug resistance; one was extensively drug-resistant, and eight remained unclassified. Of the 83 patients with these rare infections, the mortality was ~8.4% (seven of 83). Considering drug resistance and high mortality, prompt diagnosis of rare pathogens is crucial to controlling their spread. An increased awareness within the Indian health care system focusing on diagnostics, record keeping, and data sharing will be necessary to enhance surveillance.

Introduction

Microorganisms are essential for human survival because of their broad spectrum of interactions in the environment. These microbes are frequently observed interacting with people, either advantageously or adversely affecting their health [1]. Pathogenicity is defined as the ability of an organism to cause disease in its respective host. Numerous opportunistic microorganisms can infect the host under immunocompromised conditions [2]. However, some of these organisms rarely infect the human population and are termed as rare pathogens in humans. A universally standardized definition needs to be established. In the United States, the European Union, and in other national regulations, the estimation of point prevalence provides specific thresholds to categorize rare diseases [3]. To capture ~90% of rare disease cases, nations can set a baseline of five cases per 100,000 population. Fostering global research with consistent standards is crucial for research cooperation, while aiding in timely detection and treating patients appropriately.

The diagnostics for rare pathogens are generally time-consuming. Identifying rare organisms can be complex and challenging owing to lack of awareness among many health practitioners [4]. The current identification approach of organisms from clinical samples has transitioned from the slower traditional culture methods and microscopic techniques to relatively quicker genetic sequence-based methods such as gene amplification and advanced sequencing methods. The ribosomal RNA (18S and 16S) genes' internally transcribed spacer region segments belong to the genes that are frequently targeted in gene screening procedures [5]. Furthermore, other sophisticated identification methods such as matrix-assisted laser desorption ionization - time of flight mass spectrophotometry have also been used in the last decade [1]. Previous studies indicate an increased risk of infections in older people that are caused by rare organisms [6,7]. Moreover, immunocompromised patients with comorbidities are at a higher risk of contracting and developing extreme infections caused by rare pathogens [8,9]. According to research based on data from the UK Biobank, the socioeconomic level of the individuals also affects the prevalence of infections in a population [10].

Drug resistance to rare pathogens is an ongoing threat, making it considerably more challenging for health care professionals to provide the proper therapeutic support. Because these organisms have not been extensively investigated, the crucial interval among patients requiring hospitalization and receiving adequate treatment lengthens considerably. To date, no studies have been reported in India that provide a collation of rare organism infections and their outcomes. Therefore, our study outlines the epidemiology of rare pathogens infections in India over the past 13 years.

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Search strategy and selection criteria

Literature search

This review is based on the literature found in the PubMed database from 2010 to 2022. The keywords used for the identification of reports were "rare," "organism," and "India." A total of 974 articles published in English comprising different types of publications, including case studies, comments, data sets, classical articles, editorials, letters, meta-analyses, and observational studies, were extensively reviewed. In addition, the global perspective about the pathogenicity and burden of infections caused by these genera were also investigated and categorized as extremely rare (less than 500 reports), rare (less or equivalent to 5000 reports), or common (more than 5000 reports), as determined by the number of published literatures on PubMed. For instance, *Bertiella* showed 73 research articles on PubMed, which falls under the extremely rare category.

Inclusion and exclusion criteria

Of the 974 articles, 884 were excluded based on the exclusion criteria (Figure 1) and 90 were considered for the present study. Neglected infections, uncommon etiologies or unusual scientific findings for common infections, odd medical problems, co-occurrence with other diseases, human autoimmune disorders, irrelevant studies and so on were excluded (Figure 1). Furthermore, an individual name-based search for selected organisms was carried out on PubMed, and we emphasized the "rare" keyword. In addition, zoonotic diseases were identified, considering the potential threat of sudden outbreaks of rare pathogens in humans. The articles that were included described the rare occurrence of pathogens in the Indian population while definitively containing the keyword rare associated with the organism.

Data extraction and analysis

The shortlisted 90 articles followed secondary screening based on the three categories: bacteria (n = 54), fungi (n = 18), and parasites (n = 18). A total of 36 articles on bacteria (with a total number of 39 patients) (Supplementary Table 1), 15 on parasites (15 patients) (Supplementary Table 2), and 12 on fungi (29 patients) (Supplementary Table 3) were extensively examined as the outcome of secondary screening (Figure 1). In addition, other relevant publications were investigated by using precise keywords, including "organism name" and "India" (e.g. "*Gnathostoma spinigerum*" and "India"), to ensure that no study was overlooked. Consequently, 28 bacteria, six parasites, and five fungi were finalized for the detailed analysis.

Results

Rare pathogenic species in India

A total of 28 bacterial species belonging to 20 genera were collected from the literature and identified as rare in India. Thirty-six bacterial case studies were reviewed to identify the rare bacterial pathogens listed in Supplementary Table 1. Certain bacterial species were documented in more than one case study in the same year or in different years. The rare pathogens were further categorized into eight classes of the bacterial domain (Figure 2a). Most of the shortlisted organisms were distributed among the *Alphaproteobacteria, Betaproteobacteria* and *Gammaproteobacteria* classes of bacteria belonging to the common phylum *Pseudomonadota* (Figure 2a).

Based on global reports, bacterial species can be grouped into five genera as extremely rare, seven genera as rare, and eight genera as common. The bacterial genera categorized as extremely rare were *Globicatella, Myroides, Elizabethkingia, Pandoraea,* and *Cedecea.* The rare genera were *Gemella, Sphingomonas, Brevundimonas, Sphingobacterium, Ralstonia, Stenotrophomonas,* and *Sarcina.* The Flavobacteria class includes two genera that fell under the same extremely rare category.

A comprehensive analysis identified six parasitic species in India, broadly categorized as rare (Supplementary Table 2). These parasites were distributed across four classes, namely *Cestoda, Chromadorea, Enoplea, and Trematoda* (Figure 2b). For parasites, the global perspective showed that *Dipylidium caninum* and *Bertiella studeri* were considered scarce parasitic species. Both parasites have emerged from zoonotic origin, with wild canids, cats, dogs, andfelids serving as reservoir hosts for *D. caninum* and monkeys identified as reservoir hosts for *Bertiella*. The category of rare parasitic species comprises *Gnathostoma aspinigerum, Capillaria hepatica, sparganum* of *Spirometra*, and common species such as *Schistosoma,* indicating zoonotic origin. These pathogens can potentially infect human hosts via consumption of undercooked meat from various animals, including fish, chicken, snakes, frogs, birds, snail, and rats, and contaminated water sources. Notably, both extremely rare parasitic entities were included in the *Cestoda* class of parasites.

Five fungal species were found to be rare (Supplementary Table 3). Interestingly, *Papulospora equi* and *Scedosporium apiospermum* were under the same *Sordariomycetes* class (Figure 2b), whereas *Curvularia lunata, Saprochaete capitate,* and *Cunninghamella bertholletiae* belong to the classes *Dothideomycetes, Saccharomycetes* and *Mucoromycotina* respectively (Figure 2b). Furthermore, among five species of fungi, *Papulospora equi* and *Cunninghamella bertholletiae* were classified as extremely rare entities, whereas *Scedosporium apiospermum, Curvularia lunata*, and *Saprochaete capitata* were identified as rare organisms.

Geographical distribution of rare pathogens in India

When the geographical locations of corresponding case studies were plotted on the map of India, we observed that the rare pathogens were well-documented in two regions: the northern plains, specifically, in Delhi, Chandigarh, and Uttar Pradesh, and the southern peninsula covering Kerala, Karnataka, and Tamil Nadu (Figure 3). A scattered pattern of rare organisms was observed in other states of India. Clustering into two regions may reflect a higher density of health care facilities and research institutions. This mapping highlights the necessity for awareness of appropriate testing protocols and treatment related to rare pathogens throughout India.

Correlation of age and comorbidities with rare pathogenic infections

We categorized the patients' ages from the included case studies into seven different age groups: <1 year, 1-18 years, 19-30 years, 31-40 years, 41-50 years, 51-60 years, and >60 years. Among the patients, 18% were >60 years old, 16% were 1-18 years old, 13% were 41-50 years old, 13% were 19-30 years old, 11% were 31-40 years old, and 6% each were <1 and 51-60 years old. A total of 17% of the data on the patient's age was not provided in the articles and was termed not available (NA) (Figure 4).

Patients with rare bacterial agents reported comorbidities such as diabetes (three patients), hypertension (two patients), neurological disorders (two patients), spinal disorders (one patient), hyperthyroidism (one patient), osteoarthritis (one patient), cardiovascular disorders (three patients), pulmonary disorders (two patients), and kidney disorders (three patients) (Supplementary Table 1). HIV infection was reported in one patient with *Nocardia asiatica*, a rare bacterial species causing a disseminated and uncommon case of nocardiosis [11].

For rare parasites, of the studies reported, only one patient demonstrated steroid-induced type II diabetes mellitus with cellulitis of the left leg (Supplementary Table 2). Among the rare fungal infections, diabetes was reported in six patients, hypertension in two, kidney disorders in one, ovarian cancer in one, diarrhea in one, and graft-versus-host disease in one patient (Supplementary Table 3). Notably, rare pathogenic species were found to coinfect with other pathogens, such as the infrequently reported coexistence of *Sarcina ventriculi* with *Candida* [12]. In

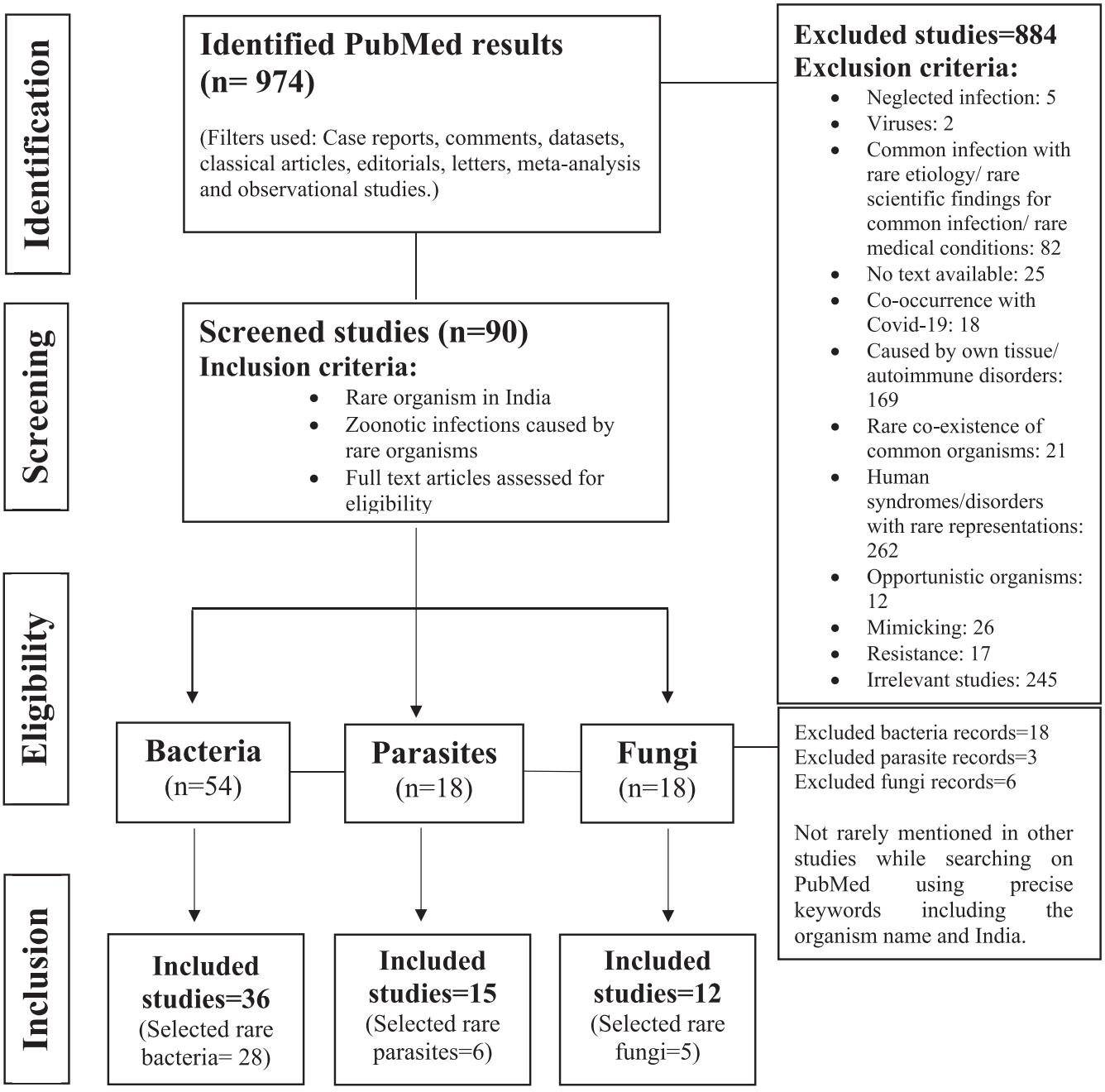

Figure 1. A flowchart illustrates the methodology for this study, representing the number of excluded and included articles, along with the reasons for exclusion.

some cases, coinfections led to misdiagnosis and residual infections. For instance, *Mycobacterium wolinskyi* was masked by *Kocuria rosea*, causing a persistent knee joint infection in a bacterium-associated study [13]. In fungal studies, *Cytomegalovirus* and *Mycobacterium tuberculosis* bacterium exhibited mixed infection with *Scedosporium apiospermum* [14] and another study showed coinfection of *S. apiospermum* with *Aspergillus fumigatus* [15].

These comorbidities are associated with several other factors, such as immune-suppressive medications, altered physiology creating favorable conditions for microbial growth, reduced mobility, chronic infections, and malnutrition that have been found to increase susceptibility by providing a suitable environment for pathogen proliferation. It is worth noting that although pregnancy is not a comorbidity, it can indeed render females more prone to infections [16,17].

Rare organisms and fatality

Of the 83 patients infected with rare pathogens, seven (~8%) deaths were reported, of which 12.8% of the cases (five of 39 patients) were infected with rare bacterial species and experienced fatal outcomes. The fatalities caused by bacterial cases were caused by the following rare bacterial species: two deaths were reported because of the Myroides genus (*Myroides odoratimimus* and *Myroides odoratus*) [18,19], two deaths were attributed to *Ralstonia pickettii* [16] and *Pandoraea pnomenusa* [20]. From rare fungal cases, 6.9% (two of 29 deaths) of fatalities were documented owing to *Scedosporium apiospermum* and *Cunninghamella bertholletiae* infections [21,22]. In contrast, no deaths were reported in the case of parasitic species possibly because of loss to follow-up in multiple cases.

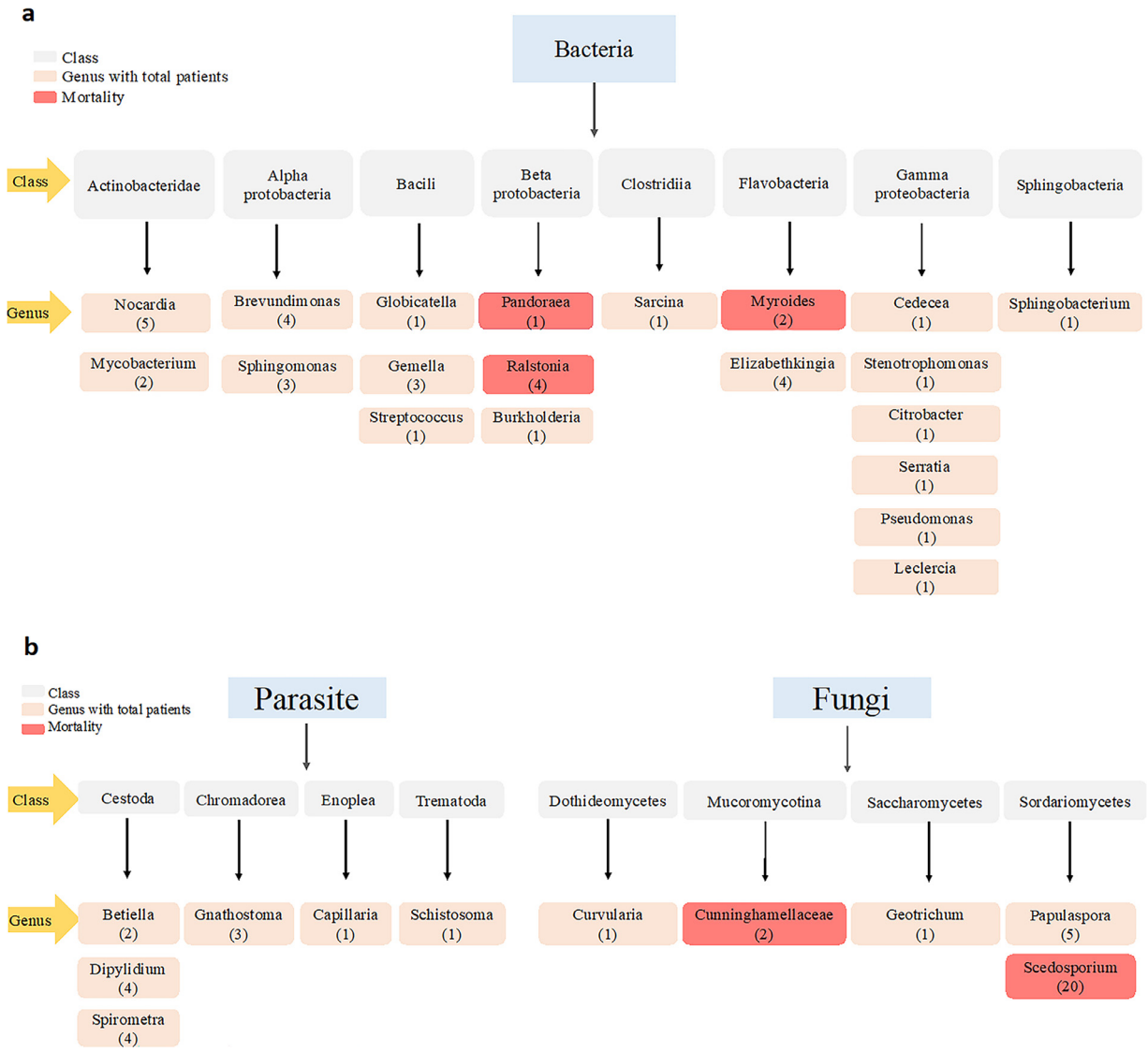

Figure 2. Genera-based classification of pathogens into their respective classes for (a) rare bacteria and (b) parasites and fungi. The yellow box denotes the genus and the total number of case reports enclosed in parentheses (beige colour). In addition, the red box highlights reported patient's death within the following genera: *Pandoraea* (one death), *Myroides* (two deaths), *Ralstonia* (two deaths out of of four patients), *Cunninghamellaceae* (one death out of two patients), and the *Scedosporium* (one death among 20 patients).

A rare bacterium, *Pandoraea pnomeusa,* presented an interesting case. A 42-year-old patient in Chandigarh with a history of chronic rheumatic valve disease had undergone prosthetic aortic valve replacement surgery 20 years back. The patient was brought back to the hospital with prosthetic valve endocarditis. Initial blood tests were sterile; however, *P. pnomenusa* was isolated in a blood culture on day 5 of hospitalization. On the administration of antibiotics, the patient's condition initially improved but the patient eventually succumbed to refractory shock and respiratory failure on day 14 [20]. In another case study, an elderly 74-year-old individual from Bengaluru, Karnataka with a *Myroides odoratimimus* infection died. The patient was diagnosed with hyperkalemia and renal failure upon hospitalization, and the treatment was complicated by a challenging resistance profile [18]. Another 69-year-old individual with chronic kidney disease was found to be infected with *Myroides odoratus* in Uttarakhand. Despite the initial positive responses to prescribed medications, the patient developed high-grade fever and ultimately succumbed to cardiac arrest. This case suggests potential antibiotic resistance development by the pathogen [19]. Two more deaths were observed in four patients with hospital-acquired *Ralstonia picketii* infection in Coimbatore, Tamil Nadu. One pregnant female (25 years old) died from intracranial bleeding, whereas the other 32-year-old male faced organ failure and severe shock because of secondary bacterial infections [16].

In the case of fungi, *Cunninghamella bertholletiae* was associated with the first recorded death in Vellore, Tamil Nadu, causing pneumonia in a 42-year-old male patient who underwent a bone marrow transplant and later developed graft-vs-host disease [22] (Supplementary Table 3). Notably, the potential of such microorganisms to infect immune-competent individuals has dramatically increased [22–26]. *C. bertholletiae* is the sole species in the *Cunninghamellaceae* family known to infect humans. In Manipal, Karnataka, *Scedosporium apiospermum* also resulted in the death of a 56-year-old male patient who had comorbidities, including diabetes and renal failure, compromising his immune system [21]. In other studies, patients were lost to follow-up with the infection of *S. apiospermum and Schistosoma haematobium* parasites owing to the unavailable infection outcome [15,17].

It is essential to highlight that treating and diagnosing these rare and deadly infections requires medical expertise above what is usually avail-

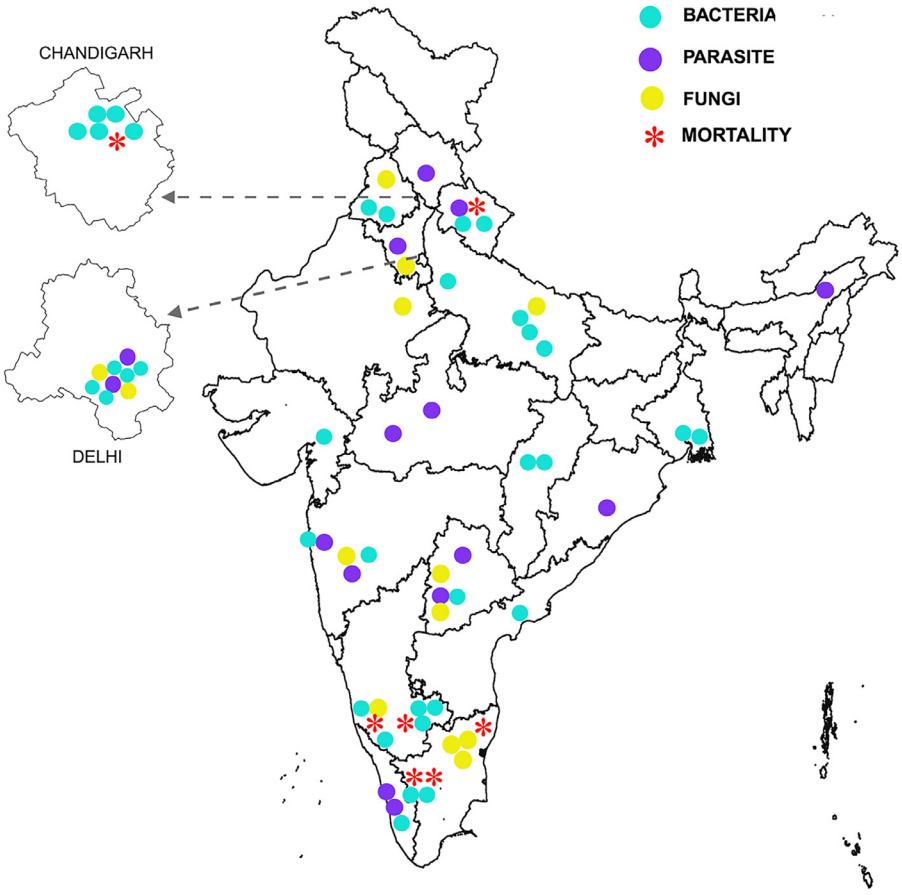

Figure 3. Geographical distribution of rare organisms in India. The red asterisk mark represents mortality in that particular geographical location.

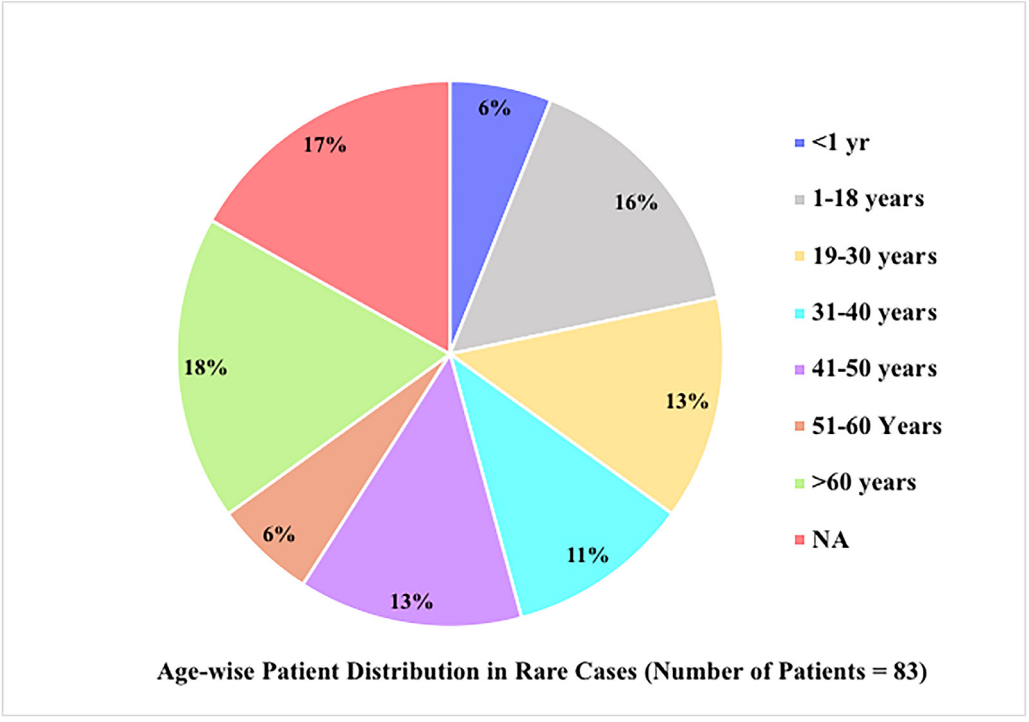

Figure 4. Pie chart depicting the age groups of patients observed in case studies involving all rare pathogens listed in this study. Each segment represents the percentage of total 83 patients within a specific age group. NA, not available.

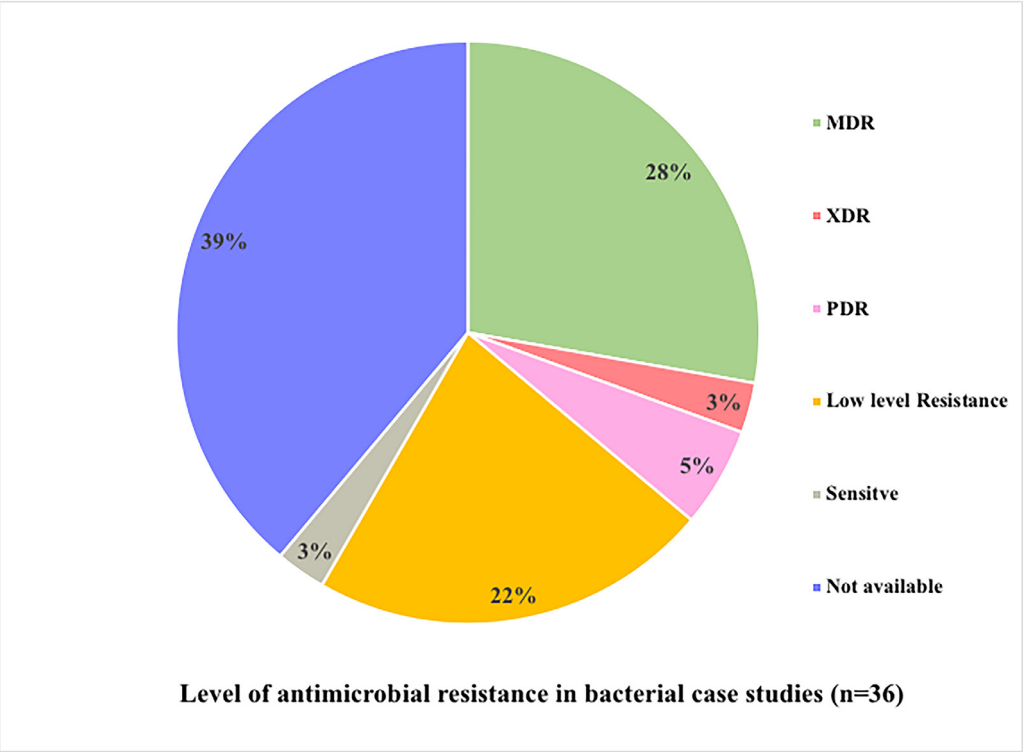

Figure 5. A pie chart depicting the levels of drug resistance observed in bacterial cases (total number of bacterial case studies = 36). The values represent the percentage of cases falling under the respective levels of drug resistance, determined according to the following criteria: MDR: an organism was classified as MDR if it was resistant to at least one antimicrobial agent in three or more antimicrobial categories, XDR: if it was resistant to at least one agent in all but two or fewer antimicrobial categories, and PDR was attributed to those organisms that were found resistant to all agents in all antimicrobial categories tested. MDR, multi-drug–resistant; PDR, pan-drug–resistant; XDR, extensive/extreme drug-resistant.

able in most health care facilities. The threat of new classes of emerging infectious agents remains a primary concern for human health worldwide and, in India, an increased awareness of the epidemiology of rare pathogens is vital.

Antimicrobial resistance in rare organisms

Antibiotic resistance data for rare bacterial organisms were available for 21 of 36 cases. These bacteria exhibited resistance to a range of antimicrobials, including broad- and narrow-spectrum antibiotics. The included case studies were classified as multi-drug–resistant (MDR), extensive/extreme drug-resistant (XDR), and pan-drug–resistant (PDR) according to the criteria mentioned by Magiorakos *et al.* [27]. An organism was classified under MDR if it was "resistant to at least one antimicrobial agent in three or more antimicrobial categories," XDR if "resistant to at least one agent in all but two or fewer antimicrobial categories," and PDR was attributed to those organisms that were found "resistant to all agents in all antimicrobial categories tested." Approximately 28% of rare bacteria were deemed MDR, ~5% PDR, and ~3% XDR according to the criteria (Figure 5). Information on drug resistance was unavailable or determined for about 39% of the cases, which were not included in our study. About 22% of cases exhibited low resistance profiles that could not be categorized as MDR, XDR, or PDR and, as a result, these cases were kept separate for better clarity (Figure 5).

In most bacterial cases, resistance extends across various antibacterial classes, including aminoglycosides, tetracyclines, beta-lactams, and others. Alarmingly, the threat of antibiotic resistance can be estimated by the fact that *Brevundimonas vesicluaris* was resistant to 18 antibiotics in one case study [28]. Moreover, 27.7% of bacterial cases (10 of the 36) reported resistance to five or more antibacterial drugs, with some species resistant to more than 10 drugs, such as *Brevundimonas vesicularis, Myroides odoratimimus, Myroides odoratus,* and *Elizabethkingia meningoseptica* (Supplementary Table 1). Alarmingly, two of the five deaths of bacterial cases were attributed to *Myroides* genus and classified as PDR in their respective studies [18,19]. The resistance profiles of the other three deaths were not available or determined. *Ralstonia pickettii* exhibited resistance primarily to beta-lactams and aminoglycosides because of the presence of two inducible beta-lactamases and aminoglycoside acetyl-transferases [16]. Similarly, *Pandoraea pnomenusa* is suspected to be resistant to most antimicrobials owing to forming a biofilm layer [20]. Interestingly, the organisms within the same genera were susceptible to different antimicrobials, as seen with *Gemella morbillorum* and *Gemella haemolysans* (Supplementary Table 1).

One of the two deaths owing to drug resistance in fungal cases was linked to amphotericin B, 5-flucytosine, and fluconazole, whereas no information was available for the other case (Supplementary Table 3). Two research articles discussed MDR tuberculosis and pulmonary infiltration resistant to antibiotics owing to comorbidity with pulmonary infections in patients infected with rare fungal pathogens [25,29]. The treatment options for these entities are listed in Supplementary Table 3. However, no data on antimicrobial resistance were provided in cases corresponding to rare parasites.

Discussion

This study aimed to characterize rare and potentially emerging human pathogens in India, a critical step in mitigating the threat posed to the communities. Most of the rare pathogens identified in our study belong to genera (but not species in all cases) frequently associated with illnesses. We categorized the bacterial species into eight classes, with 28 species under various classes. Fewer studies on rare fungal and parasitic species reflect limited literature. According to the taxo-

nomic distribution, most rare bacterial pathogens were found in three classes: Gamma-proteobacteria (six species), Bacilli, and Betaproteobacteria (three species each). Fatalities were reported among bacterial species from the Betaproteobacteria and Flavobacteria classes, emphasizing their significance.

We observed two rare fungal species, *Papulospora equi* and *Scedosporium apiospermum*, in Indian studies belonging to the Sodariomycetes class within the fungal kingdom, suggesting that certain taxonomic classes might be more prone to species diversification and hence the origin of rare pathogens from these classes [14,15,24,30,31]. The parasitic class Cestoda has the highest number of rare pathogens. Although no specific age group was identified as high risk, elderly patients (age >60 years) accounted for the highest proportion (~18%) of cases, followed by patients in the 1-18 years age group (~16%) and 41-50 years age group (~13%) (Figure 4). This indicates a slightly higher risk of contracting infection in older people, possibly because of their immunocompromised status.

Socioeconomic factors, poverty, proximity to humans to animals, undercooked or raw meat consumption, exposure to unfiltered polluted water, and related factors can allow an organism to infect the host, as noted earlier [10,32,33]. Comorbidities such as cardiovascular diseases, pulmonary diseases, kidney disorders, diabetes, and HIV infection were prevalent in the cases, making immunocompromised individuals more susceptible. Primary concerns include inadequate medical infrastructure and post-admission diagnostic capabilities in clinics or health care facilities.

Many rare bacterial species exhibited resistance to commonly used antimicrobials, including third-generation drugs. About 28% and 5% of rare bacterial cases showed MDR and PDR, respectively. This highlights the rapid development of resistance among rare pathogens. For instance, *B. vesicularis* showed resistance to 18 antibiotics (amikacin, gentamicin, tobramycin, netilmicin, amoxicillin, amoxicillin-clavulanic acid, cefoxitin, cefotaxime, cefoperazone, ceftazidime, cefoperazone-sulbactam, imipenem, meropenem, ertapenem, aztreonam, norfloxacin levofloxacin and colistin) [28], *M. odoratus* to 15 antibiotics (amikacin, gentamicin, imipenem, meropenem, ceftazidime, cefepime, cefoperazone-sulbactam, aztreonam, ampicillin, amoxicillin-clavulanate, piperacillin-tazobactam, colistin, trimethoprim-sulfamethoxazole, ciprofloxacin, levofloxacin) [19], and *M. odoratimimus* to 11 antibiotics (amikacin, aztreonam, cefepime, ceftazidime, ciprofloxacin, colistin, gentamycin, imipenem, piperacillin + tazobactam, tobramycin, trimethoprim/sulfamethoxazole) [18], limiting therapeutic options and potentially increasing treatment costs.

Conclusive remarks and the way forward

Rare organisms present a significant challenge to the medical and scientific community as they have the potential to cause a spectrum of diseases, ranging from mild to severe. To effectively mitigate the transmission of rare pathogens within the human population, several crucial measures must be taken, including regular pet deworming, ensuring the cleanliness of water bodies, implementing safety protocols for forest workers, and maintaining vigilance in the consumption of animal-based food products. Furthermore, the rapid and accurate identification of emerging rare pathogens demands the proper training of health care practitioners within diagnostic laboratories, enabling timely and precise treatment initiation. Heightened awareness among health care experts regarding the threat posed by rare pathogens can encourage proactive investigation into the causes of treatment failures and unexpected mortality in patients. Addressing challenges, such as drug resistance, social issues, inadequate medical infrastructure, and hygiene standards, is paramount in effectively managing these pathogens and averting their potential threat to the human population. Hence, an increased awareness within the Indian health care system focusing on diagnostics, record keeping, and data sharing will be crucial for enhancing surveillance of these rare infections.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

Ethical approval is not required for this study because it analyzes secondary data.

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Author contributions

SS extracted the data, analyzed, and wrote the final draft. VK assisted in data curation and initial draft writing. SS and RC directly assessed and verified the underlying data reported in the manuscript. AS conceptualized the study and critically reviewed the final draft. All authors cross-checked the extracted data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing

Not applicable.

Disclaimer

All images and tables are original and have not been taken from other sources.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2024.100359.

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