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TITLE:
The Highest Cited Papers in Brucellosis: Identification Using Two Databases and Review of the Papers' Major Findings

ABSTRACT:
Citation classics represent the highest impact work in a given field. We aim to identify and analyze the most frequently cited papers on brucellosis. We used the databases Scopus and Web of Science to determine the most frequently cited papers. The most cited fifty papers in each database were identified. We then ranked the papers according to the highest citation count recorded from any of the two databases. The most frequently cited paper received 964 citations and was by DelVecchio VG et al. reporting the complete genomic sequencing of Brucella melitensis. The papers were published in 30 journals led by the "Infection and Immunity" journal and the "Veterinary Microbiology" journal (each had 7 papers). Citation classics in brucellosis were all in English except one in French and were mostly of basic science type. In addition, we noticed that 12 articles that were identified among the highest fifty articles in one database were missed by the other database and vice versa. Therefore, we suggest that searching in more than one database would detect additional citation classics.

1. Introduction:
Brucellosis is a zoonotic granulomatous disease that can affect any organ. It is caused by Brucella species which are small, Gram-negative, and coccobacilli bacteria. Clinical presentation varies from an acute, nonspecific febrile illness to chronic, debilitating forms with features of osteoarticular and neuropsychiatric abnormalities [1].
Brucellosis was first described in 1887 by David Bruce, a British surgeon, who isolated Gram-negative coccobacilli from the spleens of five British soldiers who died of fever in Malta. In 1905, Zammit, a Maltese bacteriologist, showed that infected goats transmitted brucellosis and that banning the use of their milk would be effective in eliminating the disease. The observation that apparently healthy goats could be carriers of the disease has been termed one of the greatest advances ever made in the study of epidemiology [2].
The disease has wide geographic distribution and it is one of the most economically important zoonosis. In a review of 76 diseases of animals, brucellosis lies within the top 10 in terms of impact on poor people [3]. In low-income countries, brucellosis is endemic and neglected. It also causes large disease in animals and people and lacks effective control [1, 4–6]. Accurate epidemiological data are not available for many endemic areas, but it has been estimated that more than 500,000 new human cases occur annually [7].
In 1987, Garfield listed the "top 100" best cited articles ever published in JAMA and named them "citation classics" [8], and these classics represent the highest impact work in a given field [9]. Citation analysis in the field of infectious diseases and microbiology was reported for tuberculosis [10], nontuberculous mycobacteria [11], anthrax [12], Severe Acute Respiratory Syndrome (SARS) [13], JC virus [14], herpes simplex virus [15], Ebola virus [16], schistosomiasis [17], sepsis [18], and neglected infectious diseases [19]. Here, for the first time to our knowledge, we identify and analyze the citation classics for brucellosis.

2. Materials and Methods:
Two electronic databases, Scopus and Web of Science (WOS), were searched for the 50 most cited articles using the keyword "brucell∗." For the search in Scopus, we selected the "title, abstract, keyword" choice. For the search in WOS, we selected the "topic" and "all database" choices. The search in both databases was performed on January 30, 2017, for papers published in all times. Textbooks were excluded. The most fifty cited papers were identified in both databases. The articles' abstracts were read by the two study investigators (FGB and MHA) to determine whether the articles were specific to brucellosis [20].
We recorded the citation count from the two databases for each selected article. For articles that were among the top fifty articles in one database but not in the other, the citation count in the other database for that article was looked up and recorded. We then ranked the articles according to the highest citation count obtained from any of the two databases.
We analyzed the papers according to number of citations, publication year, authors, journal impact factor, country of origin, and article type (basic science, observational study, interventional

clinical trial, and review) [21]. Basic science articles included genetic studies [22], in vitro studies, animal studies, or in vivo studies that focused on physiology [23]. Observational studies included case-control studies, case series, and cohort studies. To classify the article type, two study investigators (FGB and MHA) reviewed all articles independently and in cases of disagreement, they discussed the article until consensus was achieved [21]. The most recent impact factor, year 2015, from Journal Citation report was used for analysis. In cases where the journal has continued as a new title, the impact factor of the new title was used in the analysis [21].

3. Results:

The list of the most cited articles found in the Scopus and WOS searches is shown in Table 1. The list included 62 articles. Of the total articles, 38 articles appeared in both databases within the highest 50 cited articles. However, among the highest 50 cited articles that were identified by the Scopus search, 12 (24%) articles were not among the top 50 articles within the WOS search. Similarly, among the highest 50 articles that were identified by the WOS search, 12 (24%) articles were not among the highest 50 articles within the Scopus search. All articles eventually appeared in both databases except for one article (position 21) which appeared only in WOS. The mean number of the highest citation count per article from any of the two databases was 284.6 citations (SD = 192.7) and the median number was 197.5 (interquartile range = 169 to 314.5).

Articles that were identified within the highest 50 articles in WOS but not in the highest 50 article in Scopus were at positions 7, 8, 11, 21, 22, 29, 41, 49, 51, 55, 56, and 58. The publication year range was 1950–2011 (mean 1991, SD = 18.3). They were all of basic science type except one article with experimental design. While articles that were in the top 50 article search in Scopus but not in the top 50 article search in WOS were at positions 33, 35, 36, 39, 42, 44, 54, 57, 59, 60, 61, and 62. The publication year range was 1988–2010 (mean 1998, SD = 5.7). They were of observational type in 5 articles, review in 4, and basic in 3.

The oldest highly cited article was published in 1950 (Harris, JAMA) and the most recent in 2011 (Tae et al., Journal of Bacteriology). The most frequently cited paper received 964 citations (Table 1). The decade from 2000 to 2009 produced the most papers with 30 articles (Figure 1). The most papers published within a given year were 9 in year 2002. Among the citation classics, there were 36 (58%) basic science articles, 16 (26%) review articles, 9 (15%) observational studies, and 1 (1.6%) experimental study.

The papers were all in English except one in French (position 21 by Renoux et al. in 1971). They were published in 30 journals. The median impact factor for journals was 4.32 (range: 1.064 (Comptes Rendus Biologies)–59.558 (New England Journal of Medicine)) (Table 2). Five journals have continued as new titles: Reviews of Infectious Diseases as Clinical Infectious Diseases, International Journal of Systematic Bacteriology as International Journal of Systematic and Evolutionary Microbiology, Journal of Tropical Medicine and Hygiene as Tropical Medicine and International Health, Quarterly Journal of Medicine as QJM: An International Journal of Medicine, and Comptes Rendus Hebdomadaires des Seances de l Academie des Sciences Serie D as Comptes Rendus Biologies.

The most productive author was Grovel PJ who had 7 articles (Table 3). Authors came from 26 countries. Authors from the United States of America (USA) contributed to the highest number of articles with 21 (34%) articles, followed by France, 20 (32%), and Spain, 8 (13%) (Table 4). Of the total articles, 17 (27.4%) were from multinational collaboration.

4. Discussion:

Our results provide a clear picture of the main cited articles in brucellosis research publications history. For example, in the group of genome sequencing, we find at positions 1, 2, 5, 7, and 22 the articles that reported the complete genome sequence for Brucella melitensis, Brucella suis, Brucella abortus strain 9-941, B. abortus strain 2308, and Brucella ovis, respectively. At position 11, we find the first report of sequencing a vaccine strain (B. abortus S19) by Crasta et al. in 2008. The most recent article by Tae et al. in 2011 (position 8) reported on the resequencing of B. suis. In the group of articles on new species identification, we find the following: at position 38, Foster et al. in 2007 studied small, Gram-negative coccobacilli resembling Brucella bacterial strains that have been reported from marine mammals since the mid-1990s. The study led to description of two novel species: Brucella ceti and Brucella pinnipedialis. At position 52, Scholz et al. in 2008 described two strains of Brucella microti as novel species. The strains had been originally isolated from clinical specimens of diseased wild common voles (Microtus arvalis) during an epizootic in Czech Republic [24]. At position 54, in 2003, Sohn et al. published the first report of community acquired human infections with marine mammal-associated Brucella in two patients. Both

patients were young men from Peru and the route of infection was not discovered [25]. At position 20, Verger et al. in 1985 challenged the separation of Brucella into different species and proposed that several biovars should be placed under a single species only: B. melitensis [26, 27].

In the group of articles on molecular diagnostic tests, we find the following: Bricker et al. (position 18, in 1994) described a PCR assay that can identify and differentiate most Brucella species and biovars found in the United States. Prior to this assay, PCR assays did not discriminate among species. Baily et al. (position 25, in 1992) developed the first PCR assay around the Brucella cell surface protein (bcsp31). This target became one of the most popular targets used in molecular assays [28]. Romero et al. (position 61, in 1992) published a Brucella 16S rRNA based PCR assay, and although similar assay was previously described by Herman and De Ridder in 1992 [29], the assay by Romero et al. was taken up more widely [28].

In the group of articles on vaccination, we find the following: at position 13, Schurig et al. in 1991 produced a live attenuated RB51 strain for vaccination. "R" stands for "rough," "B" for Brucella, and "51" for an internal laboratory nomenclature used at the time it was derived. The vaccine has become one of the most commonly used vaccines [30]. At position 21, Renoux et al. in 1971 showed that levamisole treatment of B. abortus-vaccinated mice resulted in improved protection from virulent Brucella organisms. This finding triggered a flow of papers dealing with experimental and clinical effects of levamisole [31]. Schurig et al., at position 27, and Ko et al., at position 46, present a review on Brucella vaccines.

In the group of articles on pathogenicity, we find the following: O'Callaghan et al. in 1999, at position 15, were the first to identify a new member of type IV secretion system family encoded by virB operon in B. suis during a screen for virulence factors. They also showed that the system is essential for the intracellular growth during infection [32]. The system is one of few classical virulence factors identified to date [33]. The type IV secretion system is a pumping system that selectively transports proteins or other macromolecules through membranes [34]. After Brucella is taken up by vesicles in macrophage, acidification is thought to induce VirB expression. The VirB system interacts with components of the endoplasmic reticulum, neutralising the pH and allowing the Brucella to undergo regulated cell division [34]. Other classics that further explored this system include Celli et al. in 2003 (position 16), Comerci et al. in 2001 (position 31), Boschiroli et al. in 2002 (position 34), Sieira et al. in 2000 (position 40), Kohler et al. in 2002 (position 47), and Hong et al. in 2000 (position 50). In addition, Sola-Landa A et al. in 1998 (position 45) identified the BvrR/BvrS system for the first time in B. abortus (Bvr: Brucella virulence related; R: regulatory; S: sensory). At present, the BvrR/BvrS system is one of the best characterized two component systems. Two component systems allow the bacteria to sense their environment and subsequently modulate the expression of genes [35].

Three large case series appear in the list of classics: Colmenero et al. (position 10), Buzgan et al. (position 36), and Lulu et al. (position 39). The report by Buzgan et al. in 2010 described the clinical manifestations of 1028 cases of brucellosis and was considered to be the largest case series until that time [36]. Other case series in the list were on vertebral osteomyelitis (positions 26 and 33) and neurobrucellosis (positions 35 and 43).

The oldest citation classic article was published in 1950 and was at position 29. It was by Harris who described the side effects associated with the use of aureomycin and chloramphenicol in treatment of brucellosis. Prior to the development of these treatments, chemotherapy of brucellosis yielded unsatisfactory results [37].

The list of classics did not include any article on outbreaks. We suggest the following explanations: (a) papers on Brucella outbreaks receive lower citations compared to articles in basic science: in both databases (Scopus and WOS) the highest cited article on brucellosis outbreaks was "Canine Brucellosis: Outbreaks and Compliance, Theriogenology, 2006" (78 citations in Scopus and 72 citations in WOS); (b) outbreaks in Brucella have been recognized at very early time; therefore, their findings might have become well known: we found reports of outbreaks as early as 1939 (Water-Borne Outbreak of Brucella melitensis Infection. Am J Public Health Nations Health, 1939); (c) identifying Brucella outbreaks could be difficult: Brucella is difficult to detect and identify [38]; and (d) Brucella species are genetically homogeneous, and thus, the typing of Brucella species for epidemiological purposes by conventional molecular typing methods has remained elusive [39].

We also observed the lack of papers on brucellosis in animal health and for this we suggest two explanations: (a) journals in the categories of agriculture and food sciences receive fewer citations than those in basic and clinical sciences as evidenced by the impact factor in these categories. For example, in the WOS, in the categories of "agriculture, dairy, and animal sciences" and "food science and technology," the highest impact factor for a journal was 4.7 and 7.3, respectively.

While in the category of "medicine, general and internal" and "microbiology," the highest impact factor for a journal was 72 and 23.6, respectively. (b) The possible low productivity of research that is performed on Brucella as evidenced by the lower number of articles on Brucella in agricultural journals. For example, a combined search for the word "brucell∗" and the journals "Veterinary Research" and "Journal of Dairy Science" yielded 20 and 25 papers, respectively, while the same search in the journals "Clinical Infectious Diseases" and "Journal of Bacteriology" yielded 52 and 237 papers, respectively. Furthermore, we doubt that our search missed important journals from the agricultural fields because the databases Scopus and WOS include large collection of agricultural journals. Scopus has 2608 journals included under the "agricultural and biological sciences" subject area and WOS has 58 journals included under the category "agriculture, dairy, and animal sciences" and 130 journals under the category "food science and technology."

Studies on citation classics that used more than one databases are few and have ranked the articles according to the mean of the citation counts in the databases [40–43]. Here, we ranked the articles according to the highest obtained citation count from any of the two databases. We believe that our method is more accurate because relying on the mean for ranking might lower the rank of a given article. This is because the databases differ in reporting the citation count for a particular article. The variation in citation count between databases results from differences in journal coverage and quality [44]. Scopus includes a more expanded spectrum of journals than WOS, and its citation analysis is faster and includes more articles than the citation analysis of WOS [45]. However, Scopus tends to miss older citations which results in omission of studies before 1980 [46, 47]. Here, we identified 12 articles that were listed in the highest 50 articles in one database but were not identified within the highest 50 articles in the other database and vice versa. Articles that were identified by WOS and not by Scopus tended to be older and of basic science type, while articles identified by Scopus and not by WOS were more recent and mostly of observational and review type.

We found that many countries had contributed to the classics including American, European, African, and Mediterranean countries (Table 3). This might reflect the epidemiological distribution of Brucella. In addition, the finding that the most recent classic article was in 2011 indicates that brucellosis is a dynamic field of study [21, 48–51].

Our study has several limitations that are similar to other studies in citation classics [21]. These limitations include the presence of inherent problems in the citation process itself, for example, incomplete or inappropriate citations, biased citation [44, 45, 52, 53]; changes in the list of citation classics with time making it a snapshot of the current state of research [54]; absence of articles with languages other than English which is mostly because authors are more likely to cite articles in their own language, and English articles are more likely to be cited overall [20]; and finally, missing of important studies because their findings became well known [55]. The latter point is relevant here because brucellosis was discovered in 1887 and it is possible that some important studies were not indexed in current database but their findings are now considered well known. Despite these limitations, the study provides a picture for the main cited articles in brucellosis research publications since the discovery of Brucella 130 years ago.

In conclusion, the citation classics in brucellosis were (a) all in English except one in French, (b) contributed by authors from several countries where brucellosis was or is still endemic, (c) mostly of basic science type, and (d) published in relatively high numbers in recent years indicating a dynamic field of study. In addition, we suggest that performing the search in more than one database would detect additional articles.