Bioinformetric studies show that ethical issues continue to be under-represented in scientific studies.

‘Nobody had blood, nobody had name, we had neither body, nor spirit. We had no face.’

_Sleepless Night_
Octavio Paz

Small Family
Nelson Domínguez
Mixed on canvas; 65 × 65 cm
INTRODUCTION

The term Bioinformetrics is used here to refer to the mathematical analysis of the biological documentation contained in digital repositories (local or distributed, in the Internet and in databases) using the resources (concepts, methods, techniques, etc.) of several disciplines (e.g. bibliometrics, informatics, and computer intelligence). In this chapter, scientific research since 1950 on the TB vaccine is analyzed.

The study takes advantage of the huge databases on scientific research articles at present publicly available in digital format, as well as the new information technologies, enabling automation of certain stages of the analysis process, such as visualizing quantitative results using different geometric representations. Based on the use of bibliometric indicators, the information available on the Internet, and in software systems based on artificial networks, the neural networks present study is set within the emergent fields of Data Mining (1) and Knowledge Discovery in Data Bases (2).

Data on TB vaccine research for the past 57 years were extracted from MEDLINE, the database which is accessible online through the PubMed\(^1\) portal. MEDLINE, which contains more than 16 million research papers on biomedical subjects and covers about 5,000 different journal titles, constitutes a very rich source of biomedical information. Each scientific paper included is indexed according to the US National Library of Medicine’s controlled vocabulary, known as ‘MeSH’ (Medical Subject Headings). MeSH has the complex structure of a hierarchical thesaurus. This structure grows in a dynamic way and adapts as the knowledge in the field evolves. For example, for a long period of time the only MeSH term associated with ‘Tuberculosis Vaccines’ was ‘BCG Vaccine’. In 2003, the MeSH term ‘Tuberculosis Vaccines’ was finally included in the thesaurus. Following this, the term ‘BCG Vaccine’ became a subcategory of ‘Tuberculosis Vaccines’ in the most updated version of the thesaurus.

\(^1\)PubMed (http://pubmed.gov/) is the freely accessible online data base of biomedical journal citations and abstracts created by the US National Library of Medicine. One of the more important components of PubMed is the MEDLINE database.
The MeSH terms also describe the contents or topics found in an article. For this reason, the study of MeSH terms with their subheadings and major topics can be considered an indicator of the evolution of knowledge on a topic. Furthermore, knowledge generated (or produced) by research would only be made known when it is published and scrutinized by peer review allowing scientific discourse for the generation of new ideas or theories. Therefore, scientific publications can be considered a product of scientific activity. This approach allows us to use the analysis of research articles under MeSH terms (e.g. tuberculosis vaccines) as an adequate way of characterizing a research topic.

We have found that the first papers registered in MEDLINE under the ‘Tuberculosis’ MeSH term appeared in the 1940s and the number of articles up to January 2008 stands at 132,703. MEDLINE reports the first papers related to TB vaccines since 1950 (at that time indexed under the term ‘BCG Vaccine’). All the journal articles included by MEDLINE throughout the period from 1950 to January 2008 will be analyzed in the following sections.

The ViBlioSOM (3) methodology, installed in the ViBlioSOM v.1.0 beta (4) software system, was used to carry out the exploratory analysis of the volume of information contained in MEDLINE. This is a neurocomputational technology that uses artificial neural networks based on the SOM (Self Organizing Maps) family of algorithms, which is useful for cluster analysis of digital data and the automatic generation of visual representations in the form of maps or cartographies (5). This software was created specifically for the metric analysis and visualization of digital bibliographic information.

The analyzed data show the sustained interest of the scientific community in research related to this disease, as well as important variations in the research patterns during different periods. Since the year 2000, new research lines appeared and flourished in the development of TB vaccines. The exploratory analysis presented in this chapter is just an example of the type of studies which are made possible by the new technological resources available. It is not an exhaustive study but it is aimed to stimulate further research.
TUBERCULOSIS

It is well known that the scientific community has devoted a considerable amount of attention to infectious respiratory diseases, but the data found in MEDLINE showed that TB has received special attention. The volume of research published on TB since 1950 (131,459 articles) significantly contrasted with the quantity published on other respiratory infections, such as pneumococcal disease (12,609 articles), meningococcal disease (7,997 articles), or legionellosis (4,024 articles).

Figure 3.4.1 presents the pattern on the volume of articles on TB research (TB MeSH count). It can be observed that there have been notable variations during the study period (1950–2007). From an average annual number of 3,438 articles published during the period from 1950 to 1952, there was a gradual decline during the next 10 years (1952–62), down to 1,844 articles in 1962. Later, the quantity increased again, reaching 3,040 articles in 1964. The following 10 years (1964–74) showed minor fluctuations with an average of 2,459 articles annually. After this period, the number of journal articles dropped to 1,797 in 1975, while from 1975 to 1988 the volume of publications stabilized, with small fluctuations, averaging around 1,528 articles annually.

Figure 3.4.1 Evolution of scientific production indicators for TB and TB vaccines, 1950–2007
Since 1989, a trend towards sustained growth began (with a non-significant exception in 1997) reaching a total of 3,077 documents in 2007. The extrapolation from this continued growth trend indicates that in the following years the highest level of publication production of the whole study period may reach those of 1952.

Some specialists in the field have studied and given explanations for the variations in the value of the bibliometric production indicator. For example, it has been considered that the appearance of MTB strains resistant to traditional drugs and the HIV epidemic have motivated new diagnostic and therapeutic research, as well as the urgency for improving BCG and/or for new vaccine development (6–8). It is thought that all these factors have favoured considerable increases in scientific publications during the last 20 years, specifically on the topic of TB vaccines (Figure 3.4.2).

**Tuberculosis vaccines and cancer therapeutics**

Whereas the production indicator for TB for the 1950–2007 period showed an average of 2,241 articles per year, the corresponding indicator for ‘Tuberculosis Vaccines’ revealed an average of only 254 articles, with a total number of 14,847 articles accumulated during this period (Figures 3.4.1 and 3.4.2). This last sum is an important part (35 per cent) of the total production under ‘Bacterial Vaccines’ for the period, which amounts to 42,103 articles, and includes 20 different classes of this type of vaccines (Anthrax, Autovaccines, Brucella, Cholera, Diphtheria-Tetanus-Acellular, Pertussis, Diphtheria-Tetanus-Pertussis, Diphtheria-Tetanus, Escherichia coli, Haemophilus, Lyme Disease, Meningococcal, Pertussis, Plague, Pseudomonas, Rickettsial, Salmonella, Shigella, Staphylococcal, and Streptococcal).

In Figure 3.4.2 we see that the productivity indicator associated with TB vaccines shows a very outstanding peak near the year 1978. The search of an explanation for this phenomenon motivated a series of computer experiments carried out to automatically explore the database, using the neural network of the ViBlioSOM software system. This neural network has the capacity for classifying the behaviour patterns of the whole group of data obtained from MEDLINE and visually displaying the organization of the different groups of data (technically called clusters) in maps that have the appearance of biodimensional geographic cartographies (Figure 3.4.3).

The computational experiments confirmed a reasonable hypothesis: this conspicuous increment of the research activity level associated with TB vaccines, is due to the emergency of therapeutic cancer research.
The hypothesis is based on the well-known fact that BCG has a non-specific antibody stimulating capacity and confers a general immunogenic power that has antitumour effects useful in the treatment of different types of neoplasms and particularly for bladder cancer (9). In fact, the data analysis that are presented in this section reveal a burst of interest of the scientific community’s for studying the therapeutic usefulness of BCG during the decade of the 1970s and the beginning of the 1980s.

In order to carry out the computational experiments, we extracted from MEDLINE the collection of journal titles in which articles associated with the ‘Tuberculosis Vaccines’ MeSH term were published; this set of articles is called here TB-Vaccines. Then the resulting collection of journal titles was mathematically modelled in a multidimensional Euclidean space. According to this model, each journal was represented as a vector point in a mathematical space that has as many dimensions as there are years in the 1950–2007 period; each vector component of the vector associated to a specific journal, representing the number of articles of the TB-Vaccines data set that appeared in this journal in that year.

Using this model, by means of the neural network of ViBlioSOM, we automatically classified all the journals (2,079 titles) that have published articles that belong to the base TB-Vaccines (14,847 articles), according to their patterns of evolution during the period 1950–2007. A series of maps, that visually represent the evolution of the production in the journals over the years (1950–2007), where also produced with ViBlioSOM. One representative sample of these maps is presented in Figure 3.4.3. This particular map shows the distribution (and concentration) of the articles in the TB-Vaccines base in the different journals during the year 1978.
Figure 3.4.3 Mapping of the main journal titles* for the year 1978

Note: The regions of higher rate of production levels are marked in red and the lower levels in blue (according to the chromatic bar in the lower part of the figure). The journal titles specialized on cancer (see Table 3.4.1), shown in white letters, concentrate near to regions of high rate of production levels (c.1978). In black letters are shown all the journal titles in which were published at least 21 articles during the period 1950–2007, indexed under ‘Tuberculosis Vaccines’.
It is clear that the journals specialized on cancer topics (see Table 3.4.1) stood out among the journals which in 1978 exhibited the highest production levels. The maps corresponding to other years circa to 1978 are not presented here since they show a similar behaviour.

The bar in the lower part of Figure 3.4.3 chromatically codifies the proportion of articles published in the different journals. This code scales from 0.0 to 1.0, with 1.0 indicating the maximum annual production of each journal in the 1950–2007 period. The red colour indicates those regions of the map where there are located journals that had in 1978 their maximum production level with respect to TB-Vaccines. Dark blue indicates those regions of the map where there are journals that had in 1978 only a small fraction of their maximum number of ‘Tuberculosis Vaccines’ articles produced in the period 1950–2007.

### Table 3.4.1 List of journals on cancer

<table>
<thead>
<tr>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Journal of Cancer</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Cancer Immunology, Immunotherapy</td>
</tr>
<tr>
<td>Cancer Research</td>
</tr>
<tr>
<td>Cancer Treatment Reports</td>
</tr>
<tr>
<td>European Journal of Cancer</td>
</tr>
<tr>
<td>Gan To Kagaku Ryoho. Cancer &amp; Chemotherapy</td>
</tr>
<tr>
<td>International Journal of Cancer</td>
</tr>
<tr>
<td>Journal of Clinical Oncology</td>
</tr>
<tr>
<td>Journal of the National Cancer Institute</td>
</tr>
<tr>
<td>Journal of Surgical Oncology</td>
</tr>
<tr>
<td>Medical and Pediatric Oncology</td>
</tr>
<tr>
<td>National Cancer Institute Monograph</td>
</tr>
<tr>
<td>Recent Results in Cancer Research</td>
</tr>
<tr>
<td>Seminars in Oncology</td>
</tr>
<tr>
<td>Neoplasma</td>
</tr>
<tr>
<td>Tumori</td>
</tr>
<tr>
<td>International Journal of Radiation Oncology, Biology, Physics</td>
</tr>
</tbody>
</table>

**Note:** Collection of journals specialized on cancer in which have appeared articles with the MeSH term ‘Tuberculosis Vaccines’.

To support the validation of our hypothesis and emphasize the results of the data analysis, we present another two graphs (Figures 3.4.4 and 3.4.5).
In Figure 3.4.5 we compare the evolution of the total production on ‘Tuberculosis Vaccines’ (red curve) with the evolution (blue curve) of the production on TB vaccines not related to cancer: articles which are not indexed with topic descriptors (MeSH terms) related to cancer. It is to this collection of documents that we refer here using the label TB-Vaccines*.

**Figure 3.4.4** Publication trends of TB Vaccine topics in cancer journals*, 1957–2007

*Total sum of the production indicator for the whole group of journals listed in Table 3.4.1.

**Figure 3.4.5** Comparative analysis of the evolution of the production of articles on TB Vaccines (red) with that of TB Vaccine articles not linked to cancer Treatment (Blue)
RESEARCH ON TB VACCINES

In this section, the group of 10,757 articles that have the heading (MeSH term) ‘Tuberculosis vaccines’, but have no other heading related to cancer will be analyzed separately. As previously stated, this group is called in this chapter TB-Vaccines* and we remark here that from this section onwards, the group of articles to be analyzed will already be cleared of those related to cancer.

Figure 3.4.6 Qualitative correlation between publications related to TB with those on TB-Vaccines*, 1950–2007

Note: Qualitative comparison of the production relative to TB with respect to TB-Vaccines*. There is scale factor of ten among these to curves. The scale at the left is for the red curve, the green's scale is 1/10 of it.

A total of 25,527 researchers have been involved in the TB-Vaccines* production, of which 26 have been the most productive (with a level of over 40 articles during the period of study). The sum of all these contributions show (Figure 3.4.6) an evolution trend similar to that of the scientific publications related to the general heading term ‘Tuberculosis’ (131,459 articles). In this figure the TB-Vaccines* graph has been scaled up (multiplied by 10) to make a qualitative comparison of both behaviours. Although these curves represent different groups of articles, it is possible that there are global factors that have affected their tendencies to change in a similar way during most parts of the study period (1950–2007). For instance, between 1953 and 1965, a sustained decrease followed by a faster growth (1959–
1964) was a notable feature shown in both graphs. It is reasonable to infer that there should be ‘global’ factors that were responsible for the low level of activity in 1962, as well as for the sudden spurt in publications after that year. These factors are yet to be investigated.

Without intending an exhaustive analysis, in the following sections we will analyze several aspects of the information contained in the TB-Vaccines* database: distribution of the activity by countries; research on BCG alone; veterinary TB exploration; emergent trends in research; and finally, its ethical issues.

**Figure 3.4.7** Distribution of scientific activity by countries, 2000–2007

**Distribution of research by countries**

Sampling the interest of the international community for research on TB-Vaccines*, the graph in Figure 3.4.7 displays the different degrees of participation of the main contributors, from 2000 to 2007. With 37 per cent of the whole scientific production, the USA holds the first place, followed by the UK (20 per cent), and France (8 per cent). India and Japan occupy the fourth and fifth places with 7 per cent participation. From among all the Latin American countries, Brazil takes the sixth place with an activity level of 5 per cent.
In the USA, there was a 20 per cent annual increase in TB cases between 1984 and 1992; in 2006, 13,767 cases were registered (3.2 per cent less than in 2005) (10). Since then, several strategies were designed to control the disease. One of the priorities was to encourage national research (11). Countries like the UK (15 cases) and France (14 cases), showed the same trend as the USA in incidence rates. For example, the case notification rates in UK and France have fallen since 1980 and in the last five years have remained relatively unchanged. These countries occupy the third (UK) and fourth places (France) in TB incidence\(^2\) with respect to the rest of the Western European countries.

![Graph showing case notification rates for various countries from 1980 to 2007]

**Figure 3.4.8** Notification of TB cases* according to the DOTS Program, 1980–2007

**Note:** * all cases/100,000 pop/yr

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\(^2\)All statistics with respect to TB incidence were compiled by DOTS and appear published in its official site [http://www.who.int/countries/es/](http://www.who.int/countries/es/). The incidence is based on all TB cases considering the rate per 100,000 inhabitants up to 2006 (all cases/100,000 pop/yr).
Research levels in India and Japan equally stood out. The level of scientific production achieved by India on the topic was significant, considering that the country occupies nineteenth place with respect to world scientific production (12). This country has one-fifth of the world’s TB infection (13). Every year, two million people develop active TB, more than in any other country in the world, and the incidence has steadily increased from the year 2000 (13–15) (see Figure 3.4.8). In Japan, despite all the control efforts instituted since the 1950s, the case prevalence is still relatively high (12, 16), with a prevalence of 22 cases every year up to 2006, according to official reports of the DOTS Program (17).

In both countries, the main topics studied are related to epidemiological aspects and the immune response to the BCG vaccine. In the last decade, the research carried out in India by the Council of Scientific and Industrial Research in New Delhi on molecular epidemiology to characterize infection by MTB (18) and vaccine preparation against the disease are outstanding (19).

Brazil, with a 5 per cent production level, has the fourth highest incidence of TB cases in South America. According to data for 2006, Brazil recorded an incidence of 50 cases (all cases/100,000 pop/yr); Ecuador (128 cases); Guatemala (78 cases); and Honduras (76 cases). Brazil has maintained constant levels of activity on the topic since the 1980s. Analysis using the MeSH terms revealed that the activity were mainly associated with immunological adjuvants and tests using various animal models, notably the inbred-Balb/c mice.

Participation in TB-Vaccines* scientific research in different countries does not have a directly correlation with TB incidence. For example, for Latin America the disease incidence is higher in Guatemala, Honduras, and Ecuador but these are not the countries that contribute most to research on the topic. This may be due to other fundamental influence on scientific activity such as the availability of equipment, laboratories, and conducive political climate.

**TB-vaccines* and BCG**

It is well known that BCG is the only vaccine available to prevent human TB and that its improvement or the development of new vaccines is necessary for the effective control of the epidemic. In spite of the fact that several studies had highlighted the controversies on the efficacy of BCG in providing protection against TB since the 1970s (20) and trials demonstrating the lack of protection to adults (21–23), the majority of the research reported in MEDLINE has centred on BCG’s epidemiology, adverse effects, and administration, as will be seen later.
It is after the 1990s that new lines of research started to flourish. This situation is also reflected in the MEDLINE thesaurus: it was not until 2003 that the term 'Tuberculosis Vaccines' was permanently introduced in the headings tree, and, to date, ‘BCG Vaccine’ is still the only branch deriving from it. In 1964, MEDLINE introduced the term ‘Tuberculosis Vaccines’, but only a small number of articles were classified into this category during the years this term was in use (1964–1978). Twenty-seven articles were assigned to this classification up to 1966 (seven of them were also assigned to the term ‘BCG Vaccine’). And from 1966 to 1978, the year when the use of the term 'Tuberculosis Vaccines' was discontinued, no other article was classified under this category. A different situation was observed after 2003, when the term was reintroduced. A significant increase in the number of articles, not labelled under the term BCG, but classified under ‘Tuberculosis Vaccines’, appeared under this category (Figure 3.4.9), justifying the need of the term in the thesaurus (details of the way the thesaurus is made and how the vocabulary is controlled by the National Library of Medicine is depicted in Appendix 3.4.1 of this chapter).

![Figure 3.4.9 TB Vaccine publication trend, 1950–2007](image)

Thus, it is particularly interesting to analyze the group of publications that are not classified under the term 'BCG Vaccine’, since this type of articles are representative of the new research trends. This is a relatively small emerging production: of the 10,757 publications in the 1950–2007 period which form the TB-Vaccines* database, less than 3 per cent (306 papers) are not classified under BCG. However, its growth ratio is very significant, representing the 20 per cent of the total production in TB-Vaccines* from 2000 to 2007 (see Figure 3.4.9).
Analysis of scientific productions on BCG

A detailed study of the research topics included under BCG vaccines that have contributed most to the overall production in this topic, and the periods in which they were most relevant, will allow the identification of different research trends. It would be especially convenient to identify the new trends and quantify their relative importance.

As previously mentioned, the upper curve in Figure 3.4.9 represents all the BCG vaccine production in the *TB-Vaccines* database (10,757 articles) and its evolution throughout the years. This collection of articles has a total of 16,087 associated keywords or key phrases, formed by different MeSH combinations (major topics, headings, and subheadings terms). It is essential but not trivial to break down the main components of this production in order to gain understanding of the different roles of topics that are involved in this research.

Taking advantage of the MEDLINE classification, we separated the total BCG Vaccine production (Figure 3.4.9) into several components that show different behaviours and indicate different patterns of development in the production.

According to the MeSH, the term 'BCG Vaccine' is applied to articles that deal with this topic and the major topic '*BCG Vaccine' when this is one of the main subjects dealt with in the article. Therefore, it is possible to retrieve two separate databases from PubMed specifically related to BCG:

1. The *BCG Vaccine* (3,762 articles) database, containing articles in which the BCG vaccine was a main topic and is not described by any subheading, and
2. The BCG Vaccine (6,343 articles) database, containing articles in which BCG vaccine was considered a secondary topic and has associated other MeSH terms or major topics.

Analyzing the patterns of activity in these databases, it is possible to identify which topics and/or what types of research have been relevant at different times. For example, in Figure 3.4.10, it can be observed that the evolution of the *BCG Vaccine* component has sharp variations during the 1950–1965 period (minimal activity in 1959 and maximum in 1964) and shows two clearly differentiated stages: before and after 1980, where from 1980 onwards, this type of production has been greatly reduced.

On the other hand, the publications contained in the BCG Vaccine database have a radically different development pattern. Figure 3.4.10 shows the patterns corresponding to BCG Vaccine and *BCG Vaccine*. In this figure, scientific production related to BCG Vaccine has been broken down into two components.
One of them \textit{BCG Vaccine}*SubH or SubH, is the one containing those articles dealing with BCG vaccine described by some subheading (with or without *), but it is not one of the main topics of the article; the other component, labelled as \textit{BCG Vaccine}, corresponds to articles that have this MeSH term associated with it in its simple form, that is, not qualified by another subheading.

In Figure 3.4.10, it is possible to see that the \textit{BCG Vaccine} database appeared in 1965 and also, that 1980 marks an important moment for the type of research it represents. Before 1965, all the publications related to BCG was indexed with asterisks as '*BCG Vaccine', without associated subheadings or as 'BCG Vaccine/*subH', meaning that the articles in which the BCG topic has a secondary role (classified as 'BCG Vaccine' or 'BCG Vaccine/subH') started to appear in this database since that year. The major topics (MeSH terms marked with an *) that appear in these articles will be useful for identifying the subjects or research topics related to this vaccine in the article.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.4.10}
\caption{Breakdown of publications related to BCG Vaccine into its components}
\end{figure}

On the other hand, our exploration has enabled us to see that only a small part of the articles in the *\textit{BCG Vaccine} database has associated subheadings (with or without *). Therefore, to identify the research topics that are related in a more significant way with BCG in this database, we only analyzed the group of major topics that co-occurred with the term '*\textit{BCG Vaccine}'. In Figure 3.4.10 it is possible to observe that, since 1980, there is a notable reduction of articles indexed as '*\textit{BCG vaccine}', but as shall be seen, this decrease is compensated by the articles that have the compound term '\textit{BCG Vaccine/*SubH}'.

Since generically, all articles should have associated a major topic or some MeSH term qualified with an asterisk, then Figure 3.4.10 suggest the following interpretation: from 1965 onwards, the production in which the BCG topic has
a secondary role (articles labelled with BCG or BCG/subH) begin and continue appearing. Therefore, the identification of the major topics that co-occurred with BCG since 1965 will also be of interest for this study.

The development of the groups of articles contained in these databases can be better studied by dividing the analysis of research behaviour into four periods: 1950–1960, 1960–1965, 1965–1980, and 1980–2007. Below is a summary of the main aspects stemming from this analysis.

1950–1960

At the beginning of the 1950–1960 period there was a high degree of activity, which later progressively decreased. Since during this period only articles from the *BCG Vaccines* and *BCG Vaccines/SubH* databases coexist (Figure 3.4.10), analyzing the group of major topics associated with ‘*BCG Vaccine’ led us to conclude that the most relevant research activities during this period were related to TB, particularly to disease immunology, prevention, and control. Eighteen studies dealt with lung TB.

Interest was displayed towards age group studies, expressed by the descriptors: Infant, Newborn, and Child. Leprosy prevention and control also received attention. At this time the presence of tuberculin related studies was also observed. They became more important with the passing of time, playing a predominant role in the following period, 1960–1980. It is important to point out that there is a considerable contribution of many other major topics that, even though they have low levels of co-occurrence with ‘*BCG Vaccine’ (< 12), have an important effect on the total sum (see Table 3.4.2).

<table>
<thead>
<tr>
<th>Table 3.4.2 Major topics co-occurring with *BCG, 1950–1960</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Tuberculosis</td>
</tr>
<tr>
<td>*Infant</td>
</tr>
<tr>
<td>*Child</td>
</tr>
<tr>
<td>*Tuberculin</td>
</tr>
<tr>
<td>Tuberculosis: *immunology</td>
</tr>
<tr>
<td>*Tuberculosis, Pulmonary</td>
</tr>
<tr>
<td>*Infant, Newborn</td>
</tr>
<tr>
<td>Tuberculosis: *prevention &amp; control</td>
</tr>
<tr>
<td>Leprosy: *prevention &amp; control</td>
</tr>
<tr>
<td>*Mycobacterium tuberculosis</td>
</tr>
</tbody>
</table>
A different situation is observed when the group of subheadings associated with the ‘BCG Vaccine/*SubH’ database are analyzed. In the panel in Figure 3.4.11 it is possible to observe that the global behaviour of this database in the 1950s is determined by a select group of subheadings. During this decade, ‘complications’ plays a dominant role, although it decreased until it disappeared in the 1960s, when this subheading was substituted by ‘adverse effects’ in the MEDLINE database that increasingly recovered scientific productivity levels up to 2007. The subheadings ‘administration & dosage’ and ‘therapeutic use’ exhibited a similar behaviour. In these graphs it can also be observed that between 1950 and 1953, historical studies of the vaccine peaked.

Figure 3.4.11 The nine most frequent BCG qualifiers, 1950–2007

1960–1965

The articles contained in the *BCG Vaccine database during this period were the only relevant ones that contributed to the total TB Vaccines production (Figure 3.4.12). By analyzing the group of major topics associated with *BCG, it is possible to identify the research that contributed most to reach the maximum *BCG Vaccine amount of production achieved in 1964. ‘*Tuberculin Test’ and basic research issues
represented by the term ‘*Research’ together with ‘*Tuberculosis’ and particularly immunologic issues associated with this disease were prominent.

1965–1980

The 1965–1980 period could be considered one of ‘transition’ between the type of research already reported (1950–1965) and the 1980–2007 period, where research is directed towards other topics. During this ‘transition’ stage the most significant components of research come from the *BCG Vaccine and *BCG Vaccine databases (Figure 3.4.10). The latter contain the group of articles classified under the term ‘BCG Vaccine’, without any subheading qualifying this keyword. Associated with this group of articles were a group of major topics (the terms marked with *) that described the main subjects dealt with in these articles. These are displayed in Figure 3.4.13.

With respect to the research component corresponding to the *BCG Vaccine database, in Figure 3.4.12 it may be observed that interests on some previously studied subjects (during the 1950–1965 period) continued to persist. The emergence of other topics related to the function of the immune system, which, as seen before, will become dominant in the 1980–2007 period (see Figure 3.4.14), is interesting. Since 1966, prevention and control of pulmonary TB gained relevance in this database and, in a precursory way, ‘Mycobacterium bovis: *immunology’ also notably peaked at the end of the 1965–1980 period.

Figure 3.4.12 The ten dominant topics in the *BCG vaccine database, 1960–1980
Figure 3.4.13 The ten dominant topics in the BCG vaccine database, 1965–1980

* Tuberculin Test-95 Tuberculosis: 12

Figure 3.4.14 The most significant terms in the BCG vaccine production, 1950–2007
Table 3.4.3 displays the group of major topics that co-occur with any of the different ways in which BCG vaccine is indexed in MEDLINE during the 1980–2007 period. The comparison of the major topics in Table 3.4.3 with those in Table 3.4.2 reveals clear differences that have a time correlation with facts emerging since the 1980s.

Having already observed the new research activities that had peaked at the end of the 1970s, a later analysis enables to appreciate how, since the 1980s, the epidemiologic aspects of TB became more important, correlating with the appearance of the AIDS epidemic and the ensuing TB epidemic. A strong interest can be observed (rising in this last period) in the identification of cases (tuberculin test) and immunologic studies related to the disease and the different mycobacterium that cause it.
Table 3.4.3 Most significant terms in BCG vaccine publications, 1980–2007

<table>
<thead>
<tr>
<th>Term</th>
<th>*BCG</th>
<th>BCG</th>
<th>BCG/SubH</th>
<th>BCG/SubH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leprosy: *prevention &amp; control</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>*Bacterial Vaccines</td>
<td>13</td>
<td>12</td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Bacterial Vaccines: *immunology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Antigens, Bacterial: *immunology</td>
<td>13</td>
<td>42</td>
<td>42</td>
<td></td>
<td>97</td>
</tr>
<tr>
<td>T-Lymphocytes: *immunology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>*Immunization</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>*Vaccination</td>
<td>60</td>
<td>84</td>
<td>30</td>
<td></td>
<td>174</td>
</tr>
</tbody>
</table>

Our exploration reveals that the subheadings that qualify the term ‘*BCG Vaccine’ are rather unimportant. The main subheadings associated with this period’s production are displayed in Figure 3.4.14. As a result of the analysis of the graphs in this figure, the rapid growth of research in immunology stands out with a total of 712 articles. The subheadings ‘pharmacology’ and ‘standards’, present since 1966, became more important from 1980. The emergence of the more modern term ‘genetics’ takes place at the beginning of the 1990s. However, it only appears, associated with the term ‘BCG Vaccine’ in 26 articles.

**Evolution of the research topics**

The study of the research topics was carried out on the TB-Vaccine* Database (Figure 3.4.15). In the analysis it was possible to identify that, in general, most contributions to the scientific production are related to the search for a vaccine against veterinary TB (‘Tuberculosis Bovine’ or ‘Tuberculosis Avian’). Several authors point out that bovine TB is currently a severe health problem worldwide. Although the causal agent was discovered over a century ago, the control of this disease is still beyond reach of the scientific community (25). Spain and UK reported an increase in the incidence of bovine TB (0.42 per cent in 2006, as compared to the previous report of 0.31 per cent). In the UK, during the 1990–2003 period, between 17 and 50 new human cases of MTB were reported. These data remind us that an important risk for MTB infection persists in certain population groups (26, 27).
Those articles that had the MeSH terms ‘Tuberculosis, Bovine’ or ‘Tuberculosis, Avian’ were filtered. All the MeSH terms that describe the 2000–2007 articles were extracted from this subgroup; the result is shown in Figure 3.4.16.

The analysis of keyword co-occurrence is a well established and widely used bibliometric indicator (28–30). The co-occurrence matrix of MeSH terms is organized and represented visually, using the neural network of ViBioSOM, (see map on Figure 3.4.16). In this map the MeSH terms are organized according to the similarity of their co-occurrence patterns. That is, two MeSH terms that have similar frequencies of co-occurrence (with all the MeSH terms) are localized in the map close to each other.

TB Veterinary has focused mainly on immunological, prevention and control, and animal-model studies, as well as on the BCG vaccine itself (Figure 3.4.15). After the 1990s, as can be assessed in Figure 3.4.15, new lines of research appear, such as DNA vaccines and Subunit vaccines. However, since 2000, all levels of activity increased and the application of Bioinformatics to this field began. After 2000 there is an increase in the MeSH terms that are not indexed under BCG, that is, research that is completely independent from the usual vaccine topic. The growth ratio of
all these research lines is very significant: 20 per cent of the total *TB-Vaccines* publications from 2000 to 2007 (see Figure 3.4.9).

Research on TB immunization using the mucosal route registers low levels of production (Figure 3.4.15) with respect to the rest of the topics. It appeared at the beginning of the 1990s as a strategy for the development of new vaccines. Since 1993, several authors have established the advantage of the mucosal pathway over other administration routes (23, 31–33). By 2007, 11 studies related to intranasal administration were reported using different substances, such as: IgE and IgG, type II interferon, and IL-4; the inbred mouse models used were: Balb/c, C3H, C57BL, CBA, and ICR strains. The first
model was the most used in clinical trials. Even if this strategy of mucosal administration of BCG vaccine is considered a novelty, it is important to point out that since 1968 there are documents that report the interest in understanding the pulmonary response mechanisms against the bacteria (34). Others compared tuberculin sensitivity after oral or intradermal vaccination in human trials (35).

The clinical trial activity has been carried out mainly with the traditional BCG in prevention and control, administration, MTB immunology, and time factor studies, among other aspects. Clinical trials have been reported since 1960 (Figure 3.4.15). Several of these trials received support from the WHO. Table 3.4.4 shows the strategies for TB vaccine development in relation to Clinical Trials topic, in which different phases of the trials reported in the MEDLINE database are shown. As can be appreciated, the main efforts have been directed towards synthetic vaccines.

Several aspects point towards a rising trend in clinical trials, using both BCG-improved vaccines, as well as vaccines based on novel strategies. This increase was reflected in the activity levels reached using animal models and preclinical studies (Figure 3.4.15). An increase in the scientific publications on these two subjects may be related to a greater interest in efficiently shifting basic research to vaccine development. The use of bioinformatic techniques for vaccine research is expected to be a catalyzing element for achieving a more effective vaccine against the disease, however the production indicator still have marginal values (Figure 3.4.15).

<table>
<thead>
<tr>
<th>Table 3.4.4 Articles on clinical trials within the TB vaccine MeSH database</th>
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</thead>
<tbody>
<tr>
<td><strong>Descriptor</strong></td>
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<tr>
<td>----------------</td>
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<tr>
<td>Vaccines, DNA</td>
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<tr>
<td>Vaccines, Attenuated</td>
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<tr>
<td>Vaccines, Inactivated</td>
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<tr>
<td>Vaccines, Subunit</td>
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<tr>
<td>Vaccines, Combined</td>
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<tr>
<td>Vaccines, Conjugate</td>
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<tr>
<td>Vaccines, Acellular</td>
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<tr>
<td>Vaccines, Edible</td>
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</tbody>
</table>

In the search for more elements that may contribute information on the development of new vaccines, we resorted to the data on Figure 3.4.9, where a small group of articles was not associated to the main BGC vaccine MeSH term.
Filtering this segment of the data gave the results presented in Table 3.4.5 where the main technologies being used in vaccine development can be appreciated. However, when secondary terms associated with vaccines: synthetic, DNA, subunit, and others, were studied it was possible to ascertain that many studies still use the BCG vaccine as a reference.

<table>
<thead>
<tr>
<th>Table 3.4.5 Articles without BCG vaccine as a main term</th>
</tr>
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<tbody>
<tr>
<td>MeSH</td>
</tr>
<tr>
<td>Vaccines, DNA</td>
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<tr>
<td>Vaccines, Attenuated</td>
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<td>Vaccines, Inactivated</td>
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<td>Vaccines, Subunit</td>
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<td>Vaccines, Combined</td>
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<tr>
<td>Vaccines, Conjugate</td>
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<tr>
<td>Vaccines, Acellular</td>
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<td>Vaccines, Edible</td>
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</tbody>
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In Figure 3.4.17, the related terms 'Vaccines, Attenuated' are found in Cluster 1 (C1). Work has been carried out in vaccine candidates, including genetic modifications of MTB, as well as studies with respect to immunology, antibody formation, and tolerance and protection studies in animal models. 'Vaccines, Synthetic', terms which appear in Cluster 2 (C2), seems to be the most successful strategy (Table 3.4.5). A group of topics coexists related to it. It is important to point out that the first proposals for the inclusion of synthetic vaccines within the new generation of TB vaccines were dated in the 1980s with Kaufmann's proposals (36) and the initial research by other pioneers in this topic (37–39).

In Figure 3.4.15 it is possible to assess that one of the topics that emerges often is ‘Subunit Vaccines’. It has a greater amount of research (in terms of MeSH, see Figure 3.4.15) associated with it than other topics previously entered in the database (see Figure 3.4.15). Due to its closeness to cluster 5 (C5), it seems to be the strategy used most often and has greater similarity in research topics with the new generation of TB vaccines, together with DNA vaccines that appear in C5.

The genome sequencing of two MTB strains provided a great amount of information that can be used to design new strategies for vaccine development. One of its applications is the search for the best immunogenic candidates or for virulence genes, thus limiting the number of candidates to be tested (Cluster 2, C2, Figure
In this sense, research based on the identification of T cell epitopes tested in algorithms that mimic the human immune system (C1, Figure 3.4.18) has been reported. Genomic and proteomic techniques are, to a great extent, focused on the study of the MTB genome.

When exploring ‘Bioinformatics’ in the MEDLINE database, the results show that this area of research has increasing applications in biomedicine for the last 10 years. For example, in 1997, 233 studies were reported, whereas since 2005 more than 6,000 references were reported every year. It is estimated that knowledge on...
the future development of vaccines will increase to the extent that technologies, such as those associated with data visualization, hardware improvement (faster information processing) and, above all, improvement of the cybernetic algorithms that allow the translation of the problems from the laboratories towards different solutions or models in silico.\(^3\)

\(^3\) In silico: In biology, this term refers to the use of computers to perform biological studies. It is an expression used to mean ‘performed on computer or via computer simulation’.
However, the applications of Bioinformatics to the vaccine field, in general, are presently at a preliminary stage. For example, only 311 bioinformatics studies are reported as being linked to the development of these biologic substances. This number starts to increase since the year 2000 (11 articles); whereas in 2007, 56 studies were reported. The use of Bioinformatics as an aid in TB-associated research and specifically in the development of vaccines is insignificant. There are 35,287 studies reported under ‘Bioinformatics’ in MEDLINE (until December 2007 under the MeSH term ‘Computational biology’); however, only 67 of these records are related to TB records research and 23 registries to TB vaccines.

**Ethics in TB-vaccines**

The ethical issues of research associated with the topic were also evaluated. In this case, the analyzed group was the data recovered under the strategy ‘Tuberculosis Vaccines’ [MeSH] and ‘Ethics*’ (taking away all the registries related to cancer).

**Figure 3.4.19** Ethics research related to TB vaccines and TB in general

Using this strategy, only a few studies (11 registries) related to the topic was recovered. This situation does not change much if the search is extended to all the registries found under ‘Tuberculosis’ [MeSH] and ‘Ethics*[MeSH], in which

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4 The Bioinformatics term is not in the thesaurus. These items are described with the terms: ‘Computational Biology’, ‘Computational Biology’ & ‘Tuberculosis’, ‘Computational Biology’ & ‘Tuberculosis Vaccines’, ‘Molecular Sequence Data’ & ‘Tuberculosis Vaccines’.
case only 103 registries were recovered. These constituted the subgroup of data analyzed at this point. The previously mentioned proportions and their activity levels through time can be better assessed in Figure 3.4.19.

Topics associated with Ethics in TB vaccines and with TB in general have been little dealt with in the international community. This is in agreement with Snider (40), who considered it ‘too early to start examining the ethical issues that will have to be dealt with in respect to vaccination, taking into account the time that it may take to reach a satisfactory solution’.

The map in Figure 3.4.20 represents ethics from a comprehensive stand point, that covers all topics related to TB, which also includes vaccines. In this case, Ethics...
has been mainly related to disease prevention and control (Cluster 2, C2), with a special emphasis on HIV/AIDS patients. An interest in legal issues (C3), including social justice (C1), as well as studies to improve the comprehension of the factors that participate in the appearance of diseases, their prevention and elimination (‘Communicable Diseases’, ‘Public Health Programmes’, etc.) are shown.

Specifically referring to the vaccine topic (Cluster 4, C4, Figure 3.4.20), different issues related to BCG have been dealt with. Topics referring to: clinical trials, concerns about immunization in pregnant women, complications that may affect HIV patients, are observed. All of these essentially referred to developing countries.

**EVOLUTION OF THE USE OF SUBSTANCES CLASSIFIED ACCORDING TO THE CHEMICAL ABSTRACTS SUBJECT CLASSIFICATION INDEX**

To complement the knowledge on the TB topic domain, an analysis was made of the substances that appeared in each of the articles (this field was introduced in the MEDLINE database in the mid-1980s and corresponds with the classification of the Chemical Abstracts. Many chemical names are searchable as MeSH terms before that date) was carried out.

Obviously, the BCG vaccine has been the most used substance during the last 28 years of research (1980–2007), followed by immunological adjuvants and bacterial antigens (see Table 3.4.6).

Despite this prevalence, the use of BCG vaccine and its variants in research tended to decrease in the course of time (Figure 3.4.21, top left). Meanwhile, research using adjuvants has strengthened (Figure 3.4.21, top right). These studies appeared since the 1970s, but only after 1990 did they start to have a significant prevalence level.

The fourth of the topics (‘Antigens, Bacterial’) has had a similar behaviour to the adjuvants (Figure 3.4.20); however, its use in research has been more homogenous in time. An important place is held by antitubercular agents. The use of these substances in combination with the BCG vaccine classification is observed in 94 per cent of the articles (Figure 3.4.21, below right). This is a research area which is being developed and great efforts have been devoted to it in the last years. Several
of the articles dealt with studies where susceptibility of different MTB strains to antitubercular drugs is evaluated in BCG vaccinated patients.
Figure 3.4.21 Use of BCG vaccine (top left), adjuvants (top right), bacterial antigens (below left), and antitubercular agents (below right) in TB vaccines research, 1950–2007
DISTRIBUTION OF RESEARCH IN SPECIALIZED JOURNALS

The sources used by researchers to transmit knowledge were also analyzed in this study. The journals, apart from validating new knowledge and publicly transmitting it, are the depositories of a heritage that, although intangible, determines the capacity of progress in society and the interest on the topic (41). In this sense, significant changes have taken place in the interest and mobility of the topic that shifted from developing countries towards developed ones. The centredness and level of specialization achieved by the topic has also changed, being presently published in only a small number of journals and generally in English. This can be seen in Figure 3.4.22; from the 1950s till 1977 almost all the publications on TB vaccines were made in a different group of journals from the ones that presently publish them. During this period, the journals that published papers on TB vaccines were those located in the upper part of the figure (Cluster 1, C1). In this group, it is possible to find, for example, in 1958 the journal Revista brasileira de tuberculose e doenças torácicas (Rev Bras Tuberc Doenças Torac) edited in Brazil in Portuguese, which appeared in 1932. It was followed by the Br Med J (England, 1857–1980) and Arch Tisiol Mal Appar Respir (1955–1969), published in Italian; as well as other Brazilian journals, and those in Polish (Gruzlica) and Russian (Probl Tuberk, Zh Mikrobiol Epidemiol Immunobiol).

Since 1977, the situation began to change and the publication stream moved towards journals appearing in Clusters 3, 6, and 7. It is already possible to observe an interest in journals specializing in immunology and biological standards. Besides, in this period, India showed an outstanding interest, undertaking the publication of several specialized journals. In the first decade of this new century, the articles are concentrated in a small group of journals, mainly in those that are considered of impact,5 such as the International Journal of Tuberculosis and Lung Disease (Int J Tuberc Lung Dis, 1997; it was renamed Tuberculosis (Edinburgh) in 2001), Vaccine (1983), and Infection and Immunity (1970).

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5 The Impact Factor is one of the quantitative tools for ranking, evaluating, categorizing, and comparing journals. It is a measure of the frequency with which the ‘average article’ in a journal has been cited in a particular year or period. The annual impact factor is a ratio between citations and recent citable items published. Thus, the impact factor of a journal is calculated by dividing the number of current year citations to the source items published in that journal during the previous two years. (Source: PO Seglen. Why the impact factor of journals should not be used for evaluating research. BMJ, 1997; 314: 497).
Figure 3.4.22 Specialized sources which published on TB Vaccines, 1958, 1977, 1997, 2007

The journals should reflect the rise in the interest on the TB topic and be in agreement with the international situation. This should be expressed as an increase in the diversity of titles or countries involved in the publications and not in a reduction of the titles of journals for countries containing articles on TB vaccine. Likewise, the data convey that research on TB, in these last three years (2005–2007), has
focused on more specific topics, mainly related to immunologic research, vaccine development, or evaluation of the existing ones (BCG vaccines). It is important to point out that the sources represented here are only those that have a frequency of over 23 articles published in the 57 years that were studied. The total number of titles analyzed belonged to 130 journals.

**CONCLUSION**

In this chapter, we have applied a technique for the analysis of the information contained in the bibliographic databases of MEDLINE and software systems such as ViBlioSOM, to follow-up the evolution of research on TB vaccines. This investigation have contributed data and visual representations useful to observe, in a global way, the dynamics of the production of the scientific community in various topics related to TB vaccines. Using this approach, the conclusions below were reached.

The efforts devoted to the investigation on TB have been remarkably larger than those dedicated to other infectious respiratory diseases. The volume of the research production specifically committed to the development of a generation of TB vaccines, has had important variations during the period of study (1950–2007) that qualitatively correlate well with those of the general research on TB, being the latter quantitatively larger by a factor of ten. The variations of the level of production on both, general TB research and TB vaccines, show important variations during the studied period; remarkably in four years (1960–1964) the production on TB vaccines had an increment of 748 per cent. There are various hypotheses to explain some of the strong variations that the production have had. Our study has given support to some of them, the emergency of therapeutic cancer research during the 1970s and other relations cause-effect that we refer below (e.g. the pandemic effect caused by AIDS in the 1980s). However, there are still other important variations whose underlying causes are yet to be investigated. This is the case, for example, of the critical period of 1952–1954 during which the production indicator shows a large depression.

As was expected, the data analysis confirmed that the bulk of TB vaccines research in this period of 58 years has been centred on BCG and issues related to epidemiology, adverse effects, prevention and control, as well as administration and dosage. However, the indicators that were used showed only a marginal level of research on TB vaccines not related to BCG. New strategies and the interest in the search for a new vaccine or the improvement of the existing one begins become relevant only at the end of the studied period.
The analysis proved that for the last 10 years, there has been a sustained increase in research production on the TB vaccines topic. This growth is coincident with the rise in disease cases and the subsequent WHO statement, declaring it a re-emergent disease and a pandemic problem. The data also showed several elements that point towards a growth of scientific production on the topic for the following years, which might also be an effect caused by the need, in a short time interval, of a more effective TB vaccine. Among the new research elements found in the data we have observed:

- The use of the new research technologies or strategies, which appear or have been promoted since the year 2000 and may indicate new directions and changes in the traditional methodology for obtaining vaccines, such as DNA and subunit vaccines.

- The application of Bioinformatics in this field that will allow TB vaccine research access to a knowledge that will aid in a faster exploration of the MTB genome, and in identifying and testing in human models new vaccine candidates.

- The growing levels of scientific production in animal models and preclinical studies support the expectation that at some percentage of these studies will achieve success and several vaccine candidates will enter human clinical trials.

Ethics has been little dealt with within the TB vaccines and TB topics in general. Ethics focused on TB in general has mainly related to prevention and control of this disease, with special emphasis on HIV/AIDs patients. There is interest in legal questions, as well as in studies to try to improve the understanding of the factors participating in the appearance of disease, their prevention, and elimination. Essentially, in the vaccine topic, the main concerns have been associated with clinical trials, specifically in developing countries and in BCG vaccination of immune depressed people (especially HIV-infected ones).

Analyzing science from the perspective of publications, as an effective means of inquiring into the evolution of knowledge, has allowed the observation that the TB vaccines topic has achieved a greater level of homogenization and specialization. The efforts have concentrated on those journals, in which the central topics are more focused on vaccines, immunology, genetics of mycobacteria, and molecular biology. Likewise, there is a polarization of the sources publishing on the topic; of the various countries that contributed with their journals to the mainstream of science, many ceased to exist or stopped being leaders in the topic.
At present, publications on TB vaccines are concentrated in a nucleus of 10 journals. Among the journals, 80 per cent of these titles, edited in a non-Anglo-Saxon language, which concentrated all publications on this topic during the first 20 years of this study, had disappeared by the end of the 1980s. Maybe this was motivated by TB being considered a health problem for developing countries; whereas now, with its re-emergence in developed countries, these have shown a greater interest and have absorbed publications on the topic.

From the statistical data and the maps, researchers can make their inferences and reach their own conclusions on the knowledge domains accumulated on TB vaccines research.

ACKNOWLEDGEMENTS

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APPENDIX

Controlled Vocabulary of the National Library of Medicine

MeSH Terms. The MeSH is the National Library of Medicine’s Medical Subject Headings controlled vocabulary of biomedical terms that is used to describe the main subjects or topics of each journal article belonging to MEDLINE. The MeSH contains more than 23,000 terms and is updated annually to reflect changes in medicine and medical terminology. MeSH terms are arranged hierarchically by subject categories with more specific terms arranged beneath broader terms. Skilled subject analysts examine journal articles and assign to each the most specific MeSH terms applicable, typically 10 to 12. Applying the MeSH vocabulary ensures that the articles in PubMed are uniformly indexed by subject, whatever the author’s words.
MeSH Subheadings. MeSH subheadings are qualifiers of the MeSH terms to help describe more completely particular aspects of a subject. For example, the drug therapy of asthma is displayed as Asthma/drug therapy. Here Asthma is the MeSH term and drug therapy, written with lower case letters, is the associated MeSH subheading.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Subheadings for the MeSH BCG vaccine</th>
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</thead>
<tbody>
<tr>
<td>administration and dosage</td>
<td>immunology</td>
</tr>
<tr>
<td>adverse effects</td>
<td>instrumentation</td>
</tr>
<tr>
<td>agonists</td>
<td>isolation and purification</td>
</tr>
<tr>
<td>analysis</td>
<td>legislation and jurisprudence</td>
</tr>
<tr>
<td>antagonists and inhibitors</td>
<td>metabolism</td>
</tr>
<tr>
<td>biosynthesis</td>
<td>methods</td>
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<td>microbiology</td>
</tr>
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<td>pharmacokinetics</td>
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<td>pharmacology</td>
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<td>standards</td>
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<td>therapeutic use</td>
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<tr>
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<td>toxicity</td>
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<tr>
<td>history</td>
<td>veterinary</td>
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MeSH Major Topic. A MeSH term that is one of the main topics discussed in the article is denoted by an asterisk on the MeSH term or MeSH/subheading. Thus, if BCG is a central subject of an article it will be indexed by *BCG. Similarly an asterisk is associated to a subheading if it constitutes one of the main aspects of the topic treated in the article. So, Tuberculosis/*immunology would be linked to an article that does not focus on the TB disease but on immunological aspects of TB; it may also be associated with other major topics like *BCG Vaccine.
REFERENCES


SECTION 3 SUPPORTING TECHNOLOGIES FOR THE DEVELOPMENT OF NEW VACCINES


