












One health implications of bovine leukemia virus seroprevalence: a global systematic review and meta-analysis

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Evidence in Context

- Global pooled seroprevalence of BLV in cattle was found to be 26.8%.
- Significant heterogeneity observed, with seroprevalence ranging from 0% to 78%.
- Dairy cattle specifically showed a 28% prevalence rate of BLV.
- Subgroup analysis revealed variable seroprevalence based on country and testing method.
- Recommends comprehensive management and further research due to zoonotic potential and economic impacts.

To view Article



Abstract

Background: Bovine Leukemia Virus (BLV) has significant repercussions for one health and the global livestock industry. Understanding its global seroprevalence is crucial for informed decision-making and management strategies. The systematic review aims to determine the overall seroprevalence of BLV in cattle.

Methods: A systematic review was undertaken by searching literature from various databases such as PubMed, Scopus, Web of Science, and Embase until January 03, 2024. Inclusion criteria comprised studies that examined bovine samples for Bovine Leukemia Virus (BLV) and provided information on both the total sample size as well as the number of positive cases. Utilizing a random-effects model, a meta-analysis was conducted. Subsequently, a subgroup analysis was conducted, categorizing the results based on the type of testing method used and the classification of cattle. The statistical computations were carried out utilizing R software version 4.3.

Results: From the 48 studies included, 101,120 samples were tested, revealing a pooled prevalence of 26.8% (95% CI: 20.0% – 33.0%) for BLV in cattle with an $I^2=100\%$. Subgroup analysis based on the type of testing or country did not show any difference in prevalence. Of the studies, thirty focused on dairy cattle samples. A meta-analysis of these samples, drawn from a total of 75,769 dairy cattle, revealed a prevalence of 28% (95% CI: 19% – 39%) with an I^2 of 100%.

Conclusion: A significant prevalence of BLV in cattle was detected, emphasizing the need for comprehensive management strategies. Future research should thoroughly explore BLV infections, considering its effects on livestock and human health.

Keywords: one health, seroprevalence, systematic review, global health, bovine leukemia virus

Introduction

Bovine Leukaemia Virus (BLV) stands as a potent concern in the livestock and dairy industry, primarily due to its association with the onset of enzootic bovine leucosis (EBL) or, more commonly, bovine leucosis. As a member of the deltaretrovirus category within the *Retroviridae* family, BLV has piqued scientific interest for more reasons than one. The correlations this virus exhibits with the human T-cell leukaemia virus types 1 and 2 (HTLV-1 and -2) as well as the simian T-cell leukaemia viruses (STLVs) underlines its potential implications beyond the realm of cattle health [1-3]. Extensive research has illuminated the potential of certain viruses within this group to influence growth-related or neurological disturbances in not just cattle, but also in humans and other primates [2,4]. This broad spectrum of potential influence underscores the urgency of understanding BLV more comprehensively. In cattle, a BLV infection manifests in the form of a discernible weakening of their immune response, even in stages of the disease that are typically considered inactive. Such immune suppression does not merely denote a health concern; it has direct implications on cattle's productivity, affecting dairy and beef output [5].

For dairy farmers and the beef industry, an animal affected by BLV is an asset compromised. Not only is the animal's health at risk, but the efficiency with which it produces milk or gains weight is notably diminished [6]. As such, BLV doesn't just pose as a veterinary or biological concern; it's an economic challenge, making its understanding crucial for the larger livestock industry. Yet, the threat of BLV is not just confined to individual cattle or farms. The contagion has a capability for widespread transmission, potentially influencing entire cattle populations. When one factors in the extensive interconnectivity of the global livestock trade, the ramifications of a BLV outbreak take on international proportions [7]. Food safety, international livestock trade agreements, and even consumer trust hinge on how well the industry can manage and mitigate the risks associated with BLV.

Over the years, numerous studies have tried to address the prevalence, spread, and impacts of BLV. For instance, research has shown varying prevalence rates across different regions, with some studies indicating a high seroprevalence in countries like the USA and Japan, while others report lower rates in regions such as Europe and Africa [6,8-11]. However, the nature of scientific research often means that findings can vary based on myriad factors. Regional differences, variances in methodology, differences in sample sizes, or even the specific focus of a study can yield diverse results. While each study provides a piece of the puzzle, what is critically needed is a cohesive, comprehensive understanding that can only come from an aggregation and synthesis of all available research. This would pave the way for informed decisions, be it in farm management, livestock trade policies, or even in the arena of consumer information. It's against this backdrop that this systematic review and meta-analysis aims to present a synthesized perspective. By collating data from primary studies and analyzing them holistically, the aim of this systematic review and meta-analysis was to evaluate the prevalence of Bovine Leukemia Virus (BLV) in cattle serum through the examination of aggregated data derived from prior primary research studies.

Methods

Overview

This systematic review, following PRISMA guidelines **Table S1** [12], focused on the prevalence of BLV in cattle serum. It included observational studies from any region, in English, detailing both total and BLV-positive sample counts, with no restrictions on detection methods. The literature search spanned major databases, up to January 03, 2024. Two independent reviewers conducted screening and data extraction using the Nested Knowledge software, a tool for executing systematic reviews, and employed the Modified Newcastle-Ottawa Scale to assess quality. The meta-analysis employed a random-effects model, with heterogeneity assessed using I² and tau-squared metrics. Subgroup analyses and publication bias assessments were also conducted, with all analyses performed using R software.

Inclusion criteria

The research question is: What is the prevalence of BLV in cattle serum? Primary studies employing any observational design reporting the prevalence of BLV in cattle serum were eligible for inclusion

In this review. Commentaries, narrative reviews, conference abstracts, and the like were excluded. Only articles that were published in the English language were taken into consideration. Suitable studies for this review were those that reported both the total number of samples and the samples in which the presence of BLV was identified. We placed no restrictions on the method used for BLV detection. Studies from any geographical location and involving any type of animal where BLV was detected were included. **Table S2** shows detailed inclusion and exclusion criteria.

Literature search

A comprehensive literature search was conducted utilizing various databases such as PubMed, Scopus, EMBASE, and Web of Science up to the 15th of September, 2023., with subsequent updates conducted on 3rd January 2024. The search strategy incorporated various keywords related to BLV and animal populations. A detailed description of the search strategy can be found in **Table S3**.

Screening and study selection

Two independent reviewers were tasked with the screening and selection of articles. The screening process comprised two stages: initial screening involved reviewing the title and abstract, followed by a detailed evaluation of the full text to determine eligibility. Screening activities were facilitated through the utilization of the Nested Knowledge software.

Data Collection and Quality Evaluation

Data extracted from the analyzed studies was collected by two reviewers. The data that was extracted pertained to various aspects such as the author's identity, year of publication, geographical location, species of animal studied, number of samples in which BLV was identified, total number of samples tested, and the methodology utilized for BLV detection. An assessment of the included studies was carried out by employing the Modified Newcastle-Ottawa Scale (NOS), resulting in an overall score of 6.

Statistical analysis

A meta-analysis was performed to determine the aggregated prevalence of BLV presence within cattle serum. The examination involved the quantification of BLV positive samples and the total samples tested. The synthesis of findings from various studies was performed using a random effects model. The degree of heterogeneity between the studies was evaluated using the I² and tau-squared metrics [13,14]. Both metrics have the capacity to fluctuate within a range of 0% to 100%, where elevated figures suggest a higher level of inconsistency. The utilization of the 95% prediction interval served the purpose of emphasizing this inconsistency [15]. Statistical significance was determined by a p-value of less than 0.05. The tau-squared value was calculated through the maximum likelihood approach. Subgroup analyses focused on variables such as testing technique, country of study, and type of dairy cattle. To identify possible publication biases, a funnel plot was utilized. The leave-one-out method was applied to evaluate the influence of individual studies on the overall result. R software, specifically version 4.3, was used for all statistical analyses [16].

Results

Literature search

A comprehensive search across various databases yielded 6,147 articles. Of these, 3,379 were identified as duplicates. After reviewing 2,768 articles, 2,502 were excluded in the preliminary screening. A total of 266 publications underwent thorough scrutiny, with 45 research works meeting the requirements for inclusion. Additionally, 7 publications were uncovered through citation exploration, however, merely 3 satisfied the inclusion criteria. After conducting an extensive review, a total of 48 studies were included into the analysis. The methodology for selection and screening is visually depicted in Figure 1.

Characteristics of included studies

A total of 48 studies were found eligible in this review. The countries of origin for these studies varied. Six studies were from Iran [17-22] followed by six studies from USA [6,9,10,23-25]. Japan

[26-29], Colombia [7,30-32], and Egypt [33-36] each contributed four studies. China provided five studies [37-41]. Both Turkey [8,42] and Taiwan [11,43] had two studies each, as did Pakistan[44,45] and Vietnam [46,47]. The remaining countries, namely Korea [48], Germany [49], India [50], Namibia [51], Iraq [52], Bolivia [53], Zambia [54], Brazil [55], the Philippines [56], Argentina [57], and Canada [58], each had a single study. While some studies specifically focused on dairy cattle, others differentiated between the type of animal, such as buffalo or dairy cattle. The studies varied in their sample sizes, with the smallest study sampling 61 animals and the largest encompassing 28,982. In terms of testing techniques, ELISA was the most commonly employed, used in 25 studies. Nested PCR was used in 17 studies, while Western blotting was utilized in 4 studies, and agar gel immunodiffusion test (AGID) was chosen for 2 studies. Table 1 presents an overview of the key features of the studies. Based on the quality assessment using the NOS scale (0-6), 9 studies were of very low quality, 19 studies were of low quality, 16 studies were of moderate quality, and 4 studies were of high-quality in **Table S4**.

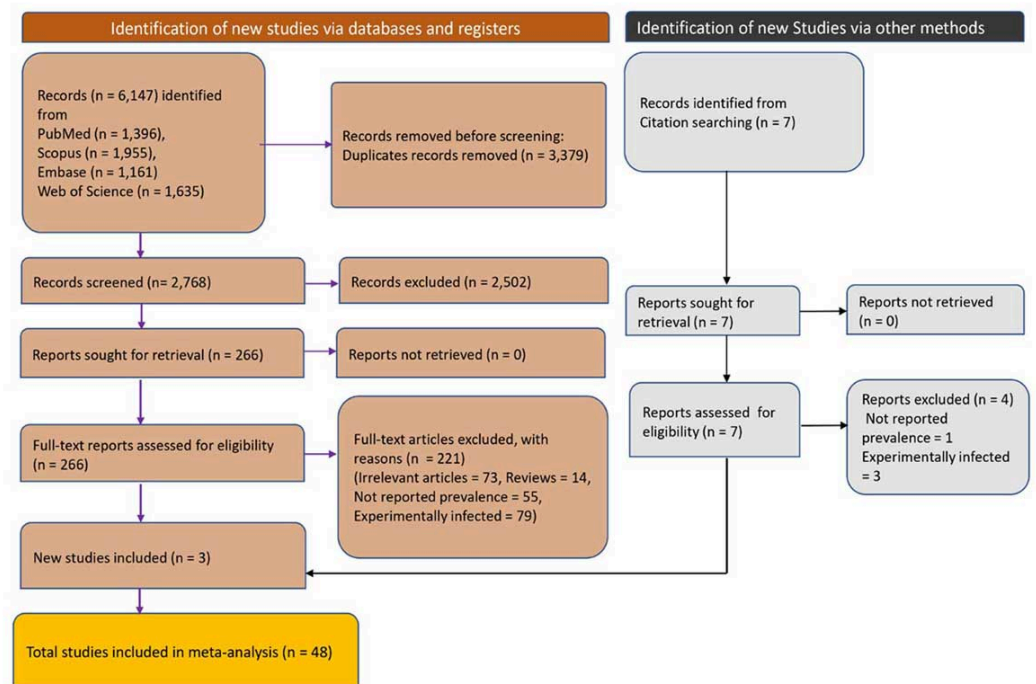


Figure 1. PRISMA flow diagram depicting the screening and selection process of studies.

Prevalence of BLV in cattle

We performed a meta-analysis using results from 48 studies that involved a total of 101,120 samples tested. A pooled prevalence of 26.8% (95% CI: 20.0% – 33.0%) was found for BLV in cattle. The analysis revealed significant heterogeneity with an I² value of 100% and a prediction interval of 0% - 78%. **Figure 2** illustrates the forest plot of the overall meta-analysis.

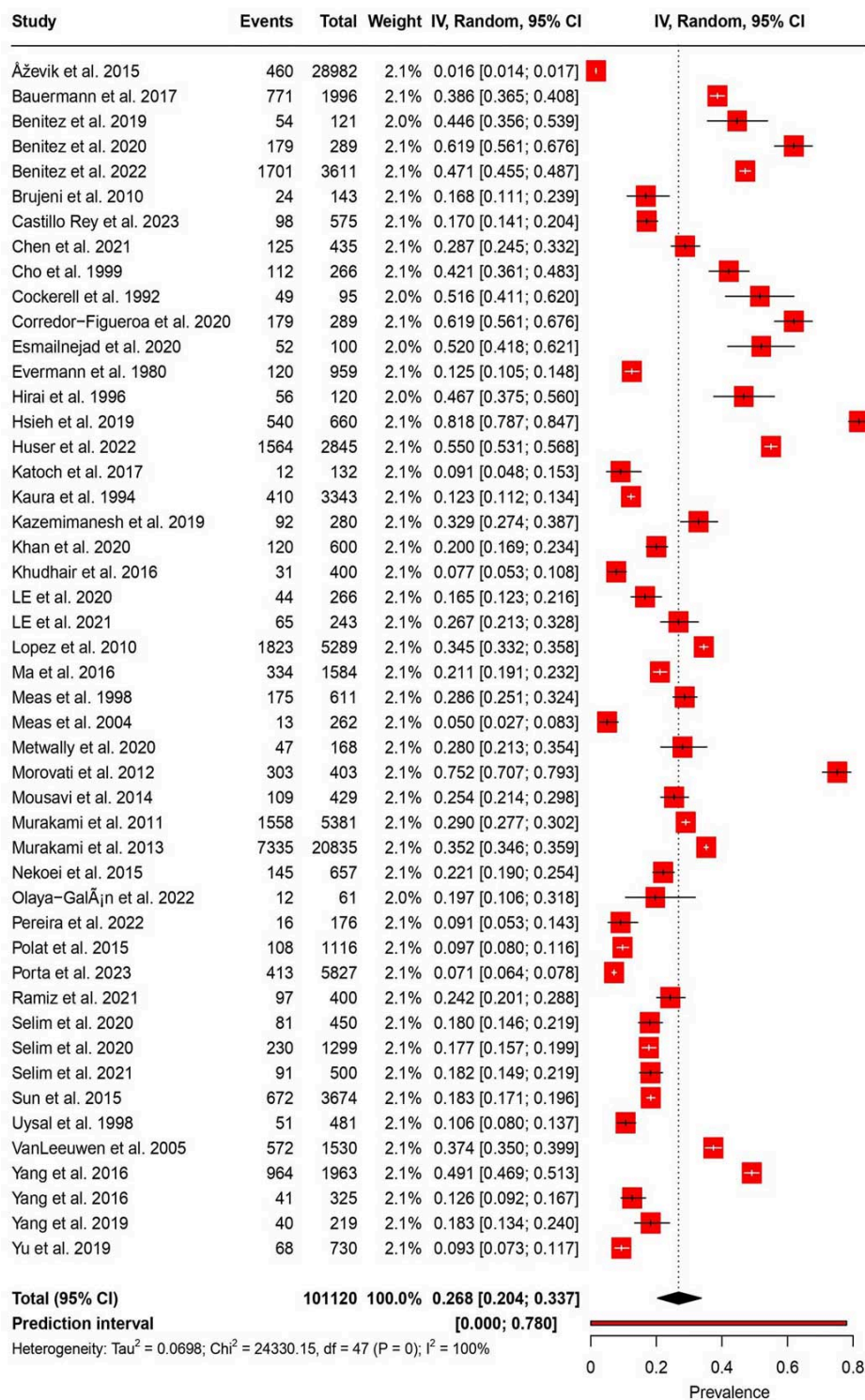


Figure 2. Forest plot depicting the overall pooled prevalence of BLV in cattle.

Thirty studies focused on dairy cattle samples. Meta-analysis of these samples, drawn from a total of 75,769 dairy cattle, revealed a prevalence of 28% (95% CI: 19% – 39%). There was significant heterogeneity with an I² of 100% and a prediction interval ranging from 0 to 87%. Figure 3 illustrates the forest plot of BLV prevalence in dairy cattle.

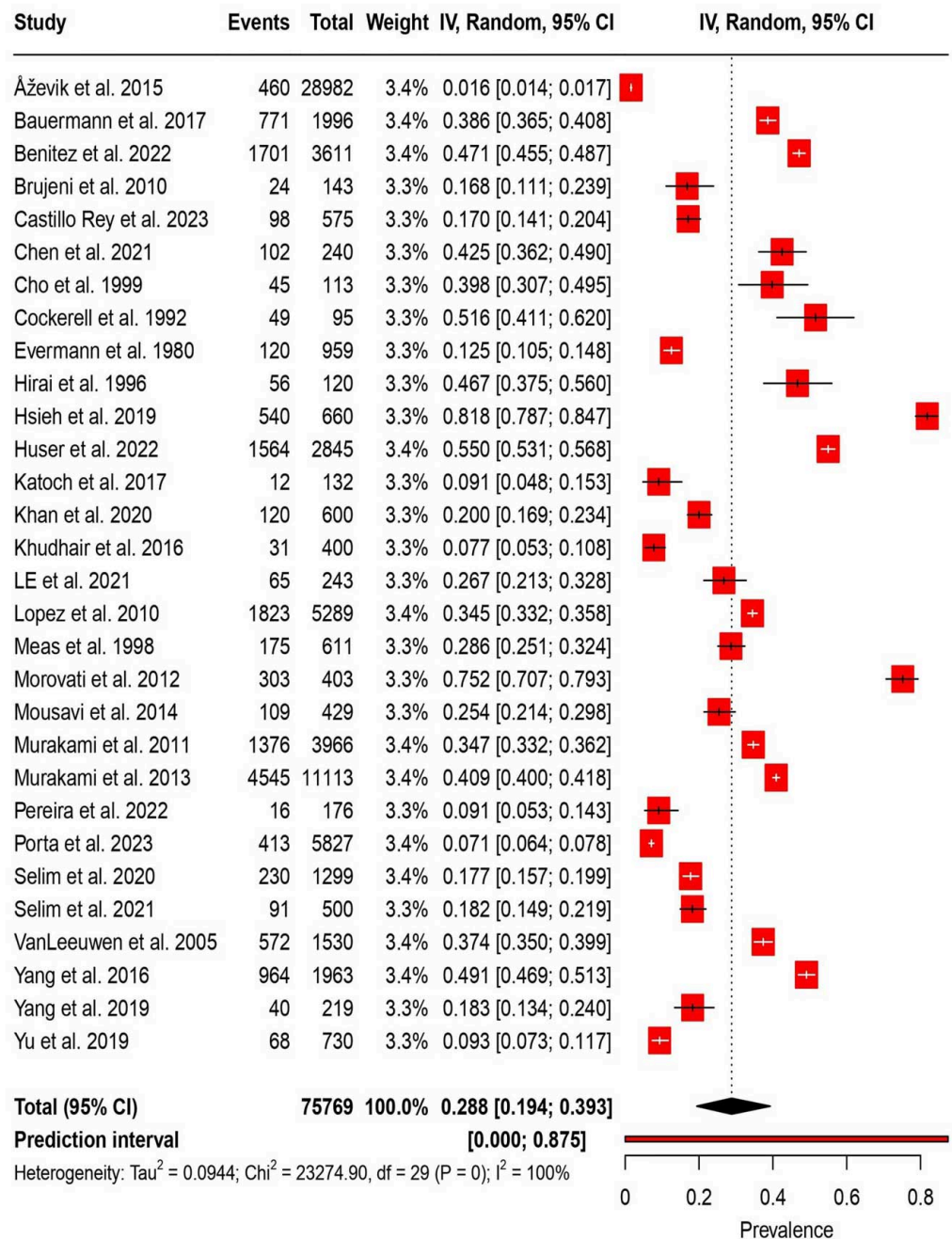


Figure 3. Forest plot illustrating the prevalence of BLV in dairy cattle

Subgroup analysis

We performed subgroup analysis based on country and testing techniques. **Table 2** summarises the results of the subgroup analysis.

From Turkey, two studies comprising 29,463 samples indicated a prevalence of 5% (95% CI: 0% – 17%) with an I² of 99%. The USA, with six studies and 8,993 samples, showed a prevalence of 40% (95% CI: 31% – 50%) and an I² of 98%. Four studies from Colombia, which tested 1,214 samples, revealed a prevalence of 39% (95% CI: 14% – 67%) with an I² of 99%. Iran's six studies with 2,012 samples demonstrated a prevalence of 36% (95% CI: 5% – 66%), and an I² of 99%. Taiwan, based on two studies and 1,095 samples, reported a prevalence of 56% (95% CI: 8% – 95%) and an I² of 100%. Korea's single study of 266 samples yielded a prevalence of 42% (95% CI: 36% – 48%). One study from Germany with 959 samples reported a 12.5%

Prevalence (95% CI: 10% – 14%). Japan, with four studies involving 26,947 samples, found a prevalence of 33% (95% CI: 28% – 38%) and an I^2 of 97%. India's single study of 132 samples showed a 9% prevalence (95% CI: 4% – 15%). Namibia's study with 3,343 samples indicated a 12% prevalence (95% CI: 11% – 13%). From Pakistan, two studies involving 1,000 samples reported a prevalence of 21.5% (95% CI: 18% – 26%) with an I^2 of 61%. Iraq, with one study and 400 samples, reported a 7% prevalence (95% CI: 5% – 10%). Vietnam's two studies of 509 samples showed a prevalence of 21.5% (95% CI: 12% – 32%) and an I^2 of 87%. Bolivia's study with 5,289 samples indicated a prevalence of 34% (95% CI: 33% – 35%). Five studies from China, testing 8,170 samples, reported a prevalence of 22% (95% CI: 10% – 36%) and an I^2 of 99%. Zambia's single study of 262 samples indicated a 5% prevalence (95% CI: 2% – 8%). Egypt, across four studies with 2,417 samples, found a BLV prevalence of 19% (95% CI: 16% – 22%) and an I^2 of 68%. Brazil's study of 176 samples reported a 9% prevalence (95% CI: 5% – 14%). The Philippines, with one study and 1,116 samples, found a 9% prevalence (95% CI: 8% – 11%). Argentina's study with 5,827 samples showed a 7% prevalence (95% CI: 6% – 7%). Finally, Canada's single study, involving 1,530 samples, indicated a prevalence of 37.5% (95% CI: 35% – 39%). **Figure S1** illustrates the forest plot for this subgroup analysis based on countries.

A subgroup analysis was conducted according to the specific testing methodology used. For ELISA, 25 studies involving 84,542 samples found a prevalence of 29% (95% CI: 19% – 39%), with an I^2 of 100%. Nested PCR was employed in 17 studies and indicated a prevalence of 23% (95% CI: 14% – 34%). Western blotting was used in 4 studies, testing 1,259 samples, and showed a pooled prevalence of 28% (95% CI: 11% – 48%), with an I^2 of 98%. AGID, also used in 2 studies with 6248 samples, revealed a prevalence of 22% (95% CI: 5% – 47%), and an I^2 of 100%. **Figure S2** illustrates the meta-analysis of the pooled prevalence of BLV by type of testing technique. The prevalence of seroprevalence BLV according to geographical location is given as **Figure 4**.

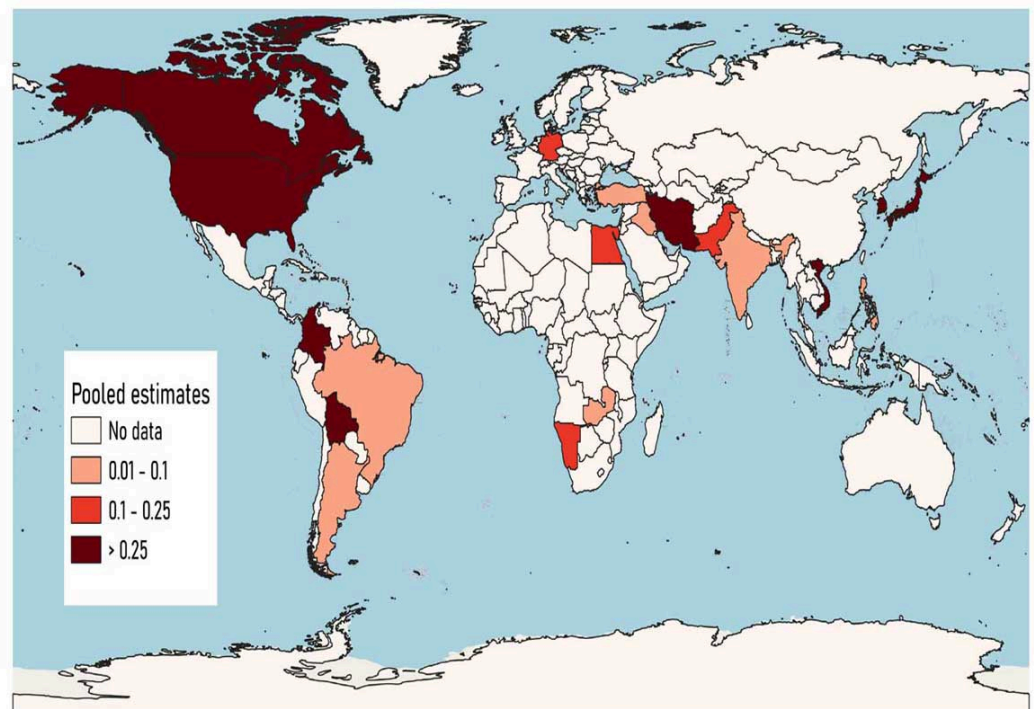


Figure 4. Seroprevalence of BLV in various geographical areas.

Sensitivity Analysis and Meta-regression

The leave-one-out method was utilized to assess the impact of individual studies on the overall heterogeneity and prevalence. This analysis helped identify how each study influenced the collective results. However, Figure S3 did not reveal any noteworthy variance in outcomes. Meta-regression was performed to assess the correlation between the year of publication and the prevalence of BLV. Notably, no significance was found between the year of publication and prevalence ($p=0.819$). A bubble plot illustrating the meta-regression results is presented in Figure S4.

Publication Bias

Publication bias was evaluated through the utilization of a Funnel plot Figure S5 and the Egger test, revealing an indication of potential bias ($p=0.04$). The presence of this bias could be attributed to the tendency for studies yielding significant or positive outcomes to be more readily published, as opposed to those producing null or negative results which are less inclined to be included in the literature.

Discussion

To our utmost understanding, this study represents the primary comprehensive evaluation conducting a meta-analysis on the frequency of BLV in bovine serum across global. We found a prevalence of 26.8% for BLV in cattle serum. However, there was significant heterogeneity in the data. Even the subgroup analysis and meta-regression couldn't fully account for the source of this heterogeneity. There might be undiscovered confounding variables influencing the study results. One potential source of heterogeneity could be the method of the study itself, although the type of testing did not show any significant difference in the pooled prevalence. Another possibility can be the difference in the breed of cattle tested.

A prior meta-analysis explored the link between BLV and breast cancer, a subject that continues to be contentious. In addressing this, a systematic review and meta-analysis were conducted, drawing data from five major databases and analyzing nine case-control studies. The findings indicated a significant association between BLV infection and an increased risk of breast cancer, with an odds ratio of 2.57. This suggests that controlling BLV in cattle and monitoring dairy products might reduce the risk of transmission to humans [59]. Another study analysed the existence of the virus in specimens obtained from humans, specifically in paraffin-embedded breast tissue and peripheral blood collected from a cohort of 10,398 subjects, employing a combination of serological and molecular methodologies. The findings unveiled a general virus detection prevalence of 27%, fluctuating within a range from 17% to 37% [60].

The prevalence of BLV in cattle serum, as indicated in this review, raises questions about potential implications for both public health and the livestock industry. With a notable percentage of cattle testing positive for BLV in various regions, it brings forth discussions about the potential risk of transmission to humans, particularly when considering studies that hint at a possible link between BLV and certain human health conditions like breast cancer. Policymakers might want to reflect on the benefits of enhancing livestock screening processes, considering the initiation or strengthening of national BLV control programs, and supporting research to further investigate BLV's possible zoonotic impacts. Raising public awareness about the potential benefits of choosing pasteurized dairy products and safely handling cattle could be explored. For the livestock industry, pondering over the idea of a BLV-free certification for dairy and beef products could potentially minimize health concerns and might have implications for market positioning, especially in regions where health-conscious consumers are prevalent. A balanced approach that integrates these considerations might help in understanding and possibly mitigating the challenges associated with BLV prevalence.

Our study emphasized the need for deeper investigations into the intricacies of BLV infections, both within cattle populations and potential zoonotic transmissions. Future research should prioritize longitudinal studies utilizing a one-health approach to understand the progression and dynamics of BLV infections in varied cattle breeds, human health, and environmental conditions. Additionally, as the source of the significant heterogeneity in BLV prevalence across studies remains elusive, there's a pressing need to delve into potential confounding factors—be it genetic variations in cattle, differences in farming practices, or divergent BLV strains. An exploration into the socio-economic impact of BLV on livestock farming would provide a more holistic view of the issue at hand. More importantly, as concerns rise about the potential transmission to humans, dedicated studies are needed to elucidate the mechanisms of such transmissions, if they occur, and their subsequent impacts on human health. As technology advances, employing machine learning and bioinformatics tools can aid in sifting through vast data sets to pinpoint patterns or anomalies that might have previously gone unnoticed. Through coordinated international efforts, future research can present clearer insights and pave the way for informed interventions against BLV.

Our investigation presents a number of limitations that necessitate examination. First and foremost, the limited focus on English-language publications could have caused the exclusion of pertinent research conducted in different languages, possibly introducing a partiality or distortion of the worldwide BLV prevalence. Moreover, despite our rigorous efforts, the root cause of the pronounced heterogeneity among the studies remained unresolved, leaving unanswered questions about underlying variables or confounding factors influencing the reported BLV prevalence. The geographical distribution of studies also posed a challenge; the unavailability of studies from many countries means our findings might not truly represent global BLV prevalence, highlighting disparities in research output across regions. Additionally, the high heterogeneity observed in BLV prevalence can be attributed to several potential confounding factors, including regional differences influenced by environmental conditions and local farming practices, and methodological variations (e.g., study design, and sample sizes). Temporal factors reflecting changes in disease management and diagnostic technologies, genetic variations among cattle breeds, and variations in sample handling and quality also contribute to inconsistent results. Furthermore, publication bias, where studies with significant findings are more likely to be published, and differences in study quality further exacerbate heterogeneity. Addressing these confounding factors in future research will help provide more accurate and consistent estimates of BLV prevalence. This inherent bias underscores the need for researchers to include both positive and negative outcomes to ensure a balanced view. Future studies should seek to address these limitations to provide a more comprehensive and precise understanding of BLV prevalence and its implications.

Conclusion

This investigation demonstrates a substantive seroprevalence of BLV across global cattle populations, highlighting the necessity for a multidisciplinary One Health approach to tackle the complexities associated with BLV. Intersectoral collaboration among policymakers, agricultural stakeholders, and the scientific community is imperative to devise and implement strategies that address the interlinked health of animals, humans, and ecosystems. Future research endeavors should rigorously investigate the zoonotic potential of BLV and assess its broader implications on public and animal health within the framework of ecological and socioeconomic variables. By adopting a One Health perspective, our understanding of BLV can be enhanced, fostering more resilient agricultural practices and bolstering the overarching public health infrastructure.

Supporting information

Provided: Supplementary Tables S1, S2, S3 and S4 and Supplementary Figure S1, S2, S3 and S4.
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Ethical Considerations

None

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Author contribution statement

The study's conception and design were led by Ganesh Bushi, Sai Mahesh Vajjala, Furqan B. Irfan. Data acquisition was performed by Dipanshu Aggarwal, Safayet Jamil, Drishti Sagar. Data analysis and interpretation were conducted by Alwin Kurian Raju, Mithun Mohan George, Aditi Pal. Manuscript drafting involved the collaboration of Ali A. Rabaan, Muhammed Shabil*. Critical manuscript revision was undertaken by Ganesh Bushi, Sai Mahesh Vajjala, Furqan B. Irfan, Dipanshu Aggarwal, Safayet Jamil, Drishti Sagar, Preetha S, Alwin Kurian Raju, Mithun Mohan George, Aditi Pal, Ali A. Rabaan, Muhammed Shabil*. Final approval for submission was granted by all authors.

All authors attest they meet the ICMJE criteria for authorship and gave final approval for submission.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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