Master of Public Health

Master de Santé Publique

Seasonality patterns and processes in mycobacterial diseases.

A review of research findings from global and spatio-temporal perspectives

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"In the story, there's a person searching for their keys under a streetlamp. When asked why they're looking there, the response is: 'It's not because they lost them there, but because it's the only well-lit spot on the street.' – Michel Colucci"

ACKNOWLEDGMENTS

"I would like to express my sincere gratitude to Prof. Jean-François Guégan for accepting me as part of his team and providing invaluable knowledge, experiences, and perspectives during my internship under his supervision. Thank you for inspiring critical thinking in your students, both in the realm of science and in life. I am immensely grateful for your concern, mentorship, and patience throughout my time in Montpellier. I would also like to extend my thanks to Dr. Ahmadou Sylla for his guidance, training in mathematical modeling, and the meaningful conversations we've shared during this period.

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I am immensely grateful for the friendships and connections I have made during this journey, both in my home country and beyond. Virginia, you hold a special place in my heart, and our mutual support has propelled us this far. Julien, thank you for sharing your friendship, the laughter, and the support. Eimy, your caring nature and love for your loved ones are invaluable gifts.

I would like to express my appreciation to the EuroPubhealth+ program for granting me the opportunity to live this extraordinary experience. This period of my life will forever be treasured."

CONTENT

LIST OF ACRONYMS

- **ACF/PACF** - Autocorrelation Function/Partial Autocorrelation Function
- **LOWESS** - Locally Weighted Scatterplot Smoothing
- **MIVEGEC** - Maladies Infectieuses et Vecteurs : Ecologie, Génétique, Evolution et Contrôle (Infectious Diseases and Vectors: Ecology, Genetics, Evolution, and Control)
- **NIFA** - National Institute of Food and Agriculture
- **NIH** - National Institutes of Health
- **NSF** - National Science Foundation
- **NTD** - Neglected Tropical Diseases
- **NTM** - No-tuberculous mycobacteria
- **SARIMA** - Seasonal Autoregressive Integrated Moving Average
- **SIR** - Susceptible-Infected-Recovered
- **UMR** - Unité Mixte de Recherche (Mixed Research Unit)
- **WHO** - World Health Organization

ABSTRACT

Seasonality patterns and processes in mycobacterial diseases. A review of research findings from global and spatio-temporal perspectives

Introduction: The rise of infectious diseases is increasing in frequency over time. Understanding the seasonal patterns of pathogen ecology is crucial for mitigating their impact on humans and ecosystems. *Mycobacterium* species play a significant role in public health, agriculture, and ecology. Investigating their seasonal dynamics requires interdisciplinary efforts. This study, conducted within a major project on *Mycobacterium ulcerans* transmission dynamics, aims to synthesize existing scientific knowledge on the seasonality of mycobacterial species.

Methodology: A hybrid approach combining bibliometric analysis and systematic review is used to examine the research structure. A diverse set of publications retrieved by the systematic search was analyzed to extract seasonal patterns with mycobacterial transmission dynamics. The analysis includes the study's main findings on mycobacterial seasonality, the geographical distribution of studies, methodologies employed, citation networks, and author collaborations. This study compares seasonal factors influencing mycobacterial disease ecology and the underlying potential drivers of research between scientific entities.

Results: Seasonal factors were well documented and classified on each *Mycobacterium* specie or category, discussed, and put in contrast with the variety of retrieved literature. Considerations about the methodology and study location were taken. Co-citation and collaboration networks were analyzed on *M. tuberculosis* and *M. ulcerans* retrieved publications, and a synthesis of the potential causes or influences on research direction was discussed.

Conclusions: Based on the analysis, this study reveals the seasonal factors associated with mycobacterial species and their ecological conditions. It emphasizes the importance of advanced methodological tools for capturing seasonal trends accurately. Additionally, it highlights the interdisciplinary nature of *M. ulcerans* research, emphasizing the necessity of collaboration across different fields. The study also underscores the significance of strong regional networks in addressing major public health concerns, such as the transmission dynamics of *M. tuberculosis*.

1. INTRODUCTION

Seasonality is a periodic pattern in which the incidence of certain diseases, infectious or non-communicable, follows certain patterns corresponding to season or calendar periods. This is an essential feature, often forgotten, of many infectious diseases of public health concern (Dowell et al., 2004). The importance of seasonal and weather-related disease outbreaks is well known, as efforts to understand malaria, cholera, and influenza are made every year to reduce the disease burden worldwide (Wu, 2016). The identification of seasonal patterns in disease dates back at least since Hippocrates (~380bc), in which this philosopher and practitioner described the role of weather and a subsequent relationship with an increased number of paralyzes, describing it as an epidemic (Hippocrates, in Chadwick, 2005). Paradigms from the classical era were not doubted until the XVIIth century and after, with the emergence of microscopy, microbiology, and physiology, causing scientific community-centered efforts to the pathogen intimacies and not the surrounding environment as the source of disease, i.e., the so-called "aerist" versus "hygienist" approaches, which put on conflict two important French health authorities, Emile Duclaux on one side and Louis Pasteur on the other side. Nonetheless, arguments supporting disease seasonality remained through the end of the XIXth century, August Hirsch commented on the seasonality of various infectious diseases, e.g., yellow fever, cholera, and measles. (Hirsch et al., 1885). Contemporary surveillance systems have allowed us to record data with a systematic methodology, and the improvement of such systems gave us valuable tools to analyze and comprehend infectious disease ecology (Guégan and Choisy, 2009).

Today, pathogens like many other organisms, have developed adaptations to cope with seasonal changes (Foster and Kreitzman, 2009). Environmental factors can affect the ecology of these organisms directly or indirectly, like exposition to ultraviolet radiation or host behavioral changes respectively. In the context of climate change, emerging and already-established infectious agents are expected to adapt to these new environmental conditions (Kronfeld-Schor et al., 2021). Contradictorily, almost no studies about environmental changes and infectious diseases are being conducted in climate change hotspots. Meaning that this is leaving vulnerable populations at risk of new emerging diseases (Liang and Gong, 2017).

Understanding climate drivers of infectious diseases is a key point in global health. This can be challenging, combining seasonal variations with biological aspects or geographical variations may be necessary to understand the specific variables (Metcalf et al., 2017). Elements to decipher seasonal factors of the disease involve a big catalog of disciplines, and researching these factors is almost impossible without an effective integration across disciplines (Ezenwa et al., 2015).

Biomedical research tends to focus on small-scale conditions, from individual to genetic, while public health is concentrated at population and individual levels. Ecology-related disciplines are covering a wider perspective, from molecular to environmental and planetary levels, but variable insights are lost without the collaboration of other fields (Ezenwa et al., 2015).

There is a marked decline in disruptive papers, a potential explanation for this phenomenon is the shifting interest of funders and policy levels (Park et al., 2023). In general, there has not been enough research on disease ecology. Investigating on Web of Science, an average of 118 articles per year about tuberculosis ecology have been published in the last 10 years, the gap is evident, 1750 articles per month about tuberculosis have been published in general. This number of articles dilutes the importance of those published focusing on other dimensions of the studied disease, this means biomedical research is still looking for responses in Petri dishes instead of looking at the bigger picture of infectious diseases.

Mycobacterium species can cause a big number of different pathologies in humans and animals, the most known and spread in humans is caused by *M. tuberculosis.* Tuberculosis is the 13th leading cause of death and the second leading infectious killer after COVID-19 In 2021, an estimated 10.6 million people fell ill with tuberculosis worldwide (WHO, 2022). Other mycobacteria groups such as *M. leprae,* and *M. ulcerans* have also a big impact on affected human populations, and the disease they cause (i.e., leprosy and Buruli ulcer respectively) are classified as neglected tropical diseases (NTD) (WHO, 2022). Moreover, *M. bovis* and *M. avium paratuberculosis,* both represent a major threat to cattle and wildlife and can also infect humans. The *Mycobacterium* genus hypothetically originated 150 million years ago, but recent reviews indicate a more ancient origin of several dozens of millions of years (Chevillon et al., forthcoming). There is evidence that the distribution of *M. ulcerans* is endemically found in places that once were assembled in Gondwanaland and now are separated by kilometers of water. Nowadays, *M. ulcerans r*emains located between the latitudes 25° and 38° south (Hayman et al., 1984). *M. tuberculosis* may have infected an early Hominid in East Africa between 20, 000 and 15, 000 years ago, since then, the first written document describing tuberculosis dates to 3300 years ago, found in India (Barberis et al., 2017).

Organisms belonging to *Mycobacterium* and their seasonality are poorly studied, older texts have referred to seasonal mortality of tuberculosis in the United States of America (Grigg et al., 1958) and increased frequency of Buruli ulcer lesions in Uganda (Uganda Buruli Group, 1971). Thorpe and collaborators (2004) put in evidence seasonal trends of tuberculosis incidence in India, and the limitations of this study were the still-in-development surveillance system and its standardized reporting system. Nonetheless, they were able to find seasonal patterns in a 5-year time series. Integrative approaches have been necessary to understand less-known pathogens. Garchitorena and collaborators (2014) conducted an ecological study to understand *M. ulcerans* dynamics in Cameroon, with the main results demonstrating the complexity of biotic and abiotic interactions on disease transmission. The next year, the same authors constructed an epidemiological mathematical model (i.e., the *SIR* model) to estimate *M. ulcerans* transmission dynamics and fitted the model to previously collected data. Simultaneously, Landier and his contributors (2015), in collaboration with Garchitorena and part of the same research team have assessed seasonal patterns of Buruli ulcer cases in a highly disease-endemic area of Cameroon. Using advanced time series analysis methods, they were able to evidence an important seasonal fluctuation in Buruli ulcer incidence. The same research consortium has studied the economic inequality and interactions of poverty and Buruli ulcer, incorporating mathematical models into socioeconomic and disease systems (Garchitorena et al., 2015). This is an example of an interdisciplinary study that aims to study a disease extensively, translating knowledge from different disciplines to better understand the complex causes of disease, and which corresponds to the now so-called One Health approach (Guégan et al., 2023).

The less complex path to approach seasonality may be through the aggregated cases during the year's seasons, with the help of counts, rates, and proportions. This approach can be inappropriate given the complexity of disease patterns and processes during seasons (Fisman et al,. 2007). Time series, a sequence of observations made over time, assumes that observations close together are usually correlated with each other (Zeger et al., 2006). Time series analysis aims to give a simple description, explanation, and prediction of a register of events through time (Chatfield, 1984). Mathematical modeling has undertaken a comprehensive role in understanding infection seasonality (see Appendix B.1). A well-known approach is the compartmental model of infection, e.g., SIR, in which populations transit through different states depending on the status of infection (Keeling and Rohani, 2008).

The hypothesis sustained to conduct this study is that there is enough evidence to confirm mycobacterial seasonality and that the current scientific production on *Mycobacterium* seasonality is highly clustered and little or no information transit from research domains. The specific objectives of the present Master's degree project are to retrieve the available information on *Mycobacterium* seasonality, analyze the current research methodology on *Mycobacterium* seasonality and the results of these statistical tools, and identify intellectual trends and flow between different research groups.

This study was done in the frame of the EVOPath-Amazonia research project funded by the National Science Foundation-National Institutes of Health-National Institute for Food and

Agriculture of the United States of America through a funded Ecology of infectious diseases award (#1911457, PI: Pr. M.E. Benbow, Co-PI: Pr. J.-F. Guégan). This forms an international collaboration aiming to understand the transmission dynamics of *M. ulcerans* in the Amazonia region, where such a pathogen is present. The original objective of my student's internship was to analyze field-collected data, but data retrieved at the starting date of my internship was not enough to conduct the planned research. The present study and specific topic of research were proposed to enrich the conceptual frame of the ecology of infectious diseases in this international program.

2. MATERIALS AND METHODS

2.1. Study design

The study comprehends mixed techniques of bibliometric analysis and literature review. The characteristics of these methods allowed us to understand the relationship between the main entities of science production and the current knowledge structure about mycobacteria and seasonality trends.

Databases

The bibliometric analysis and literature review were conducted in March 2023. Using the following databases: Scopus, PubMed-Medline, and Web of Science Clarivate Analytics. Access to the databases was granted through the student's institution.

Search strategies

Following the main literature, a meticulous process of keyword selection was followed by the construction of the string to execute the research, and it aimed to cover pathogens related to the phylotype *Mycobacterium* spp., including tuberculous and non-tuberculous mycobacteria and seasonality-related subjects. Specific fields were integrated to cover the infectious disease concept of tuberculosis and Buruli ulcer (Guégan et al., 2020).

The string used was the following:

("*Mycobacterium ulcerans*" OR "Non-tuberculous mycobacteria" OR "Buruli ulcer" OR "Mycobacter*" OR "*Mycobacterium tuberculosis*" OR " tuberculosis") AND ("Season*" OR "climate trend" OR "climate pattern" OR "Periodicity" OR "seasonality" OR "seasonal trend*" OR "seasonal pattern*" OR "climate-driven" OR “seasonal variation" OR "seasonal demonstration" OR "seasonal evidence" OR "seasonal cycles" OR "seasonal cycling" OR "seasonal periodicity" OR "Climate variability" OR "Weather pattern*" OR "Climatic fluctuation*" OR "Atmospheric cycle" OR

"Meteorological trend*" OR "Environmental rhythm*" OR "Climate oscillation*" OR "Atmospheric dynamic*" OR "Climatic change*" OR "Weather cycle*")

We built a Boolean search query with two main fields mycobacteria-related terms and seasonality-related terms. Using logical operators such as “OR” and “AND”, truncates using “*” to account for all the possible variables of a word.

Selection criteria

On each database, filters were applied to decrease the non-relevant items. The languages chosen were English, French, and Spanish for logistic reasons, as well as only articles published in peer-reviewed journals. No more filters were applied.

The next bibliographic information was automatically extracted from the source database: citation information (e.g., article title, journal, year of publication, authors, citation count, document type, DOI), bibliographical information (e.g., affiliations, the language of the original document, correspondence address, abstract, keywords, references, funding, acronym, sponsor, funding text).

After retrieving the bibliographic data, a first stage of screening was done to discard articles that did not include the concepts of mycobacteria and seasonality based on the information in the article title and the abstract.

After this screening, the content of each article was revised, and only those articles that provide seasonality data have been considered for the analysis.

Data management

After retrieving the bibliographic data and metadata, Mendeley™ bibliographic manager was used to gather the corresponding articles. *R*™ version 4.3.0 has been used to merge the bibliographic data using the package “bibliometrix”. After extracting the data frames in format. “.xmls”, bibliographic data was cleaned looking for duplicates and typing errors in the different columns.

Data extraction

Each article has been manually analyzed to retrieve important information. Additional to the information obtained through the database extraction, bibliographic data was complemented by retrieving the number of authors, the country of author’s affiliation, the number of institutions participating, the number of institution countries, countries participating, the number of funding, funding organizations, and the country of the funding organization.

Regarding the scientific content of each article, the next information has been retrieved: studied pathogen species or category, host or substrate studied, biomarkers for detection, geographic location and extent of study, length and temporal period of study, the statistical method of analysis, the relevance of findings (support or not support of seasonality), peak periods of positive results, graphical representation, statistical or mathematical tools used for seasonality demonstration.

Complementary data from external sources

Latitude and longitude coordinates were obtained from Google Maps, indicating the geographical center, and for those countries with more than 7,000 million km^2 of surface (Australia, Brazil, China, United States of America) latitude was extracted at the regional level corresponding to the region of study or studies.

Data analysis

Descriptive analysis

A descriptive analysis was done to calculate summary statistics (mean, median, standard deviation) for variables such as the number of authors, length of study, and publication year.

Frequency tables have been created to visualize the distribution of variables like the type of mycobacteria, localization of study, and peak seasons.

Network Analysis

We designed co-citation and collaboration networks to visualize the structure of knowledge within the retrieved papers. We have reviewed the relationship between countries of authors and countries of funding using network measures such as betweenness and PageRank score (Borgman et al., 2005)

Relational citation/collaboration analysis is used to respond to research questions such as “Who is related to whom?”. This is translated as the production of maps or networks of nodes representing documents or individuals, positioned in a way that demonstrates their relatedness to one another. This map can describe the structure of organizations, fields, or geographical areas (Borgman et al., 2005). Google website wanted to build more sophisticated methods to measure the importance and connectedness of websites and commissioned Brin and Page (1998) to develop the PageRank formula for ranking individual Web pages. As described by Brin and Page (1998) “The probability that a random websurfer visits a page is its PageRank”. The elements with a high PageRank are the most cited by items with a high incoming link but low outcoming number of links (Borgman et al., 2005). Betweenness, on the other hand, according to Zhang and collaborators (2017) measures the “mediation” role in a network. A high betweenness score usually means the node is positioned in a highly transited way of connection and it serves as a “bridge” in the network structure.

Senanayake and collaborators (2015) discussed the relevance of the PageRank score to quantify the scientific impact of researchers. Stating that this score can represent the importance of an author in a network. And it can cope with undesirable artifacts such as self-citation and authors with low collaborations but high-impact publications.

Data representation

Data have been represented using different software. *R*™ version 4.3.0 have been used to construct graphics and charts for statistical analysis (Crawley, 2013). QGIS was used to design the geographical maps of the study. Bibliometrix ™ was used to produce the network analysis graphics (Aria and Cuccurrullo, 2017).

Assessment of Seasonality Graphics and Methodology:

To evaluate the presence and strength of seasonality patterns in the included studies, we qualitatively analyzed the graphics provided in the publications. Due to the absence of standardized measures for quantifying seasonality, we adopted a subjective approach based on visual inspection. Each seasonal graphic was visually examined, and an accentuation rating was assigned to categorize the observed seasonality as either accentuated, moderate, or flat.

Statistical methods to evaluate seasonality were reviewed, given the nature and complexity of the different statistical or mathematical tools used to evaluate seasonality. We categorized the different methods into four different classes, a class zero (0), for no statistical method and pretextual evidence, a first category (1) compounded by descriptive statistics (e.g., mean, median, standard deviation, prevalence, incidence), a second class (2) based on inferential methods (e.g., Chi-square, analysis of variance, Pearson’s test) and a third class (3) that corresponds to time-series evaluation methods (e.g., generalized linear models, autoregressive integrated moving average, autocorrelation functions, locally weighted smoothing, wavelet analysis or more sophisticated approaches).

Two independent reviewers performed the assessment, and any discrepancies were resolved through discussion and consensus. Reviewers were blinded to the study details during the evaluation process to minimize bias. To enhance reliability, a random subset of papers was independently evaluated by both reviewers, and inter-rater agreement was calculated using Cohen's Kappa coefficient (McHugh, 2012).

It is important to note that this approach relies on the visual interpretation of graphics, which may introduce some subjectivity. However, given the absence of standardized measures for assessing seasonality across studies, this qualitative evaluation provides a valuable initial insight into the presence and strength of seasonality patterns in the literature.

Ethical statement

No ethical considerations were considered given the nature of the study. No conflicts of interest were declared by the three participants (1 Master's degree student, 2 co-supervisors) in the organization and following up of the present study.

3. RESULTS

From the three different explored databases, a total number of 3414 publications were retrieved as bibliographical data. After managing the bibliographic data and eliminating the duplicated articles, we reduced the number of papers to 1830 items.

Following a manual and individual revision of the titles and abstracts, during the screening process, we discarded a total of 1584 papers because they did not contain relevant data about seasonality, or they just vaguely mentioned this characteristic but did not afford any information of interest to the present review.

After the screening, we retrieved a total of 221 papers for deeper analysis, and during this process, we encountered one article that required payment and we were not able to obtain it from coauthors either. Another article was nonexistent when we looked for it in different search engines using bibliographical information.

As a last step, an extensive analysis of each paper was executed by the research team to determine the variables mentioned in the protocol. We finally end up with a total of 122 articles with enough quality and quantity of information (see Appendix A)

3.1. Publication year

The study retrieved documentation dated from the year 1971 till the year 2023 (present). There is a notable upsurge of publications happening since the beginning of the XXI[th] century. The emergence of seasonality research on non-tuberculous mycobacteria is evident, but *M. tuberculosis* is remarkable (Figure 1. Overall publications per year**.** Histogram with the frequency of publication **on mycobacteria-seasonality relationships** by year since the first publication retrieved. 2020 was the year with more publications in specific groups of mycobacteria (Figure 2). In specific groups of mycobacteria, the tendency is not so evident, nonetheless, we can see a slight increase in frequency in publications through time.

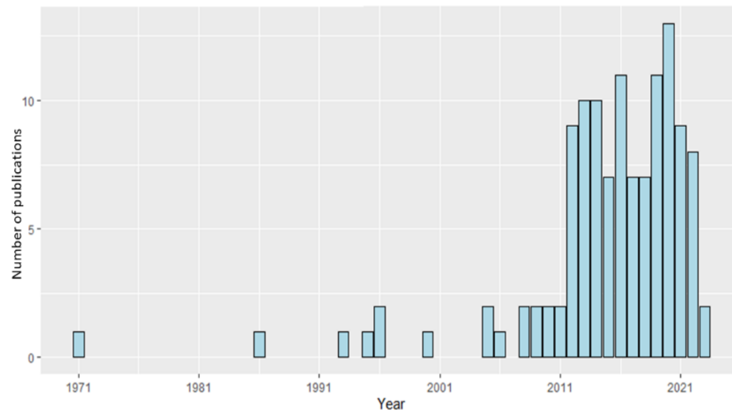

Figure 1. Overall publications per year. Histogram with the frequency of publication on mycobacteria-seasonality relationships by year since the first publication retrieved.

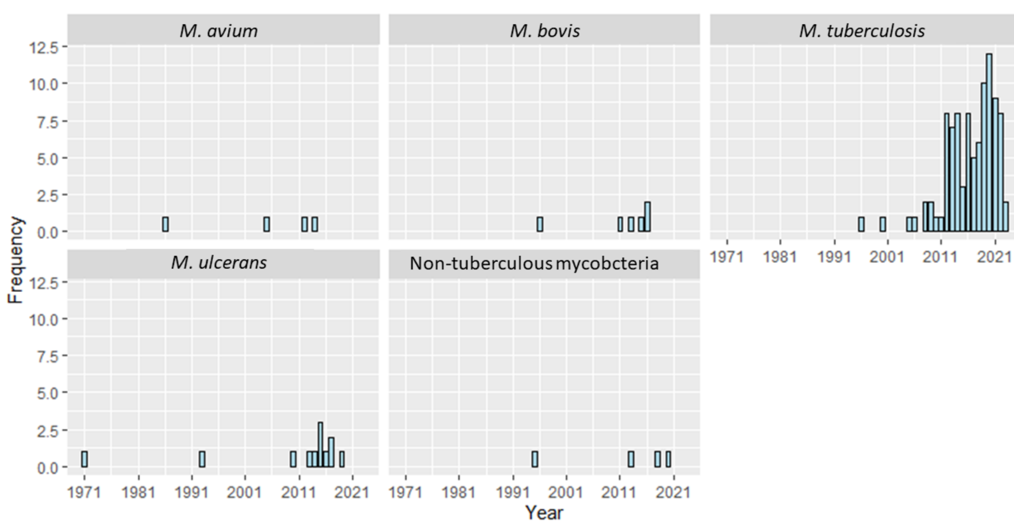

Figure 2. Publications per year grouped. Frequency of yearly publications by mycobacterial species or category on the mycobacteria-seasonality relationships..

3.2. Authors

A total amount of 119 (97.5%) papers constituted original studies from time-series studies of populations that described and forecasted mycobacterial seasonality and 3 (2.5%) studies used theoretical knowledge as mathematical models without data input. The range of authors per paper was 1 to 15, with a mean of 6 and a median of 5 (s.d. =±11.37). The first paper was published in 1971.

A total of 6 different categories of mycobacteria were analyzed by the retrieved articles from our review (see Figure 2), *M. tuberculosis* (N=96, 78%), *M. ulcerans* (N=12, 9.8%), *M. bovis* (N=6, 5%), *M. avium* complex (N= 4, 3%), *M. leprae* (N=1, 1.2%) and non-tuberculous mycobacteria (N=4, 3%). Given that *M. leprae* was only studied in only one publication, we have decided to exclude it from further analysis. This study was conducted in Louisiana, United States of America, and studied the presence of *M. leprae* in nine-banded armadillos, and it was not possible to demonstrate the existence of a seasonal trend from it. Even if *M. bovis* is a variant of *M. tuberculosis*, also called *M. tuberculosis* var. *bovis,* we have considered it in a different category for its epidemiological and agricultural implications. A similar analysis of authorship was done per each group of mycobacteria. The group of mycobacteria with the highest mean of authors per article was *M. tuberculosis* (mean of 6.06, s.d.=±10.4).

3.3. Institutions

The range of participant institutions per article was 1 to 10, with a mean of 3.43 and a median of 3 (s.d.=±4.56). The group or species of mycobacteria with the highest mean was *M. ulcerans* with a mean of 4.83, a median of 4, and a s.d. of ±8.7.

The range of participating countries per article was 1 to 6, with a mean of 1.5, a median of 1, and a s.d. of ±0.65. *M. ulcerans* was de group of mycobacteria with the highest mean of 1.83, a median of 1.5, and a s.d. of ±0.87.

3.4. Study localization

A total of 46 different nations have studied mycobacteria seasonality in their territory. China was the country with the highest number of articles being studied in its territory (N=39, 57%) followed by Cameroon, the United States of America, and the United Kingdom (N=7, 5.73% each).

M. tuberculosis has been studied in 38 different countries, in all the different continents except Antarctic. China was the country that has conducted more studies on this group. *M. ulcerans* have been studied in 7 different countries, especially in tropical regions (Cameroon, Ghana, Côte d'Ivoire, Uganda, and French Guiana) but also in other regions further from the Equator (Japan and the United States of America). *M avium* complex, *M. bovis,* and non-tuberculous mycobacteria have been conducted in 3 different countries each (Australia, Czech Republic, India, Nigeria, United Kingdom, United States of America, Australia, and New Zealand). The spatial distribution of conducted studies is represented in Figure 3Figure 3

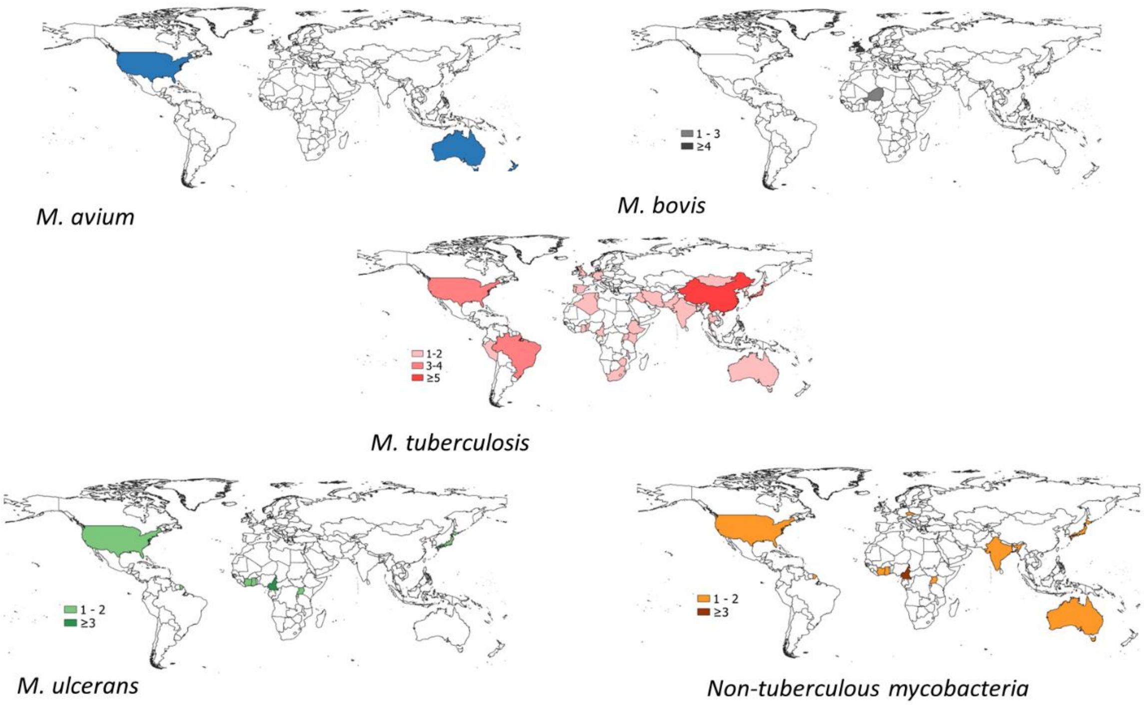

Figure 3.Geographical distribution of research studies for the different mycobacterial species or category. One paper per country is assumed when there is no scale legend on the map.

In total, studies were conducted in specific locations with 104 (88%) of them being conducted in the northern hemisphere and 14(12%) in the southern hemisphere. The mean latitude was 23° and a median of 29°. The mean longitude was 56.7°, with a median of 78.6°.

3.5. Content analysis

The number of articles that have studied the presence of mycobacteria in humans is 100(82%), 11 (9%) detected the causative microorganisms in the environment, and 11 (9%) of the articles focused the research on non-human animals.

The length of the study period ranged from 2 months to a maximum of 1,284 months. The longest study constituted a retrospective analysis of tuberculosis cases in the city of Cape Town, South Africa (Andrews et al. 2020). Overall, the mean was 114.2 months, and the median of 100. The mean length of *M. tuberculosis* studies is 133 months, with a median of 108, a range from 24 to 12,284 months. *M. ulcerans* presented a mean of 22.8 months, a median of 12 months, and a range from 2 to 125 months. Non-tuberculous mycobacteria presented a mean of 79 months, a median of 60, and a range from 7 to 192 months. *M. avium* complex presented a mean of 20, a median of 12, and ranged from 24 to 36. Lastly, *M. bovis* presented a mean of 57.4 months, a median of 41, and a range of 12 to 138.

The temporality of each study was analyzed, with a big proportion of the studies focusing on retrospective analysis of epidemiological surveillance. The beginning of the studies had a range in the years 1903 to 2018, the mean in 2002, and a median in 2005. The end of data collection ranged from 1966 to 2017, with a mean in 2011 and a median in 2013. The shortest study was focused on a 2-month Buruli ulcer epidemiological profiling in Ghana (Amofah et al., 1993) and the oldest study was about the analysis of the 114-year-old record of tuberculosis cases in Cape Town, South Africa (Andrews et al., 2020).

3.6. Seasonality

For those papers that indicated a peak during the year in their analysis (N=106, 86.9%), months were extracted and, the mean period of peaks was May-April (Figure 4), and a median in May with a s.d. of ±2.93 months. *M. tuberculosis* presented its peak in May as the mean and median, on the other hand, *M. ulcerans* showed an increase in notifications mean in August as the median in September.

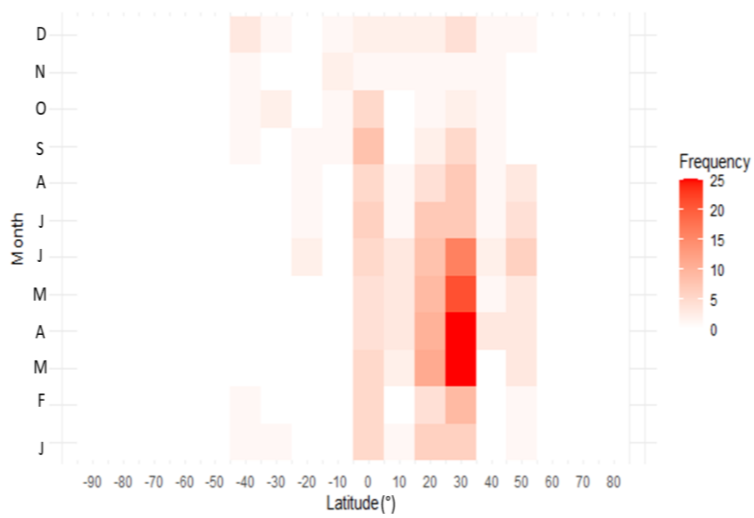

Figure 4. Heat map of the frequency of months indicated as peaks on the reviewed documents. Classified by location of study in latitude intervals of 10 degrees. Areas with intense red color represent a higher frequency of months.

A graphical representation of the peak month frequency (Figure 5) indicates the level of agreement between different articles. While tuberculosis peaks were mostly indicated around the month of April. Buruli ulcer peaks we more frequent around the months of September and October.

A qualitative score estimation of each seasonality trend was calculated during the study (see Figure 6). A 4-category scale was used to assess the intensity of seasonality. In the methodology it was expected to run Cohen's kappa coefficient to assess the level of agreement between the two reviewers (Jean-François Guégan and Carlos Vargas), however, the mentioned coefficient was calculated unilaterally and is planned to be standardized after the presentation of this document as part of the preparation of a scientific publication corresponding to the present work (starting by the mid-July to the end of August). The categories should express no proven seasonality in 0, subtle seasonality with a "1", moderated seasonality with a "2", and evident seasonality with a "3". The mean value was 2.10 for the entire set of studies, with a s.d. of ±0.91 and a median value of 2. *M. tuberculosis* showed a mean value of 2.22, a s.d. of ±0.76, and a median of 2.0.

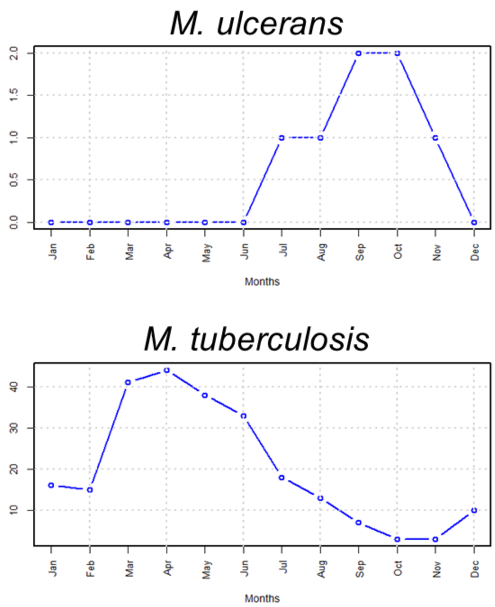

Figure 5. Mycobacterial infection temporal trends of accumulated peaks' months. Figure composed of 2 temporal trends: Frequency of months indicated as peaks in the reviewed articles of *M. ulcerans* and *M. tuberculosis.* Given the seasonal shift in higher latitudes, we only considered the northern hemisphere for tuberculosis analysis. This was disregarded for *M. ulcerans* because of its tropical-subtropical endemicity.

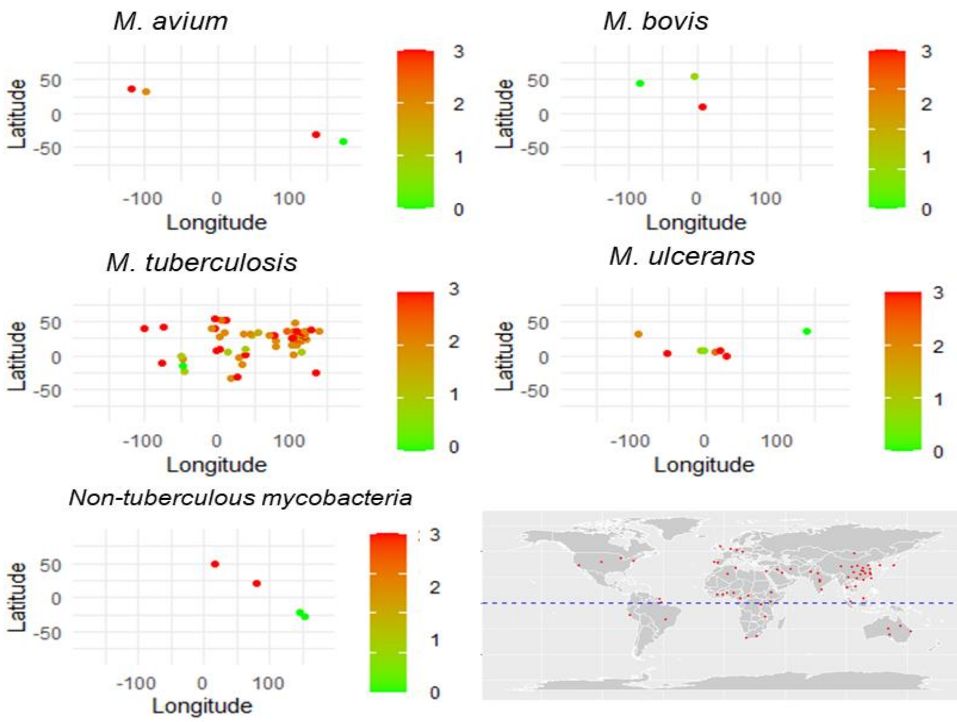

Figure 6. Geographical distribution of studies in relation to their results on seasonality score by group of mycobacteria. Each point represents the location of a study, its value is graduated from 0 to 3 depending on the seasonal amplitude an indicated by a color. World map with the global location of each study represented by red points with a blue line in the center indicating the Equator latitude (bottom right).

3.7. Methodology of the studies

The overall score for methodology was 2.45, with a median of 3 and a s.d. of ±0.91. The group of mycobacteria which implemented the most complex time series analysis was *M. tuberculosis*, with a mean score of 2.63, median of 3, and s.d. of ±0.65. *M. bovis* presented the lowest score of 1.5, a median of 1.5, and a s.d. of ±1.9. This represents that they used predominantly low-complexity methods such as prevalence, incidence, and descriptive statistics as methods to evaluate seasonality.

The bibliographic set consists of various methods. Among these, generalized linear models have the highest frequency (N=23, 18.5%), followed by SARIMA (N=22, 18%) and ACF/PACF (N=19, 15.6%). Descriptive statistics were mentioned 18 (14.7%) times, while inferential statistics were mentioned 16 (13.1%) times. LOWESS was used 9 (7.4%) times. The frequencies of, mathematical models, Wavelet analysis, and Fourier's method, were relatively lower, with 7 (3.3%),5 (4%), and 3 (2.4%) mentions, respectively.

3.8. Network analysis

Given the results we obtained during this research, we focused our attention on two evident situations. The first one is the contribution of China’s scientific production on tuberculosis seasonality research, with 39 (40.6%) articles produced by Chinese research teams and institutions. The other remarkable evidence is the integrative approach of *M. ulcerans* research, research on Buruli ulcer accounting for the largest variety of hosts reservoirs, from humans, animals (vertebrates and invertebrates), plants, and environmental substrates (i.e., soil and water) to be scrutinized for their roles and function in this disease agent transmission and ecological niche. For these reasons, we decided to recreate bibliometric networks to analyze the potential collaborative trends.

The co-citation network displays the documents used as a reference by the articles included in the review indicating the author and year of publication as a label. A link between two nodes represents that the mentioned references have been cited together in at least two articles of this review (Figure 7). The authors’ collaboration network structure represents the authors’ collaboration as co-authors. Nodes represent authors and a link between them means they have collaborated a minimum of one time in scientific production (Figure 8).

China’s tuberculosis research intellectual structure was formed by 50 nodes, Thorpe et al., (2004), had the biggest PageRank score (0.054), considered the most influential node, being cited alongside other influential nodes. The next four documents with the highest scores were as follows: Leung et al. (2005) with a score of 0.053, Willis et al. (2012) with a score of 0.047, Nagayama et al. (2006) with a score of 0.04, and Fares (2011) with a score of 0.036. Thorpe et al. (2004) also had the highest betweenness value of 377.92(Figure 7, A).

The more relevant publications in *M. ulcerans* research intellectual structure we analyzed. Merritt et al. (2010), had the highest PageRank score (0.05) of the 47 nodes. Marion et al. (2010), (0.04); Marsollier et al. (2004) (0.039); Williamson et al. (2012) (0.039); Fyfe et al. (2007), (0.034); and Benbow et al. (2008) (0.02) had the consecutive highest scores. Merritt et al. (2010) also showed a betweenness value (160.86) (Figure 7, B).

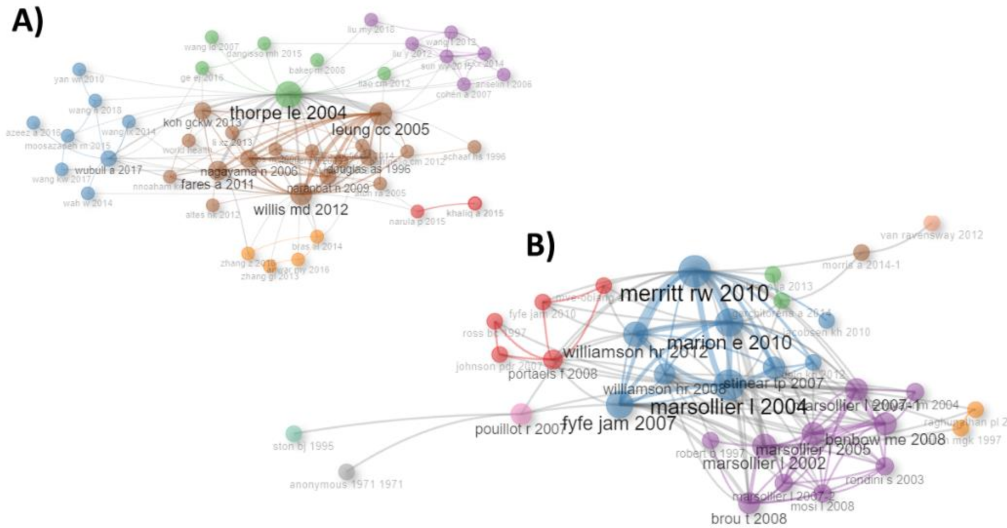

Figure 7. Intellectual structure. Co-citation network of reviewed China's scientific production on *M. tuberculosis* seasonality (A) and *M. ulcerans* seasonality (B). Each node representing a cited reference and the edges indicating a minimum being cited 2 times in the analyzed bibliography. Colors produced by automatic clustering.

In China's authors' collaboration on tuberculosis research 22 different clusters are formed, from which 6 of them have worked independently. 16 different clusters are compounded by authors that have collaborated between them at least once. The authors with the highest PageRank score were Zhang Y (0.016)., Wang J. (0.015), Li X. (0.014), Zhang X. (0.012), and Li Y. (0.012), all of them connected by the main network. The author with the highest betweenness value is Zhang Y (6676.07) (Figure 8 A).

M. ulcerans collaboration network evidenced two distinctive research clusters having collaboration links, representing 26 (53%) authors of 49 in total. Other 6 independent clusters have produced literature ranging from 3 to 7 authors. The main authors with the highest PageRank core were Landier (0.04), Eyangoh (0.04), Marsollier (0.03), Garchitorena (0.03), Fontanet (0.02) and Guégan (0.02). Please note that Landier was a *Ph.D.* student of Fontanet and Garchitorena from Guégan. All the mentioned authors belong to the principal cluster (Figure 7B). The author with the highest betweenness value is Eyangoh (52.73) (Figure 8 B). Studies and collaboration networks will be analyzed in the discussion section of the study.

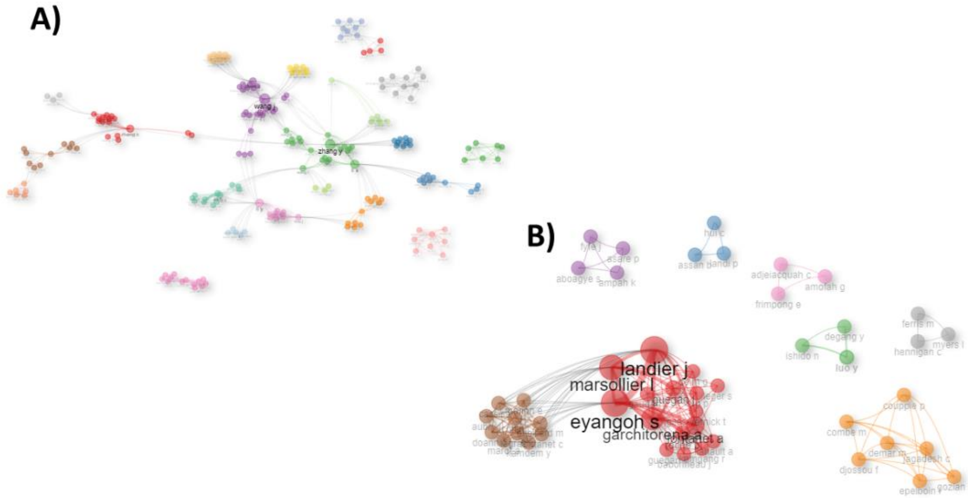

Figure 8. Co-authorships. Collaboration network of reviewed China's scientific production on *M. tuberculosis* seasonality (A) and *M. ulcerans* seasonality (B). Each node representing an author and the edges representing at least being collaborated once in the analyzed bibliography. Colors produced by automatic clustering.

4. <u>Discussion</u>

4.1. Seasonality patterns

To synthesize time series findings is important to understand the nature of the studied phenomena. Not accounting for important factors such as north-south shifted seasonality or the pathogen's latency period, can lead to inconclusive results (see Figure 4). On the other hand, when important factors such as those mentioned before are addressed, clear tendencies can be evidenced. In Figure 6, we can appreciate a more pronounced seasonal pattern in higher latitudes, given that the environmental shifting is more drastic in these regions compared to tropical regions. The interaction climatic conditions and pathogens could be explained by the long latency period of *Mycobacterium* species, which can remain dormant in the hosts for long periods (Trubiano et al., 2013; Parrish et al., 1998). Pathogens transmitted by human-to-human contact, i.e., contagious, tend to increase infection rates during winter and produce symptoms after a variable latency period. (e.g., *M. tuberculosis*), and water-related pathogens of the tropics (e.g., *M. ulcerans)* respond to rainy seasons under a relatively constant temperature (see Figure 6) These findings correspond to previous research evidencing the relevance of latitude in infectious disease distribution (Guernier et al., 2004; Martinez et al., 2018)

The lack of research in the southern hemisphere is one of the major limits to conducting more complex analyses on this topic (see Figure 6). This pattern of northern-oriented bias in research is not exclusive, since there is a clear trend of “scientific colonialism” in health research that contributes to increasing the knowledge gap between regions (Edejer, 1999). However, emerged land-mass regions in the southern hemisphere are less numerous also contributing to this “natural” bias.

4.2. Seasonal factors and their influence on mycobacterial dynamics

The changes in environmental conditions and how it interacts with a disease’s ecology are diverse. In the next paragraphs, we are going to discuss the major findings and observations of the reviewed articles.

M. tuberculosis

The variability in temperature levels influences in different ways hosts and pathogens. Onazuka and Hagihara (2014) established a relationship between extreme temperatures and an increase in tuberculosis transmission. Possible explanations for this phenomenon are the predominant indoor activity, crowding, and decreased airflow inside homes (Ghadimim-Moghadam et al., 2020). This explanation may be one of the most popular in the medical field. Wingfield and collaborators (2014) found a close relationship between vitamin D deficiency and tuberculosis, as this nutrient has an immune-modulator role in the organism. Other host-related theories are that the increase of CD4 T-cells during winter delays the onset of symptomatology to spring (Maharjan et al., 2021). The seasonal trends in tropical regions could be related to the wet season (Fares 2011). Famine is subject to seasonal changes and its effects on cell-mediated immunity against tuberculosis es well documented (Cegielski and McMurray, 2004).

M. ulcerans

M. ulcerans is endemic to tropical and subtropical areas are also reliant on these seasonal patterns, a characteristic dry/wet climate shifting annually. Garchitoerna and collaborators (2014) explored the presence of *M. ulcerans* in the water ecosystems of Cameroon, the increasing periods were variable and dependent on the specific ecosystem (i.e., rivers, flooded areas, swamps, streams). This supports the idea of run-off bacteria into the aquatic environment during periods of intense rainfall by Williamson and collaborators (2012). After extracting the incubation period and diagnosis delay, human infection peaks occur from August to October, this seasonal pattern has been observed by other studies in different locations (Figure 6) (French Guiana, South America: Morris et al. 2014; Cameroon, Africa: Landier et al. 2015 and Ravisse, 1997; Cote d'Ivoire, Africa: Marston et al. 1995, Uganda, Africa: Revill and Barjer 1972). The social aspects also play an important role in the epidemiological impact of Buruli ulcer, seasonal trends of human activity are closely related to incidence variation. Seasonal harvesting, working, or living near bodies of water and the protective dressing during labor can potentially influence the risk of infection (Pouillot et al., 2007).

M. avium

Heat stress in cattle has been studied by Strickland and collaborators (2005) as a possible cause of *M. avium paratuberculosis* in farms, a condition that can cause immune suppression. Incidence peaks in summer have been documented by Carpenter et al. (1985) in swine farms, supporting the previous theory. Stable environmental concentrations of *M. avium* in pipelines throughout the year have been demonstrated in Australia by Whiley et al (2014).

M.bovis

M. bovis affects mainly cattle and wildlife, but human infections are well documented. An experimental study about *M. bovis* persistence in soil, conducted by Fine and collaborators (2011), found a decrease in *M. bovis* concentrations in warmer seasons (spring/summer), associated with lower humidity levels and high solar radiation. Reservoir behavior can also be affected by seasonal conditions, an increased incidence during spring in the badger (*Meles meles)* population has been correlated with reproduction and breeding season, causing physiological stress in the individuals (Delahay et al., 2013). As with human populations, increased transmission of *M. bovis* has been documented in colder seasons, related to overcrowding and less airflow in barns (Okeke et al., 2014).

No-tuberculous mycobacteria.

No-tuberculous mycobacteria (NTM) is the denomination of *Mycobacterium* species other than *M. tuberculosis* and *M. leprae*. NTM are opportunistic pathogens that can infect humans, especially those with an increased risk (e.g., immune suppression, lung disease comorbidity) (Bonnet, 2017). NTM thrive in a wide variety of climatic conditions (Walsh, 2019), this is the possible reason why many studies have found peaks of environmental concentration at different moments of the year (Mishra et al. 2017; Thomson et al. 2013; Kubalek et al. 1995). Thomson and collaborators (2020) analyzed the relationship between climatic conditions and NTM infection in Australia, discussing the difficulties to find associations due to the long latency of the infection.

4.3. Global distribution of scientific production

As mentioned in the results section, a minority of studies took place in the southern hemisphere. A map representation of this trend is shown in **¡Error! No se encuentra el origen de la referencia.**. The inequity in science production is still a constant, and a disparity of authorships and publications between high-income and low and middle-income countries (Smith et al., 2014). In the reviewed documents, research groups from low- and middle-income countries tend to collaborate with research groups from high-income countries, and little or no collaboration is observed at the intra-regional or subregional levels (Figure 6). The low intra-regional collaborations and gaps in health research have been evidenced by previous research (Paraje et al., 2009), and seriously impact recent interdisciplinary and transdisciplinary development in health and public health research whatever the current “One Health” moto militating for more integrative studies (Fasina et al., 2021).

4.4. Methodological approaches to explore seasonality

Statistical-based methods

Generalized linear model: This method resulted in the most popular approach in the reviewed studies. These are statistical modeling tools able to process non-normally distributed response variables or non-linear relationships. Seasonal patterns can be analyzed by incorporating such factors as predictors. Cautiousness is important because equations usually rely on ad hoc assumptions regarding the dependency of the factors (Crawley, 2012). In the next paragraphs, the most important advanced statistical-based methods to determine seasonality are discussed.

Seasonal Autoregressive Integrated Moving Average Model (SARIMA)

SARIMA is a time series forecasting model that combines elements such as autoregressive (AR), differencing (I), and moving average (MA), with seasonal patterns. It is particularly useful to analyze and forecast time series with clear seasonal patterns, such as monthly, quarterly, or yearly cycles. This approach is more useful when the data exhibit stationary behavior (Box et al., 2015). SARIMA is the second most used method to approach seasonality in our review, and it is especially popular in China’s research network on tuberculosis, and this will be discussed later in the text.

Autocorrelation Function and Partial Autocorrelation Function (ACF/PACF)

These methods are used to measure the correlation between a time series and its lagged values at different lags. Both tools are used in time series analysis, with an important role in determining the order of autoregressive (AR) and moving average (MA) terms in SARIMA models.

In short terms, ACF/PACF allows us to evidence the presence of seasonality and SARIMA models rely heavily on them to determine the model specifications (Brockwell, 2016).

Locally Weighted Scatterplot Smoothing (LOWESS)

LOWESS is a non-parametric regression method used to fit a smooth curve in a scatterplot of data. One of its important features is the ability to capture nonlinear relationships between variables. LOWESS divides the data into smaller fragments and fits a locally weighted regression line to each one of these. This allows the smoothing algorithm to adapt to the structure of the data. Resulting in a curve that provides an estimate of the underlying relationship of the data (Cleveland, 1979).

Fourier's analysis

This technique allows us to transform time-domain patterns into frequency-domain representations. This is important to identify the most prevalent frequency, harmonic relationships, and periodic patterns of the data (Bracewell, 2000).

Wavelet analysis

Wavelet analysis is used to analyze and decompose time series in different components. It can be applied to detect various features (i.e., trends, oscillations, transient patterns). Wavelet analysis put in evidence high and low-frequency components. Moreover, is used to capture localized features and handle non-stationary patterns (Percival et al., 2000).

4.5. Mathematical modeling

The compartmental *SIR* model, first proposed by Kermack and McKendrick (1927) relies on the context of a population divided into compartments depending on the state of their health in relation to an infectious disease, such as susceptible (*S*), infected (*I*), and recovered (*R*). These models are explored through techniques for ordinary or partial differential equations. The *SIR* model incorporates important parameters such as "β", which quantifies the probability of transmission per contact between a susceptible and an infectious individual, this value is obtained by the analysis of previous epidemiological data. The basic reproduction number (R_0) is a measure of the average number of secondary infections generated by an infected individual in an entire population.

Incorporating seasonality into mathematical models

Most of the models tend to incorporate seasonal forcing phenomena such as *sine/cosine* waves. However, seasonality trends can be much more complex and could not conform to a sinusoidal pattern. It is, therefore, very important to understand the shape and duration of seasonal factors we integrate mathematical modeling (Altizer et al., 2006).

Efforts to explain seasonality through mathematical models are present in our review. Heuer et al. (2012). Their model examined the infectivity differences between different strains of *M. avium paratuberculosis* in red deer and the seasonality of this pathogen's survival. Liu and collaborators (2010) designed a tuberculosis model with seasonality based on China's epidemiological data. Lastly, Belthasara and collaborators (2017), tried to frame Buruli ulcer dynamics in a mathematical model as did previously Garchitorena et al. (2015). Mathematical modeling is an important tool to shape transmission dynamics, and it requires big interdisciplinary support to address the most important variables and parameters that shape disease ecology.

A mathematical model to exemplify seasonality lag was developed under the supervision of Dr. Ahmadou Sylla and Dr. Jean-François Guégan, as part of a parallel project to model *M. ulcerans* ecological dynamics in rainforest water bodies. The mentioned graphic representation can be found in Appendix B.2.

4.6. Network analysis

China's intellectual structure and collaboration network

Given the results obtained from the bibliometric analysis, we decided to investigate science interaction within the country with the highest number of publications about mycobacteria. China has produced more articles about mycobacteria seasonality than any other country, specifically about *M. tuberculosis.*

The most influential cited references will be discussed in the next paragraphs. One of the first modern documents evidencing tuberculosis had the biggest presence in the bibliographic structure of China's scientific production, i.e., Thorpe et al. (2004): "Seasonality of tuberculosis in India: is it real and what does it tell us?" evidences the presence of tuberculosis seasonality and the usefulness of a strong surveillance system to detect this temporal trend. This article also studied seasonality at a regional level, demonstrating different seasonal patterns in a north-south global trend. Even if there is a lack of advanced time-series analysis, the inferential methods used proved significant differences and a temporal fluctuation of cases along the year and could be a milestone for research on tuberculosis seasonality. Leung et al. (2005) presented the article "Seasonal pattern of tuberculosis in Hong Kong" which analyzed tuberculosis records in Hong Kong from 1999 to 2002, developing a model to fit seasonality, their results were positive finding a summer predominance of tuberculosis cases this document represents the first publication researching on tuberculosis seasonality in the database, and it is, understandably, one of the most cited papers in this group. (Figure 7, A).

China's publications on tuberculosis seasonality are composed of a well-connected network of collaborations, more than 89% are connected by at least one collaboration to the main structure. PageRank scores show the influence of an author inside a network, this means that Zhang Y has collaborated with other important authors in the field. The role of influential authors acting as a bridge between research groups can influence scientific production trends, like the use of certain methodologies and approaches (Newman, 2010) (Figure 8, A).

China's intricate collaboration network can be a sign of an emerging perspective to understanding mycobacteria seasonality. An entire number of articles have been published after the article of Leung C. et al. (2005) and all of them have used advanced methods to analyze time series datasets.

Intellectual structure of research on *M. ulcerans* seasonality

Analyzing the most influential citations around a specific group of mycobacteria helps to understand the structure and direction of the research trends. *M. ulcerans* was described for the first time in 1948, since then, it has been reported in at least 34 different countries. Classified as NTD, efforts to understand the transmission of this cryptic pathogen have been made at different levels of research and public health surveillance (Ezenwa et al., 2015). Buruli ulcer and its pathogen's seasonality have not been clarified yet and the medical field has needed to collaborate with other disciplines to better understand the patterns and processes underlying *M. ulcerans* transmission (Röttgen et al., 2019). Such complex conditions have made necessary the integrative approach to understanding transmission dynamics (Guégan et al., 2023). Merritt et al. (2010) elaborated a systematic review of the scientific literature on the ecology and transmission of *M. ulcerans*, nonetheless, this paper summarizes previous findings on clinical case trends. Marion et al. (2010) mainly researched the presence of *M. ulcerans* in arthropods, specifically in water bugs and Marsollier et. al (2004) proposed snails as a passive host of *M. ulcerans,* Another influencing paper by Benbow and collaborators. (2008) debated the role of water bugs in transmission. Fyfe et al. (2007) discussed molecular techniques for *M. ulcerans* identification. Lastly, Williamson et al. (2010) investigated the relationship between *M. ulcerans* in the environment and the prevalence of Buruli ulcer (see also Receveur et al., 2022). The variety of disciplines (e.g., biology, ecology, entomology, epidemiology, microbiology, environmental science, biomathematics) in the presented articles unveils the complexity of this disease condition in a multi hosts-disease agent-environment triad, and the necessity of both interdisciplinary and translational science to comprehend its population dynamics (Guégan et al., 2023) (Figure 7, B).

Collaboration networks demonstrate the presence of two main clusters collaborating, which is related to French-Western and Central African collaborations. The authors mentioned in the collaboration network analysis worked as bridge nodes between these two groups: this is notably S. Eyangoh in Cameroon (exclusive collaboration with France) and C. Johnson in Benin (multilateral and opportunistic collaboration with France, Belgium, United States of America, Switzerland) to give two instances. However, these researchers serve as bridge/hosts for access to field conditions and biological materials but are not major contributors to scientific productions, and they do not occupy top-leading authorships in scientific productions. Isolated clusters represent distance in time (Uganda Buruli Group, 1971) or geography (Hennigan et al., 2013; Luo et al., 2015). The dominance of multidisciplinary research groups is important to understand the integrative approach from science to *M. ulcerans* seasonality existence (Figure 8, B).

4.7. Limitations

There are research-intrinsic and methodological considerations in this study. The notification number is usually underestimated; this is part of the passiveness of the surveillance system. There is a clear gap between Buruli ulcer and tuberculosis surveillance (Choi et al., 2022). This is the opposite in environmental research, which frequently is based on an active search of the pathogen in the environment and few studies are based on a constant surveillance basis of patients.

Variable periods of mycobacteria latency play a major role in understanding seasonality (Lin and Flynn, 2010). This variability can obscure seasonal patterns, issues we are recently tackling with advanced time series analysis methods.

The studies reviewed do not consider the same confounders in their analysis. Depending on their specific objectives, each research considered different confounding factors. In the same context, ecological fallacy needs to be accounted and we need to be cautious when generalizing these findings (Duque et al., 2006).

5. CONCLUSION AND RECOMMENDATIONS

Infectious disease paradigms change with the implementation of novel techniques (Faladori, 2005). Methods to understand temporal trends are refined and used in public health research with more frequency (Zeger et al., 2006). Medical *a priori* postulates stating the inexistence of seasonality patterns on *M. tuberculosis* are being challenged by modern methodology on time-series analysis (Thorpe et al., 2004). These precepts of no-seasonality may have been supported by variable latency periods of mycobacterial infections (2-3 months to several years), with this variability interfering with lags that shape seasonality in disease ecology (i.e., weather, populations behavior) (Wah, 2014). The most recent studies here presented and summarized have shown that this paradigm is changing and interesting China's research work is taking the lead on this topic. Efforts at the national level are evident in the case of China, which has contributed a large proportion of scientific production on tuberculosis population dynamics. Interdisciplinary collaborations to describe *M. ulceran's* ecology are also exemplary in unraveling the importance of the environment, and specifically biodiversity and multi-host components, in disease transmission.

Systematic reviews are effective methods to understand existing knowledge of a field. Systematic reviews' meticulous approach and reproducibility turn them into essential tools to identify research gaps (Linnenluecke, 2019). But those gaps may not be caused by technological incapacities or scientific limitations, but by research trends and external influences on science production. Bibliometric analysis helps us to describe and explain the reasons for those gaps in knowledge production (Moura et al., 2017).

The present study also highlights the necessity of a broader perspective in medical sciences. The emergence of potential pandemic infectious diseases urges the health sector to look at interdisciplinary and transdisciplinary collaborations in these fields are essential (Guégan et al., 2023). The exchange of insights and different angles to approach a major problem is well exemplified by Buruli ulcer and *M. ulcerans* research, a field that converges medical science, molecular science, disease ecology, and social sciences such as economics and anthropology, among other disciplines. Outside public health, transdisciplinary and interdisciplinarity are mostly rejected by the medical field (Van Teijlingen, 2019). In most cases, medical doctors are not trained to collaborate with professionals that do not belong to the healthcare sector. This implies a big challenge to public health actions because medical attention and interventions without a broader perspective of the underlying health problem that can become unfruitful.

Current problems cannot be contained in a single field. The complex conditions that conform to the main burdens of public health need complex approaches and solutions. An integrative perspective to cover these problems will only be achieved with inter and transdisciplinary. It has been proven that the isolation of research fields causes the vortex phenomena to research what is already known, neglecting all the other possible questions and answer to discover (Park et al., 2023). It is important, then, to acknowledge the limitations of certain fields to cooperate on research and implementation strategies and promote the integration of these disciplines. This integrative approach may be the missing key to preventing (or reducing) the next major world emergency.

This research is being prepared to be a publication under the title “Seasonality patterns across mycobacterial diseases in animals and humans. Implications for public health and actions”, with co-authors (I act as the main author) being members of the NSF-NIH-NIFA research program. A simultaneous review, invited to be published in the journal “Current Landscape Ecology Reports”, is conducted with the title: “Land-use changes and emerging non-tuberculous and tuberculous infectious diseases in humans and animals: a review of research findings from global and spatiotemporal perspectives” in collaboration with the same research group from which I am a second author.

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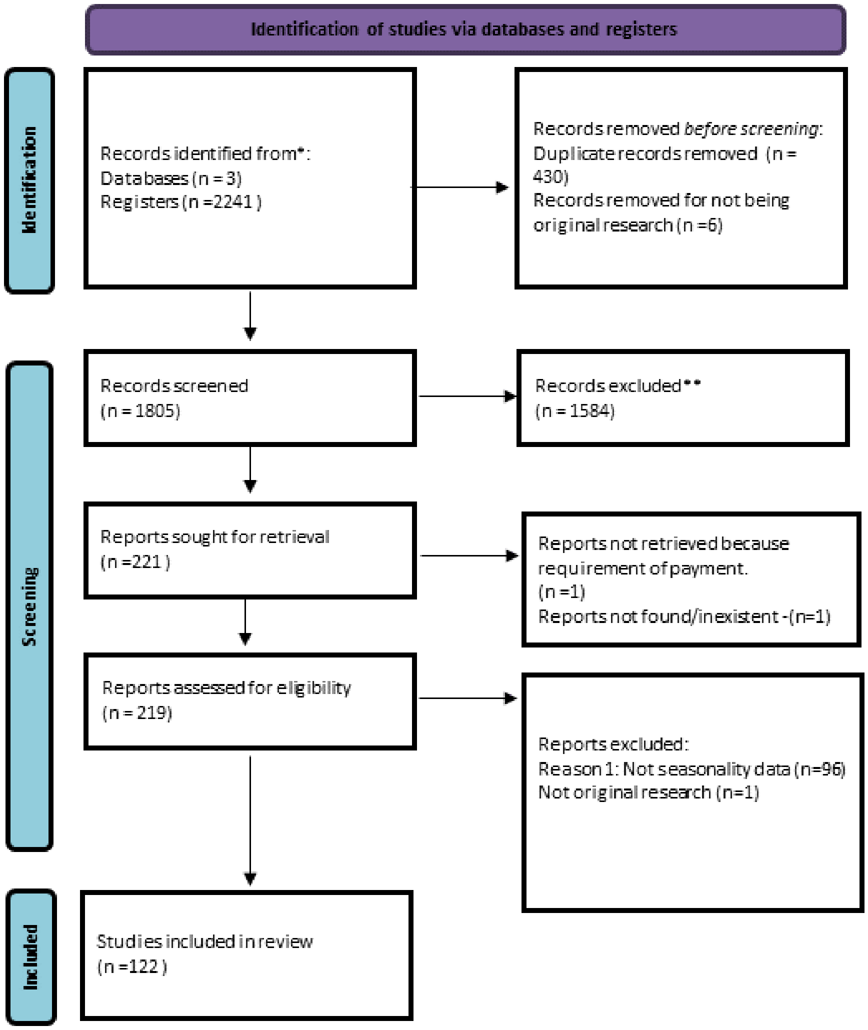
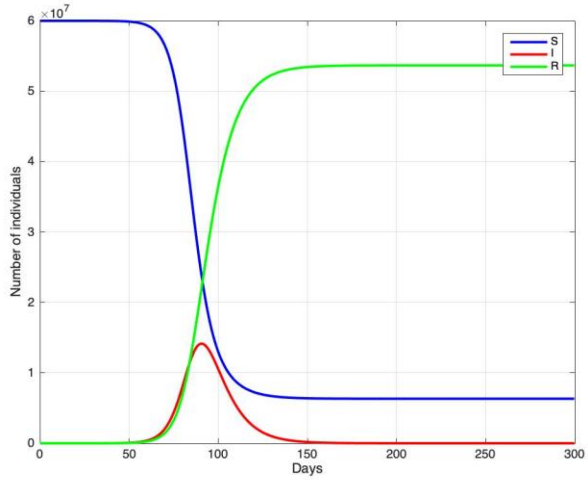
7. APPENDICES

A. Systematic review algorithm

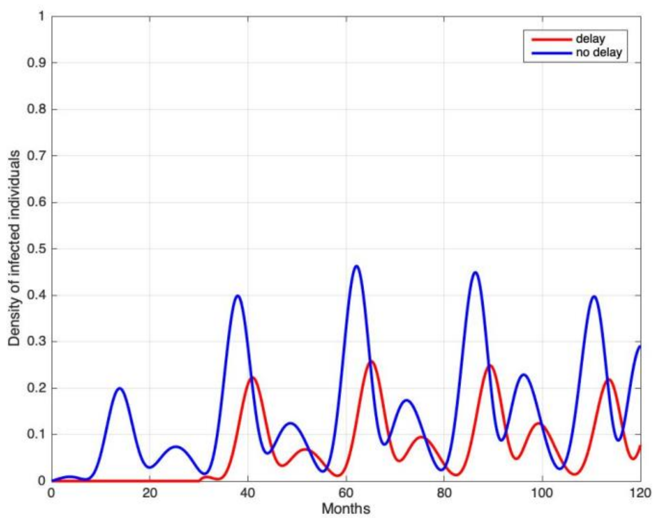


From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

B. Mathematical modeling



Appendix B.1: Graphical representation of compartmental model. A *SIR* in a close model without demographic elements.



Appendix B 2 Mathematical modeling of the seasonal pattern. The blue line indicates an immediate seasonal pattern and the red line indicates a 30-day latency period.

ABSTRACT IN FRENCH

Motifs et processus saisonniers dans les maladies mycobactériennes. Une revue des résultats de recherche selon des perspectives globales et spatio-temporelles.

Introduction : La recrudescence des maladies infectieuses augmente en fréquence au fil du temps. Comprendre les motifs saisonniers de l'écologie des agents pathogènes est crucial pour atténuer leur impact sur les êtres humains et les écosystèmes. Les espèces de *Mycobacterium* jouent un rôle important dans la santé publique, l'agriculture et l'écologie. L'étude de leur dynamique saisonnière nécessite des efforts interdisciplinaires. Cette étude, menée dans le cadre d'un projet majeur sur la dynamique de transmission de *Mycobacterium ulcerans*, vise à synthétiser les connaissances scientifiques existantes sur la saisonnalité des espèces de mycobactéries.

Methodologie : Une approche hybride combinant une analyse bibliométrique et une revue systématique est utilisée pour examiner la structure de la recherche. Un ensemble diversifié de publications récupérées par une recherche systématique a été analysé pour extraire les motifs saisonniers de la dynamique de transmission des mycobactéries. L'analyse comprend les principales conclusions des études sur la saisonnalité des mycobactéries, la répartition géographique des études, les méthodologies utilisées, les réseaux de citation et les collaborations entre auteurs. Cette étude compare les facteurs saisonniers qui influencent l'écologie des maladies mycobactériennes et les principaux moteurs potentiels de la recherche entre les entités scientifiques.

Résultats : Les facteurs saisonniers ont été bien documentés et classés pour chaque espèce ou catégorie de *Mycobacterium*, discutés et mis en contraste avec la variété de la littérature récupérée. Des considérations sur la méthodologie et le lieu de l'étude ont été prises en compte. Les réseaux de co-citation et de collaboration ont été analysés à partir des publications récupérées sur *M. tuberculosis* et *M. ulcerans*, et une synthèse des causes potentielles ou des influences sur l'orientation de la recherche a été discutée.

Conclusions : Sur la base de l'analyse, cette étude révèle les facteurs saisonniers associés aux espèces de mycobactéries et à leurs conditions écologiques. Elle met l'accent sur l'importance des outils méthodologiques avancés pour capturer avec précision les tendances saisonnières. De plus, elle souligne la nature interdisciplinaire de la recherche sur *M. ulcerans*, en insistant sur la nécessité d'une collaboration entre différents domaines. L'étude souligne également l'importance des réseaux régionaux solides pour faire face à d'importants problèmes de santé publique, tels que la dynamique de transmission de *M. tuberculosis*.

Mots-clés : Maladies infectieuses, mycobactéries, saisonnalité, dynamique de transmission.