zoonotic diseases

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Systematic Review

Seroprevalence of *Coxiella burnetii* in Occupational Settings: A Meta-Analysis of Italian Studies

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Simple Summary: Q fever is a disease caused by the bacteria *Coxiella burnetii*. This pathogen usually infects some animals (i.e., goats, sheep, and cattle), their birth products (i.e., placenta, amniotic fluid), as well as urine, feces, and milk of infected animals. Albeit quite rarely, humans can get infected by breathing in dust that has been contaminated by feces of infected animals, handling products contaminated by urine and birth products, as well as by drinking the milk from infected animals. In other words, people working in farm settings are at high risk of developing this disease. Interestingly, the actual occurrence of this disease is unclear, as some people never get sick, and the large majority of the infected only develop flu-like symptoms including fever, chills, fatigue, and muscle pain.

Abstract: *Coxiella burnetii* (*C. burnetii*) can cause a serious human disease known as Q Fever (QF). Our study summarized seroprevalence data from occupational settings in Italy, a country characterized by low notification rates of QF (17 cases between 2015 and 2021). Through systematic research on 3 databases (PubMed, EMBASE, MedRxiv), all studies including seroprevalence rates of *C. burnetii* in Italy were retrieved, and their results summarized and compared. We identified a total of 7 articles for a total of 1178 workers, mostly from agricultural settings. A pooled seroprevalence of 44.0% (95% Confidence Interval [95%CI] 27.6 to 61.8) was calculated. Subgroup estimates ranged from 2.8% (95%CI 0.9–6.3) in forestry rangers to 49.2% (95%CI 26.8–72.0) in livestock farmers, and peaked at 73.7% (95%CI 56.9–86.6) and 75.9% (95%CI 13.4–98.5) in abattoir workers and veterinary professionals, respectively. Seroprevalence rates for *C. burnetii* largely exceeded the official notification rates, suggesting its substantial underreporting in Italy.

Keywords: seroprevalence; *Coxiella burnetii*; occupational settings; Italy

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1. Introduction

Q Fever (QF) is a zoonotic infectious disease with global distribution caused by the obligate intracellular bacterium *Coxiella burnetii* (*C. burnetii*) [1,2], a small (0.2 to 0.4 μm × 0.4 to 1.0 μm) gram-negative pathogen belonging to the *Coxiellaceae* family [3]. *C. burnetii* infects a wide range of domesticated and wild animals, and human cases result from contact via airborne routes, after the organism settles in dust and becomes aerosolized [3–5].

With a case fatality ratio ranging between 0.9% to 2.4%, QF in humans rarely represents a deadly disease, but it is usually acknowledged as a debilitating one [3,6–8]. Even though up to 60% of incident cases may go unnoticed, the large majority of remaining cases evolves into mild syndromes characterized by common and unspecific symptoms such as fever, asthenia, chills, headache, myalgia, skin rashes, sweating, nausea, vomiting, and diarrhea [2,3], and in some cases may evolve into pneumonia, hepatitis, myocarditis, and even meningoencephalitis (Acute QF); moreover, QF may also develop into a chronic

disease (Chronic QF) characterized by endocarditis, vascular alterations, hepatitis, and chronic pulmonary lesions [2,3,9–11].

Since its discovery in 1935 among Australian abattoir workers [3,11,12], QF has been characterized as an occupational infectious diseases associated with the livestock industry, laboratory personnel [5,11,12], and, in general, with occupational tasks leading to the close contact with animals [13], particularly sheep and goats [13,14], as the pathogen largely remains both uncontrolled and highly prevalent in livestock [3]. In these settings, seroprevalence can range from 30% to 70% [1]. Still, a considerable share of cases occurs in individuals not occupationally exposed to livestock but reporting any contact with wildlife, where several species represent an effective reservoir for *C. burnetii* [3,11,12,15–22]. As a consequence, three types of reservoirs can be distinguished, including: (a) domestic animals (e.g., ruminants such as goats, sheep and cattle); (b) wild animals (mostly rodents, then small mammals, birds, and reptiles); and (c) ticks, that maintain the viability of micro-organisms in nature [13,14,18,23].

Since the large majority of acute cases can be exclusively detectable by seroconversion [1,23], the true incidence of QF in the general population as well as in high-risk occupational groups remains disputed, even in the European Union (EU), for several reasons. First of all, reporting is not universally compulsory: as a consequence, a considerable share of incident cases may go unreported to the competent Health authorities [24], leading to the general underestimation of the true burden of disease [1,2,13,14,23,25]. Moreover, the clinical case definition is not consistently shared by all EU/EAA Countries. For instance, between 2017 and 2021, a total of 3559 cases have occurred in the 27 EU countries: of them, 710 have been reported from France alone (19.9% of all incident cases), and 500 from Germany (14.0%) [24]. Interestingly, not only is the notification of QF mandatory in Germany and voluntary in France, but the very same case definition is quite heterogenous [23,24]. In other words, the occasional absence of symptoms, the low clinical suspicion, and the need for serological diagnostic tests, all of them characterized by different techniques and cut-off points, may lead to general underdiagnosis of this disease [5,23,26]. In turn, the underestimation of the actual QF burden may lead to the inappropriate definition of preventive measures, even in high-risk groups, ultimately leading to the persistence of this disorders as an occupational health threat [2,4,13,15,16].

With a total of 17 cases of QF officially reported between 2015 and 2021 (58.8% occurring in age group 25 to 65 years), Italy is usually acknowledged as being at very low risk of infections from *C. burnetii* [9,17,20,23,27,28], but their actual occurrence largely remains undefined [17,23,28]. As around 3.9% of the Italian workforce is to date involved in the agricultural sector (compared to the 2.4% of France and 1.4% of Germany) [29,30], the crude number of workers potentially exposed to *C. burnetii* is consistent, suggesting the substantial underreporting of incident cases. Through a systematic review, our study aimed to ascertain the published measurement of seroprevalence for *C. burnetii* in Italy, and to reconcile possible variations in seroprevalence rates with occupational exposures.

2. Materials and Methods

This systematic review has been conducted following the PRISMA (Prepared Items for Systematic Reviews and Meta-Analysis) guidelines [31,32], and was registered in PROSPERO with the progressive number CRD42023367891.

The research concepts were preliminarily defined according to the "PICO" (Patient/Population/Problem; Intervention; Control/Comparator; Outcome) strategy, as reported in Table 1. More precisely, the population of interest (P) was identified in workers potentially exposed to *C. burnetii*; the investigated result (I) was identified in the seroprevalence of biomarkers for any previous exposure to *C. burnetii*; the control (C) was defined as the healthy individuals not occupationally exposed (where available); and the outcome (O) was identified in the seroprevalence of previous *C. burnetii* infection among occupational exposed individuals, as a proxy for the risk of QF in occupational settings.

Table 1. PICO worksheet.

Item	Definition
Population of interest	Workers potentially exposed to *C. burnetii*
Investigated result	Seroprevalence of biomarkers for previous exposure to *C. burnetii*
Control	Healthy individuals not occupationally exposed
Outcome	Seroprevalence of previous infection of *C. burnetii* among occupationally exposed individuals; risk of Q Fever in occupational settings.

Two conventional scientific databases (i.e., PubMed and EMBASE) and the preprint repository MedRxiv were searched through a combination of the following keywords: ("Q Fever" OR "Coxiella burnetii" OR "Coxiella") AND ("Italy" OR "Italian") AND ("epidemiology" OR "seroprevalence" OR "prevalence" OR "frequency" OR "occurrence"). No chronological restrictions were applied.

Documents eligible for review were original research publications available online or through inter-library loan, including case studies, cohort studies, case-control studies, and cross-sectional studies. Retrieved documents were excluded if: (1) full text was not available to the reviewers; (2) articles were written in a language not understood by reviewers (i.e., Italian, English, German, French, or Spanish); (3) reports lacked timeframe (i.e., the prevalence year) and geographical settings, or it was only vaguely defined; and (4) a proper definition of the occupational settings was lacking.

Retrieved entries were initially screened for their titles in terms of relevance to the subject. Titles that were considered consistent with the research outline were subsequently analyzed by their abstracts. If the content was in turn consistent with the design of the present review, full-text versions of eligible articles were independently read by two investigators (AB and FM). Disagreements were resolved by consensus between the two reviewers; where they did not reach consensus, input from a third investigator (MR) was obtained.

Data abstracted included: (a) Settings of the study: prevalence year, Region; (b) Occupational settings of the sampled cases; (c) Total number of prevalent cases; (d) Number of reference population (if available); and (e) Characteristics of the serologic assay.

Retrieved studies were then rated about their potential risk of bias by means of the National Toxicology Program (NTP)'s Office of Health Assessment and Translation (OHAT) handbook and respective risk of bias (ROB) tool [33,34]. Briefly, the ROB tool evaluates the internal validity of a given study in order to assess whether the study's design and conduct have compromised the credibility of the link between exposure and outcome. In its current version, OHAT ROB tool covers six possible sources of bias (i.e., participant selection, confounding, attrition/exclusion, detection, selective reporting, and other sources) with potential answers ranging from "definitely low", "probably low", and "probably high" to "definitely high". Interestingly, OHAT ROB tool does not apply an overall rating for each study, and OHAT handbook also recommends that even studies with "probably high" or "definitely high" ratings should not be removed from consideration of the overall body of evidence.

Characteristics of the included studies were initially summarized through descriptive analysis, with subsequent calculation of crude prevalence figures. If a study did not include raw data, either as number of prevalent cases or referent population, such figures were reverse-calculated from available data. Pooled prevalence estimates were then calculated by means of prevalent cases per 100 population.

Meta-analysis of retrieved studies was performed through a random effect model in order to cope with the presumptive heterogeneity in design of the included reports. The amount of inconsistency between studies was estimated by means of I^2 statistic (i.e., the percentage of total variation across studies that is due to heterogeneity rather than chance). For the aims of this study, I^2 values were categorized as follows: 0 to 25% low heterogeneity; 26% to 50% moderate heterogeneity; and $\geq$ 50% substantial heterogeneity. Contour-enhanced funnel plots and radial plots were generated in order to visually assess

potential publication bias and small study bias, respectively. Funnel plot asymmetry was eventually assessed by means of the Egger test statistic. All calculations were performed in R (version 4.0.3) [35], and RStudio (version 1.4.1717; Rstudio, PBC; Boston, MA, USA) software by means of the meta package (version 4.9-9).

3. Results

Results of the inquiry are summarized in Figure 1. Briefly, a total pool of 313 entries (i.e., 142 from PubMed; 6 from MedRxiv; and 165 from EMBASE) were initially retrieved; of them, 107 were duplicated entries, therefore being removed. The remaining 206 records were then screened by title and abstract (65.8% of the original pool), and a total of 184 entries (58.8% of the original pool) were eventually removed from the analyses. The remaining 22 entries were assessed and reviewed by full-text.

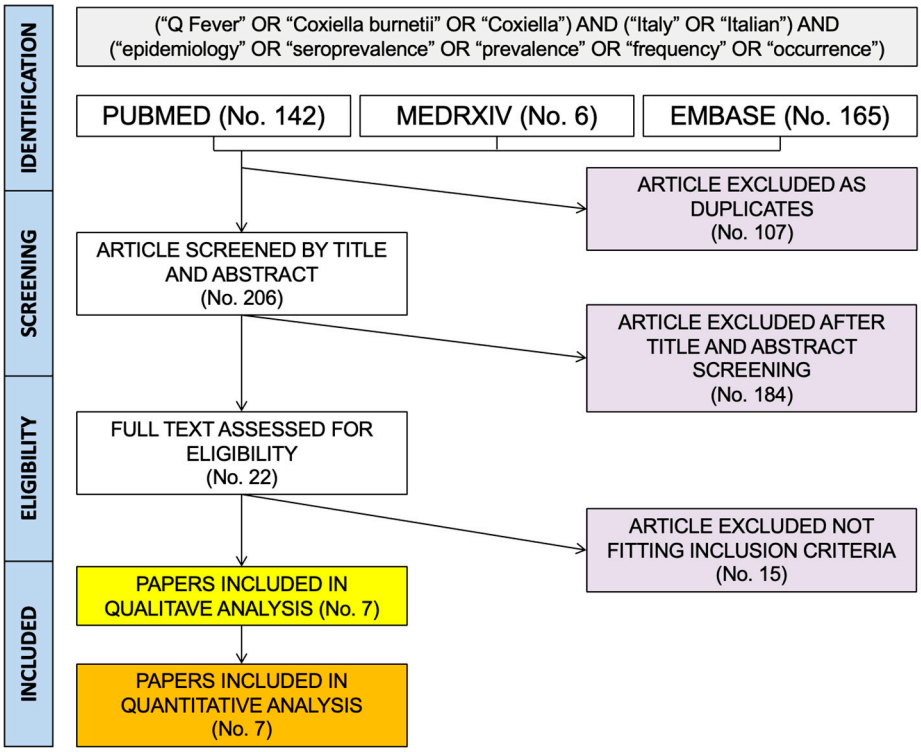

Figure 1. Flow chart of included studies.

Eventually, 15 of them were excluded due to not fitting the inclusion criteria. The remaining 7 papers were eventually included in qualitative and quantitative analysis (2.2% of the initial sample).

The retrieved studies (range: 2006–2022) [13,14,18,25,26,36,37] included a total of 16 estimates from occupational settings and 3 reference groups. Of the aforementioned studies, 3 were based on immunofluorescence assay (IFA), 3 on enzyme-linked immunoassay (ELISA), and one complement fixation test (CFT).

A total of 1670 specimens from individuals living and working in 6 Italian regions (i.e., Lombardy, Friuli Venezia Giulia, Tuscany, Apulia, Lombardy, and Sicily; Appendix A Figure A1) and belonging to 9 distinctive occupational groups were retrieved. Of them, 1314 were potentially exposed to *C. burnetii* because of their professional tasks (78.7% of the sample), and more precisely, agricultural workers operating as livestock farmers (No. 158, 9.5% of the total sample); agricultural workers having mixed tasks, including caring for animals (No. 223, 13.4%); agricultural workers not caring for animals (No. 32, 1.9%); forestry rangers (No. 181, 10.8%); forestry workers (No. 538, 32.2%); veterinarians (No. 94, 5.6%); abattoir workers (No. 38, 2.3%); laboratory workers (No. 20, 1.2%); and geologists and agronomists (No. 30, 1.8%) (Table 2).

Table 2. Summary of retrieved seroprevalence studies for Q Fever in Italy, occupational settings.

Study (Year)	Region	Occupational Settings	Procedure	Subjects (No.)	Positive (No., %)	Reference
Aquilini et al. (2000)	Tuscany	Forestry Workers	IFA	507	126, 24.9%	[18]
Cinco et al. (2006)	Friuli Venezia Giulia	Forestry Rangers	ELISA	181	5, 2.8%	[36]
Monno et al. (2009)	Apulia	Animal Farmers (breeders)	IFA	50	42, 84.0%	[13]
		Agricultural Workers (mixed tasks)		66	40, 60.6%	
		Veterinarians		12	12, 100%	
		Healthy donors (Controls)		280	38, 13.6%	
Tabibi et al. (2013)	Lombardy	Animal Farmers (breeders)	CFT	64	32, 50.0%	[14]
		Agricultural Workers (non breeders)		32	10, 31.2%	
Fenga et al. (2015)	Sicily	Veterinarians	ELISA	38	28, 73.7%	[25]
		Abattoir workers		38	28, 73.7%	
		Animal Farmers (breeders)		44	24, 54.5%	
		Laboratory workers		20	4, 20.0%	
		Healthy donors (Controls)		42	6, 14.3%	
Verso et al. (2016)	Sicily	Agricultural Workers (mixed tasks)	IFA	126	30, 23.8%	[37]
Stufano et al. (2022)	Apulia and Basilicata	Forestry workers	ELISA	31	9, 29.0%	[26]
		Farmers		31	21, 67.7%	
		Veterinarians		44	8, 18.2%	
		Geologists/Agronomists		30	8, 26.7%	
		Administrative employees (Controls)		34	5, 14.7%	

Note: IFA = Immunofluorescence Assay; CFT = complement fixation test; ELISA = enzyme-linked immunoassay.

Interestingly, while two studies [13,25] also estimated seroprevalence for *C. burnetii* in healthy blood donors from the very same geographic areas, with a total of 42 subjects over 322 samples (13.0%; actual range from 13.6% [13] to 14.3% [25]), the study from Stufano et al. included administrative workers (No. 34) not exposed to *C. burnetii* in occupational settings [26]. Overall, a total of 356 not-occupationally exposed individuals were reported and represented the reference group (21.3% of the total sample).

A detailed description of the risk of bias (ROB) assessment on retrieved studies is summarized in Table 3 and Figure 2.

Table 3. Tabular representation for the Risk of Bias (ROB) assessment according to the National Toxicology Program (NTP)'s Office of Health Assessment and Translation (OHAT) handbook and respective risk of bias (ROB) tool [33,34]. Note: D1: possibility of selection bias; D2: exposure assessment; D3: outcome assessment; D4: confounding factors; D5: reporting bias; D6: other bias. ☹☹ = definitively high; ☹ = probably high; ☺ = probably low; ☺☺ = definitively low.

Study	RISK OF BIAS					
	D1	D2	D3	D4	D5	D6
Aquilini et al. (2000) [18]	☹☹	☹☹	☹	☹	☺	☺
Cinco et al. (2006) [36]	☹	☹	☺☺	☹	☺	☺
Monno et al. (2009) [13]	☹	☹	☹	☹	☺	☺
Tabibi et al. (2013) [14]	☹☹	☹	☹☹	☹	☺	☺
Fenga et al. (2015) [25]	☹☹	☹	☺☺	☹	☺	☺
Verso et al. (2016) [37]	☹	☹	☹	☹	☺	☺
Stufano et al. (2022) [26]	☺	☺	☺	☺☺	☺☺	☺☺

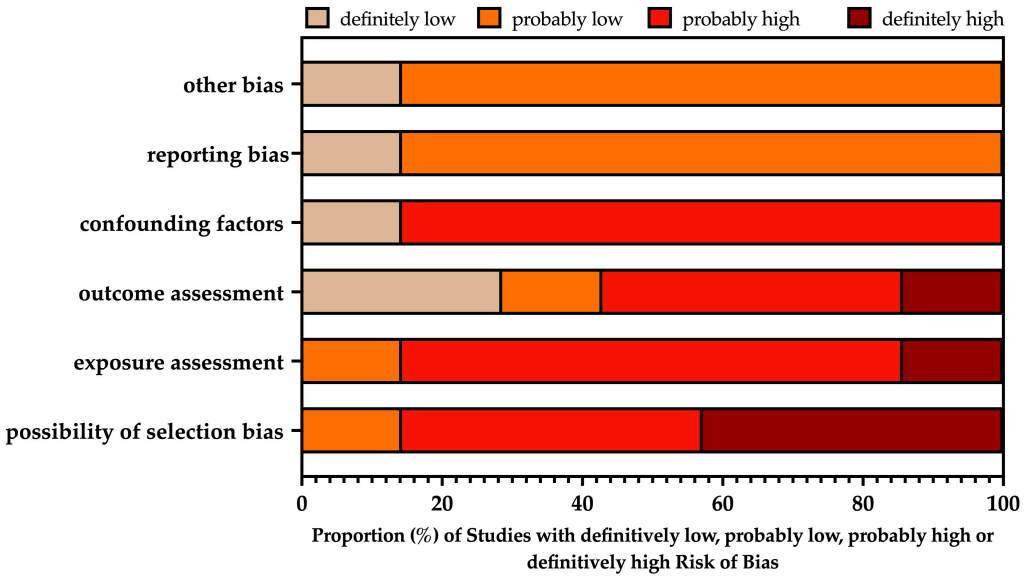

Figure 2. Summary of risk of bias assessment according to the National Toxicology Program (NTP)'s Office of Health Assessment and Translation (OHAT) handbook and respective risk of bias (ROB) tool [33,34].

Overall, the overall quality of retrieved studies was largely unsatisfying. First of all, in nearly all studies, how the sample was ultimately recruited remains largely unclear. Moreover, in the large majority of retrieved reports, the very same exposure is not clearly stated. For example, in the study by Aquilini et al. [18] we are only briefed that the sampled individuals (i.e., 507) were "forestry workers", and even though Authors did recall an estimate for the exposure assessment, it was not reported through the actual tasks performed by study participants, and the risk were summarized in terms of exposure to milk, ticks, and animals. Similarly, the study of Fenga et al. reports on the seroprevalence for *C. burnetii* among "laboratory workers" [25]. It is quite unclear whether the participants had any occupational interaction with specimens possibly contaminated by the pathogen. Moreover, more than half of the included studies were based on laboratory techniques such as IFA [13,18,37] and even CFT [14], that are far less sensitive and specific than ELISA [25,26,36]. Eventually, the analysis of the possible role of non-occupational exposures was not clearly addressed in the majority of the assessed studies, while no clear reporting bias could be identified among the pooled reports.

In the meta-analysis, the pooled seroprevalence for *C. burnetii* was estimated through a random-effect model at 44.0% (95% Confidence Interval [95%CI] 27.6–61.8) (Figure 3), with substantial heterogeneity across the assessed subgroups. For instance, individual estimates ranged from 2.8% (95%CI 0.9–6.3) in forestry rangers to 20.0% (95%CI 5.7–43.7) in laboratory personnel, and 25.1% (95%CI 21.6–28.9) among forestry workers; 26.7% (95%CI 12.3–45.9) in agronomists and geologists, 31.2% (95%CI 16.1–49.0) in agricultural workers not caring for animals, 49.2% (95%CI 26.8–72.0) in farmers having mixed tasks that included breeding animals, 64.2% (95%CI 44.0–80.4) in livestock farmers, and peaked at 73.7% (95%CI 56.9–86.6) and 75.9% (95%CI 13.4–98.5) in abattoir workers and veterinary professionals, respectively. The estimates were affected by substantial heterogeneity ($tau^2 = 2.004$; tau = 1.4157; $I^2 = 92.4\%$ [95%CI, 89.3%; 94.6%], Q = 197.88, $p < 0.001$).

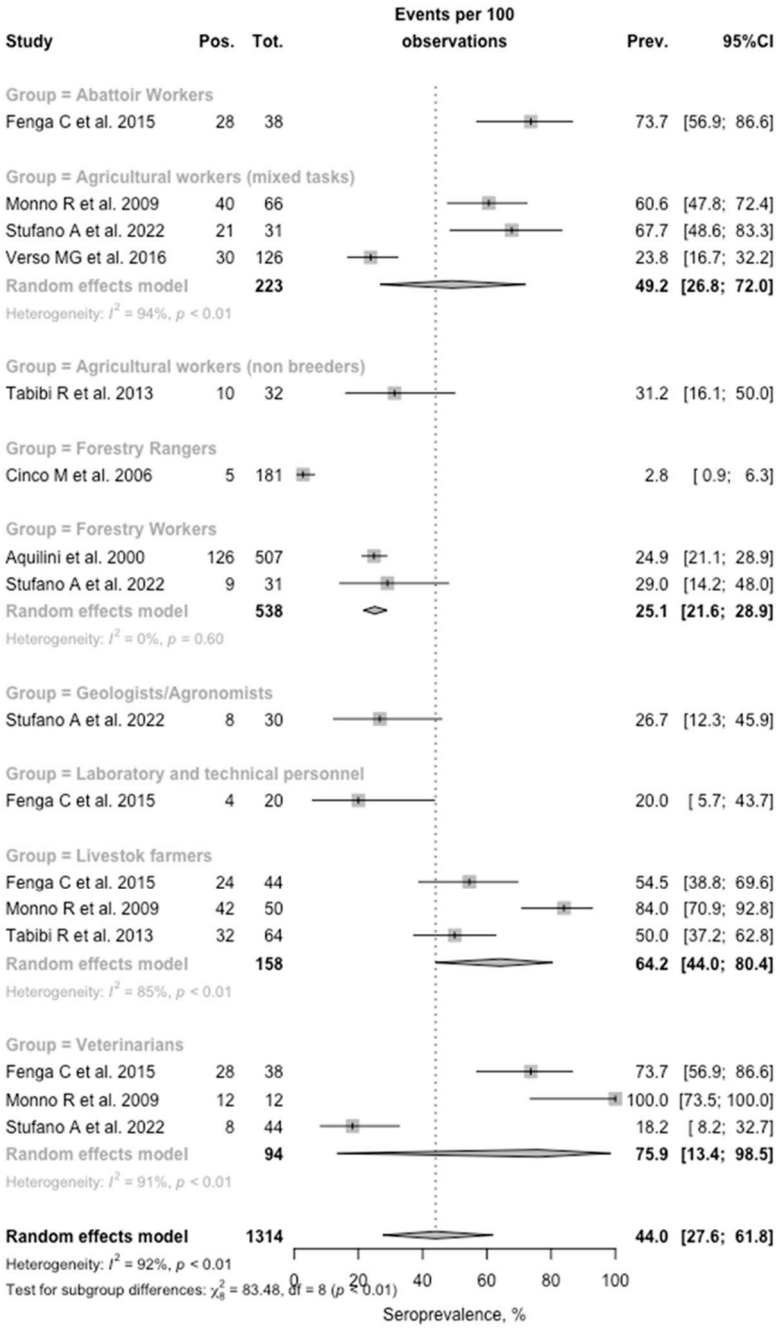

Figure 3. Forrest plot for retrieved seroprevalence studies about *C. burnetii* infection in Italy, from occupational settings. A pooled seroprevalence of 44.0% (95% Confidence Interval [95%CI] 27.6 to 61.8) was eventually calculated, with substantial heterogeneity (tau^2 = 2.004; tau = 1.4157; I^2 = 92.4% [95%CI, 89.3%; 94.6%], Q = 197.88, p < 0.001) [13,14,18,25,26,36,37].

Interestingly, by assuming non-occupationally exposed individuals as the reference group (Figure 4), a substantially higher occurrence of seropositivity was reported among agricultural workers in all of the three subgroups: livestock farmers (Risk Ratio [RR] 4.506, 95%CI 3.381 to 6.006), individuals performing mixed tasks (RR 2.965, 95%CI 2.187 to 4.019), and non-breeders (RR 2.270, 95%CI 1.276 to 4.039). An increased risk was also associated with forestry workers (RR 1.823, 95%CI 1.353 to 2.457), abattoir workers (RR 5.343, 95%CI 3.897 to 7.387), veterinary professionals (RR 3.710 95%CI 2.676 to 5.144), as well as for geologists and agronomists (RR 1.937, 95%CI 1.014 to 3.703). On the contrary, a reduced risk was associated with individuals working as forestry rangers (RR 0.201, 95%CI 0.081 to

0.495), and no substantial differences with non-exposed individuals were identified among laboratory and technical professionals (RR 1.453, 95%CI 0.582 to 3.625).

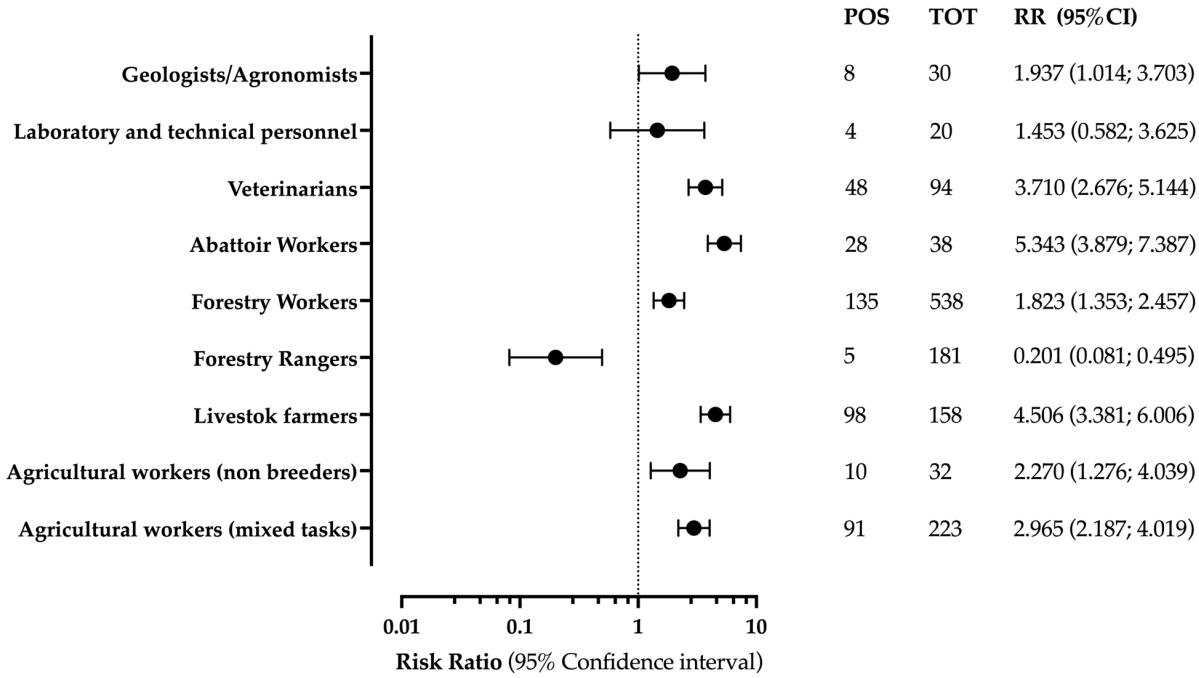

Figure 4. Forest plot representing risk ratio on main occupational groups compared to non-occupationally exposed workers (49 cases out of a total of 356 donors, 13.8%). Note: RR = Risk Ratio; 95%CI = 95% Confidence Interval.

When seroprevalence was compared by the parent Italian region, after the exclusion of non-exposed individuals, it ranged between 2.8% from Friuli Venezia Giulia to 49.0% in Apulia (Appendix A Figure A1). Assuming workers from Lombardy (the most populated Italian region, with around 10,000,000 inhabitants, that is 1/6 of the total Italian population) as the reference group, the risk ratio for reporting seroprevalence on *C. burnetii* ranged between RR 0.063 (95%CI 0.026 to 0.154) in the North-Eastern Region of Friuli Venezia Giulia to RR 0.568 (95%CI 0.432 to 0.746) in Tuscany and RR 0.980 (95%CI 0.751 to 1.278) in Sicily, with the greatest estimates for Basilicata (RR 1.087, 95%CI 0.767 to 1.593) and Apulia (RR 1.119, 95%CI 0.861 to 1.453) (Figure 5).

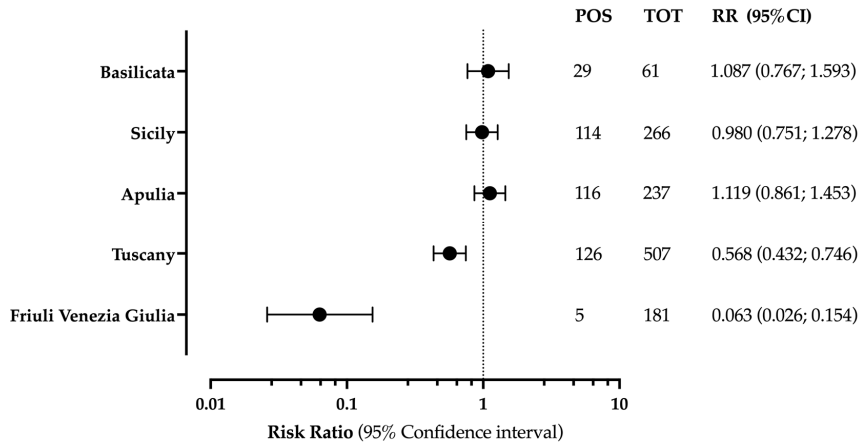

Figure 5. Forest plot representing risk ratio on main occupational groups by parent Italian region, and assuming Lombardy region (42 positive cases over a total of 96 samples; 43.8%) as the reference one. Note: RR = Risk Ratio; 95%CI = 95% Confidence Interval.

When dealing with the assessment of the potential publication and small study bias, mixed results were retrieved. On the one hand, the radial plot calculated by single prevalence estimates (Figure 6), hinted towards no effects for the small size of samples included in the estimates. On the other hand, the substantial asymmetry of the corresponding funnel plot (Figure 7) suggested a residual publication bias, that was substantially rejected by the Eggers's test (t = −1.50, df = 14, intercept = 2.5879, SE = 1.7307, *p*-value = 0.157).

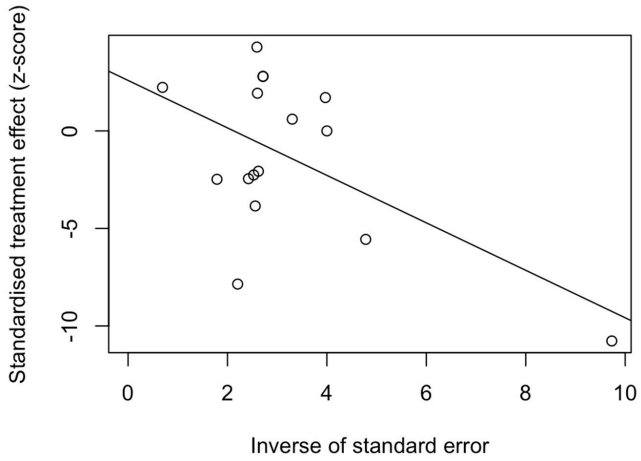

Figure 6. Radial plots for estimates included in the meta-analysis. Visual inspection reported all the estimates as substantially scattered across the regression line, suggesting no significant small study effect.

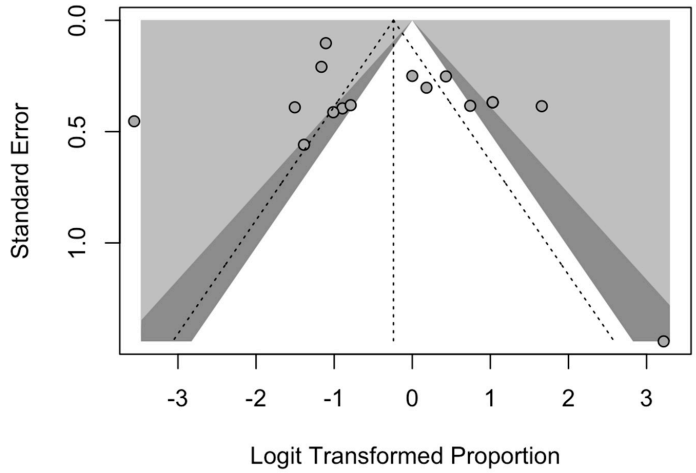

Figure 7. Border-enhanced funnel plots for estimates included in the meta-analysis. Visual inspection of contour-enhanced funnel plots suggested the substantial evidence of publication bias, but this was substantially rejected by Egger test (i.e., t = −1.50, df = 14, intercept = 2.5879, SE = 1.7307, *p*-value = 0.157).

4. Discussion

In our systematic review and meta-analysis, a pooled prevalence of seropositivity for *C. burnetii* on occupationally exposed individuals was estimated at 44.0% (95%CI 27.6 to 61.8). The risk for seropositivity was greatest among veterinary professionals, followed by abattoir workers, livestock farmers, agricultural workers, geologists/agronomists, and forestry workers, while laboratory professionals had no substantially increased risk, and forestry rangers exhibited a conversely reduced seropositivity risk.

In other words, the present study is consistent with some previous reports, suggesting that seroprevalence for *C. burnetii* among professionals working with animals or involved in meat processing may be up to 50% [1,6,7,10,16,19,38–40], largely exceeding estimates in non-occupationally exposed individuals from the index areas (where prevalence estimates

ranging between 13.6% and 14.3% were retrieved) [13,25], and national figures for non-occupational exposed individuals [6,19,37,41,42]. In this regard, it should be stressed that according to official reports, between 2015 and 2021, a total of 17 cases of QF have been reported to Italian health authorities, for an annual reference rate well below 0.1 cases per 100,000 persons [23,24]. These figures are clearly inconsistent with animal records, as provided by the joint European Centre for Disease prevention and Control (ECDC) and European Food Safety Authority (EFSA) report on Zoonoses in the European Union for 2021 [24], where seroprevalence rates of 20.9% in sheep, 17.9% in goats, and 15.1% in cattle were provided. Therefore, when pooled estimates are compared to official figures, QF in Italy appears as substantially underestimated, with notification rates reasonably representing the tip of a very larger burden of disease, particularly in occupational settings. Occupational physicians, i.e., the medical professionals responsible for health promotion in the workplaces [43], should therefore be made aware of the actual transmission of *C. burnetii* in occupational settings, promoting appropriate surveillance programs and improving the adherence to proper preventive measures among at-risk workers.

In fact, not only do pooled estimates substantially mirror several international reports on this pathogen [1,6,7,10,16,19,38,39,41,44], but they are also quite consistent with some previous Italian reports, where the relatively high occurrence of this pathogen in various agricultural settings was highlighted [20,45]. For example, by 1992, 13.1% of 99 sampled farms, 4.4% of sampled animals, and 6.5% of raw milk samples from the Apennine region of Emilia Romagna were contaminated by *C. burnetii* [20]. Similarly, a more recent study from the Autonomous Province of Bolzano reported an overall seroprevalence of 13.6% for cattle, 11.7% for sheep, and 7.9% for goats [45]. Moreover, in 2003 a large outbreak of QF among prison inmates did occur in the Como area following the exposure to dust contaminated by a passing flock of sheep [27,28].

As a consequence, the status of QF in Italian agricultural and forestry workers would be quite similar to other zoonotic pathogens of occupational interest, e.g., Hantaviruses, Tick-borne Encephalitis virus, and *Borrelia burgdoferi* (the causal agent of Lyme disease) [46–50]. More precisely, our analyses stress the strong association of seroprevalence for *C. burnetii* with the meat industry (more precisely, for abattoir personnel) and farm tasks that cause the interaction between men and animals, i.e., animal breeders, but also with veterinarians [1,14,23]. On the contrary, even though *C. burnetii* may be acquired as a tick-borne disease [13,18], the relatively low seroprevalence in forestry rangers was not unexpected, for several reasons. For one, despite their role in maintaining the wildlife reservoir, ticks are only marginal agents of Q fever in humans. As a consequence, a marginal transmission in these specific settings was largely foreseen. Moreover, the estimates on forestry rangers were mostly obtained through the study by Cinco et al. [36], whose results should be carefully assessed as obtained through the complement fixation test, whose sensitivity and specificity are quite lower than those associated with IFA and ELISA.

Limitations. Despite the potential interest, our study is affected by several limitations. First of all, the studies that were retrieved and included in the analyses were mostly of limited quality, as summarized by the ROB tools. In this regard, two main shortcomings should be stressed. On the one hand, nearly all studies did not report how the sample was eventually recruited. In other words, the actual representativity of the assessed occupational groups, even in the targeted areas, remains unclear. On the other hand, as previously stressed for other infectious diseases affecting agricultural workers [46,47,51], the job description could fail to appreciate other exposures, possibly associated with residential and environmental factors, as agricultural settings hardly dichotomize occupational and residential environments [46,47,52,53]. Moreover, the studies were also quite heterogenous in geographical terms, sample size, and sampling strategy [13,18,25,37]. As a consequence, retrieved estimates could only be limitedly comparable.

Third, as the collected studies were performed across a very broad timespan (2000 to 2022) and laboratory techniques were quite heterogeneous (i.e., IFA, CFT, and ELISA), we cannot rule out whether differences in estimates are the result of the specificities of the

diagnostic procedures or the actual seroprevalence [2]. Fourth, the pooled population was quite small, both in general and when dealing with individual occupational groups, which is not representative of Italian workforce [14].

5. Conclusions

In conclusion, further studies are required in order to better understand the actual occurrence of *C. burnetii* infections in Italian, not only in occupational settings, but also in the general population. Even though the large majority of cases clearly occur either asymptomatically or pauci-symptomatically [2,16,43,45], more accurately tailored interventions for at-risk workers should be implemented in terms of surveillance programs and informative campaigns on the appropriate preventive measures.

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Appendix A

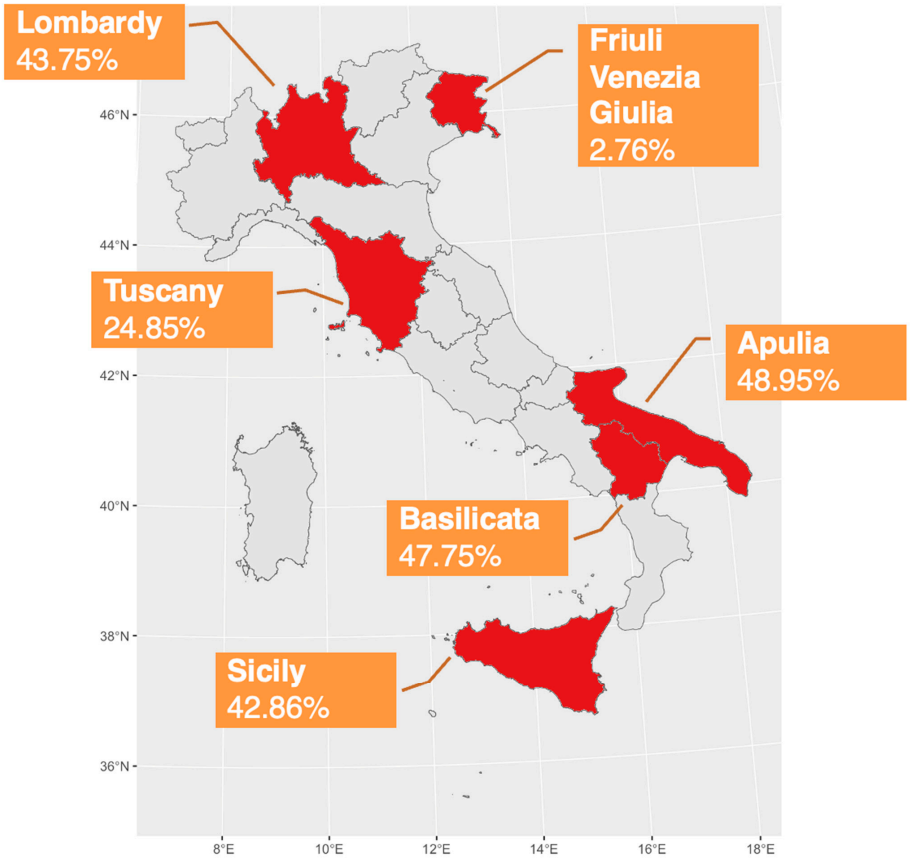

Figure A1. Geographical areas involved in the studies included in the analyses.

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