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Watch-and-wait approach for inactive echinococcal cysts: scoping review update since the issue of the WHO-IWGE Expert Consensus and current perspectives

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Purpose of review
This work aims to provide an update of knowledge on the evolution of inactive cystic echinococcosis (CE) cysts (CE4-CE5) managed by 'watch-and-wait', by means of a scoping review of the literature published after the publication of the WHO-IWGE (Informal Working Group on Echinococcosis) Expert Consensus document in 2010.

Recent findings
A total of 31 articles were included. Population ultrasound-based studies showed that spontaneously inactivated CE cysts represent 50.2% (95% confidence interval 38.7–61.8) of all detected untreated CE cysts, and that the prevalence of CE4-CE5 cysts tends to increase with age. Four longitudinal population-based studies showed that CE cysts naturally tend to evolve towards inactivation and that spontaneously inactivated cysts reactivate in a minority of cases. This was confirmed by four hospital-based studies, showing that spontaneously inactivated cysts reactivate rarely, while rate of reactivation is higher if inactivity was obtained posttreatment. It was not possible to drive conclusions on any difference in the clinical course of infection in immunocompromised or pregnant patients.

Summary
CE cysts tend to evolve spontaneously to inactivation over time. The published literature supports the safety of the watch-and-wait approach for inactive cysts, sparing treatment to a substantial proportion of asymptomatic patients. A regular follow-up with ultrasound of all inactive cysts is required to detect reactivations.

Keywords
CE4 and CE5 stages, cystic echinococcosis, inactive stages, untreated, watch and wait

INTRODUCTION

The WHO-IWGE (Informal Working Group on Echinococcosis) Expert Consensus published in 2010 [1] recommended that patients with cystic echinococcosis (CE) harbouring uncomplicated, asymptomatic, inactive (CE4-CE5 stages of the WHO-IWGE classification) CE cysts, especially localized in the liver, be monitored with ultrasound imaging, in the absence of treatment, with 'strength of recommendation: B (Moderate); Quality of Evidence: III (from experience or case reports)'. This was defined as 'watch-and-wait' approach. The attitude of leaving CE cysts with solid content untreated originated from previous observations that some CE cysts become solid (i.e. inactive) spontaneously and remain stable over time (reviewed in [2,3]). We provide an update knowledge on the evolution of untreated inactive CE cysts gathered after the publication of the WHO-IWGE Expert Consensus document [1] by means of a scoping review of the literature.

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Curr Opin Infect Dis 2023, 36:326–332

DOI:10.1097/QCO.0000000000000943

KEY POINTS

- The watch-and-wait approach is the long-term monitoring with ultrasound imaging, in the absence of treatment, of patients with cystic echinococcosis (CE) harbouring uncomplicated, asymptomatic, inactive CE cysts (CE4-CE5 stages of the WHO-IWGE classification).
- Population ultrasound-based studies show that CE cysts tend naturally to evolve towards inactivation; that spontaneously inactivated CE cysts represent about 50% of all detected untreated CE cysts; and that the prevalence of inactive cysts tends to increase with the age of the individuals.
- Spontaneously inactivated cysts reactivate rarely, while rate of reactivation is variable and higher if inactivity is obtained by benzimidazole treatment.
- The watch-and-wait approach for inactive cysts, with regular follow-up by ultrasonography, is well tolerated, sparing treatment to a substantial proportion of asymptomatic patients.

LITERATURE SEARCH

On 5 February 2023, we performed a PubMed (MEDLINE) literature search using the following strategies:

(1) '((cystic echinococcosis) OR (hydatid) OR (echinococcus granulosus)) (ultraso*) AND ((prevalence) OR (screening) OR (population))' for data on ultrasound population-based studies;
(2) '((cystic echinococcosis) OR (hydatid) OR (echinococcus granulosus)) AND (('watch and wait') OR (follow-up) OR (untreated) OR (inactiv*))' for hospital-based data;
(3) '((cystic echinococcosis) OR (hydatid) OR (echinococcus granulosus)) AND ((immunosuppr*) OR (immunocompr*) OR (HIV) OR (transpl*) OR (cancer) OR (pregn*))' for particular immune conditions.

We restricted the search to human studies published after April 2010, when the WHO-IWGE Expert Consensus [1] was published. No language restriction was applied. Original prospective and retrospective cohort studies, case–control studies and cross-sectional studies, as well as reviews of the topics of interest were reviewed. Data (absolute numbers and summary statistics, timeline) were extracted on the prevalence of inactive CE cysts in ultrasound-based all-age population studies, the rate of spontaneous inactivation of active cysts over time, and the rate of reactivation and of complications of inactive cysts over time. Baseline figures were extracted from untreated individuals. When the full text was not available, data were extracted from the abstract, when possible. In case the Gharbi cyst type classification was used [4], conversion to the WHO-IWGE staging classification was applied [5]; in all cases of nonunivocal attribution of Gharbi type to WHO-IWGE classification (especially differentiation between CE3b and CE4), the study was excluded. Pooled prevalence was computed for prevalence of cystic echinococcosis and for prevalence of inactive cystic echinococcosis on total cystic echinococcosis cases, using STATA v.17 software (StataCorp, College Station, Texas, USA). The flow diagram of electronic searches and selection of publications is shown in Fig. 1. The full list of articles finally included in this review is available in Supplementary file 1, http://links.lww.com/COID/A48.

SPONTANEOUS INACTIVATION OF ABDOMINAL CYSTS: RESULTS FROM POPULATION STUDIES

The natural progression of CE cysts seems to go from CE1 to CE4/5 stages, with different developmental pathways through the other cyst stages [2] (Fig. 2). Among cross-sectional studies, 18 eligible articles (Supplementary file 2, http://links.lww.com/COID/A49) reported ultrasound population surveys in 15 countries encompassing South America, Europe, Asia and Africa, for a total of 130 093 people screened by ultrasound. The forest plots of pooled cystic echinococcosis prevalence and proportion of inactive cystic echinococcosis on all cystic echinococcosis cases found in population-based cross-sectional studies are shown in Fig. 3. Prevalence of untreated abdominal cystic echinococcosis ranged from 0 to 18.3% [pooled prevalence 2.1%, 95% confidence interval (95% CI) 1.3–3.2] (Fig. 3a) and inactive cysts accounted for 10–100% of all cysts diagnosed by ultrasound (pooled prevalence 50.2%, 95% CI 38.7–61.8) (Fig. 3b). Only seven articles (Supplementary file 2) reported results of cyst stage distribution by age, overall showing an association between age and increased prevalence of CE4-CE5 cysts. This was also found in the analysis of field surveillance data of cystic echinococcosis in Turkana pastoralists published by Solomon *et al*. [6]. It is important to note that population-based studies not applying random sampling may suffer from selection bias [7], and inactive cysts are most commonly asymptomatic (thus, not generally diagnosed before the survey); therefore, it is possible that individuals with CE4-CE5 cysts are over-represented in these surveys. Nevertheless, results are consistent with CE cysts tending spontaneously to inactivation over time, as biologically plausible [2].

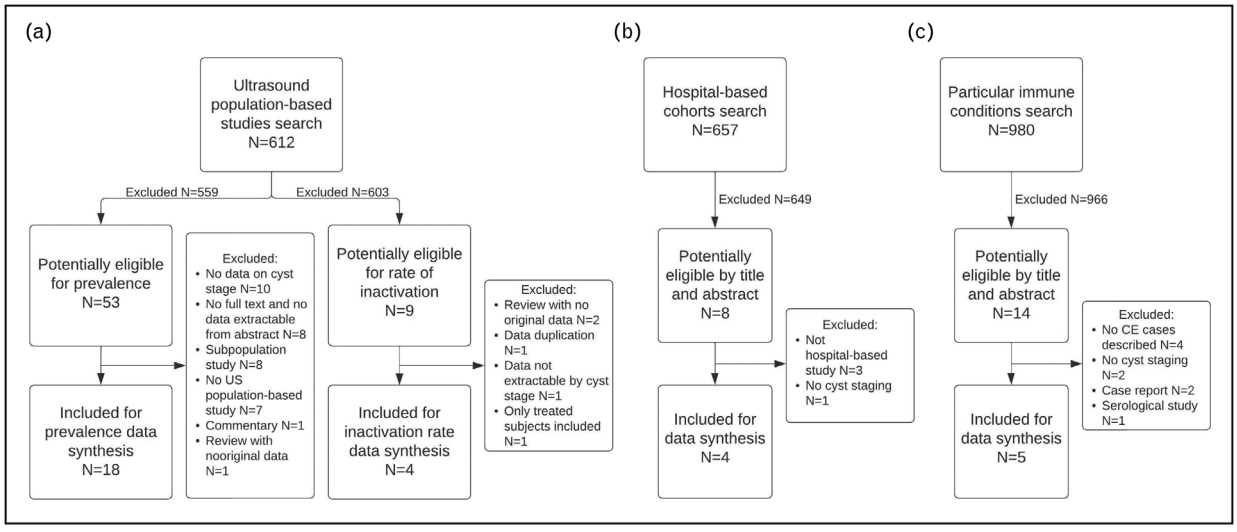

FIGURE 1. Literature search and selection.

The rate and average speed by which such spontaneous inactivation occurs is extremely difficult to ascertain, as this would require observing infected individuals over time without treating them, which is logistically extremely difficult (it would imply regular screening over years of the same individuals, in most often difficult to access geographical areas or mobile populations such as nomads or migrants). Even more importantly, such management would be considered ethically unfeasible, despite the natural history of cystic echinococcosis being still poorly known [8]. Four studies published in the last decade reported the results of the follow-up over time of untreated CE cysts, from the observation of screened cohorts of individuals who were not treated, either because of individuals' choice (no need for treatment was perceived due to the asymptomatic condition [6,9,10]) or as per protocol of the control programme [11]. Three of these studies [6,9,10] retrospectively analysed data available from periodic ultrasound screening of transhumant pastoralists in Turkana, Kenya, followed over 30 years during the cystic echinococcosis control programme launched in 1983 by Kenyan Ministry of Health and of Agriculture, AMREF Health Africa and other local nongovernmental organizations. During this period, individuals were screened intermittently, but usually at the same location and time of year [9]. Comparison of population surveys carried out between 1983 and 2012 found a significant association between population age distribution over time and all cyst stages, suggesting not only a positive achievement of control

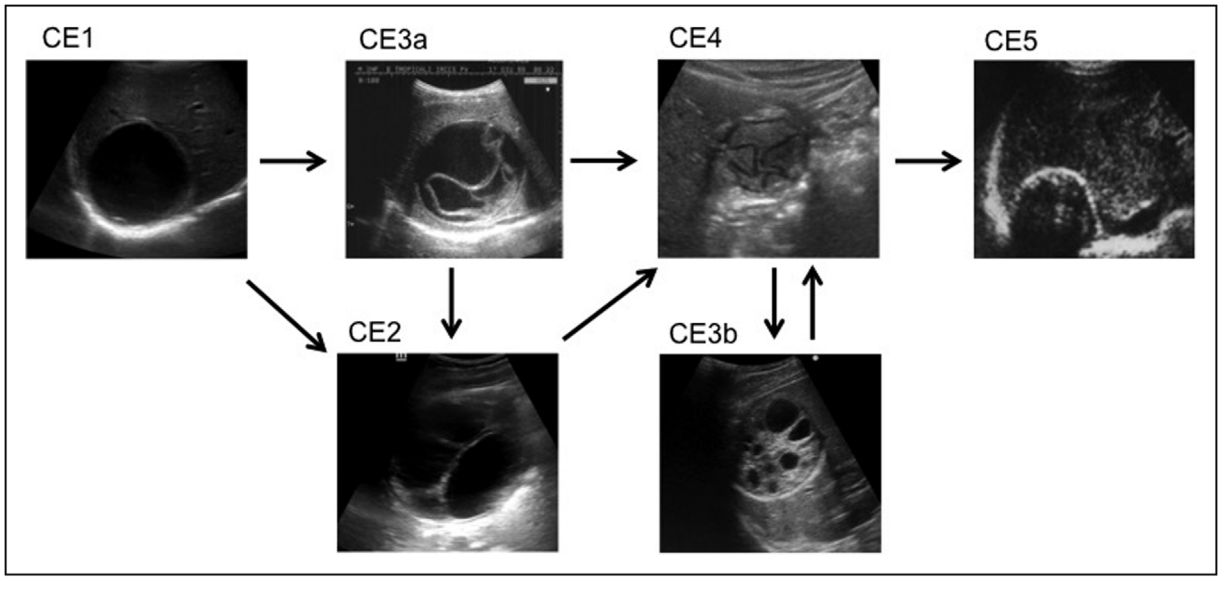

FIGURE 2. Schematic representation of the possible natural history of CE cysts.

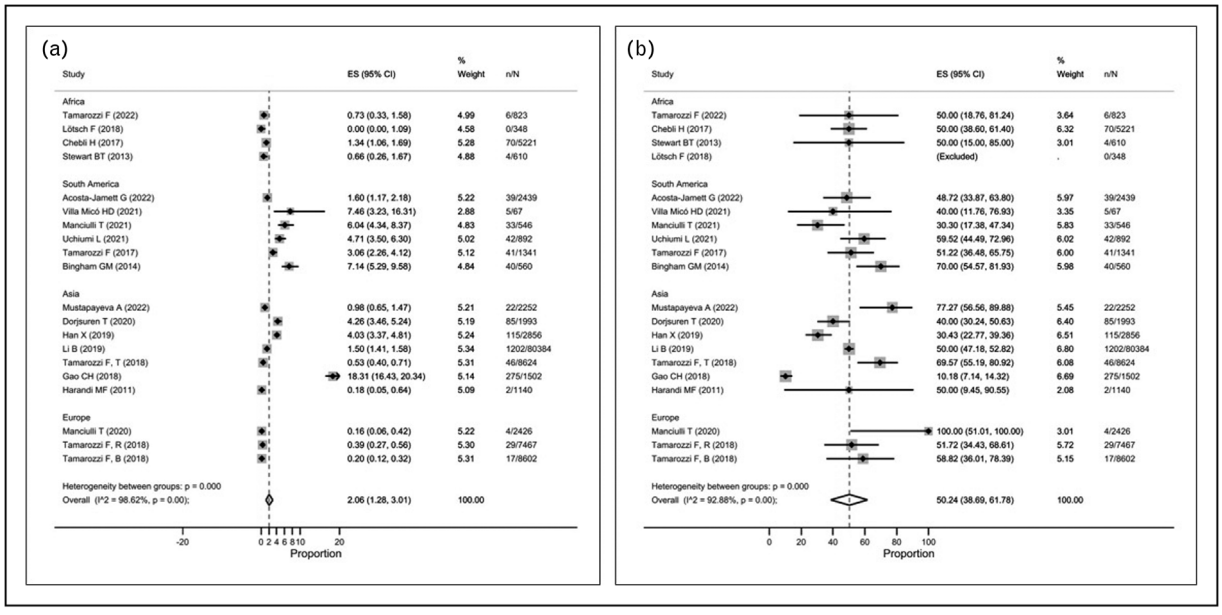

FIGURE 3. (a) Pooled prevalence of untreated CE in population-based US studies. (b) Pooled prevalence of untreated inactive CE on the total of all untreated CE cysts in population-based US studies.

programme activities, but also the natural evolution of CE cyst stages from active to inactive stages over time [9]. The proportions of cyst stages detected over time (1983–2015) were also significantly different when the authors examined only the subset of untreated people (240 individuals with 293 cysts) for whom complete data were available for at least two observations [6]. In a further before-after analysis of data from the same individuals (257 individuals with 360 cysts) followed over time (at least twice and at least 2 years apart) in the Turkana control programme and in a community-based ultrasound screening survey of Berber people of the Mid Atlas, Morocco, the authors showed that in the majority of observations (99.2%), the cyst remained in the same stage (87.3%) or progressed along the evolution path from CE1 to CE2-CE3a-CE3b to finally CE4-CE5 stages (11.9%) [10]. 'Regression' along this evolution path (i.e. reactivation) from CE4 to CE3b occurred in only 6% of CE4 cysts (7/116 CE4 cyst observations) [10]. Similar observations were derived from Rio Negro Province of Argentina, where regular ultrasound screening in schoolchildren is carried out since 1984 in the context of the Hydatidosis Control Program, having started in 1980, and which continues today [12,13]. In this programme, a clinical management algorithm endorsed by the Provincial Ministry of Health is applied, assigning a 'watch-and-wait' approach to CE1 cysts less than 3 cm and to CE4–5 cysts [11]. In reviewing data of 16 observed-only children examined 10 years apart, Larrieu *et al.* [11] reported that at the beginning, 14 (87.6%) cases were CE1-CE3a and two (12.6%) CE4-CE5, while 10 years later, CE cysts were CE1-CE3a in three cases (18.8%), CE4–5 in eight cases (50.1%), in four cases (25%) a 'total involution' was observed, while one (6.3%) was treated surgically. Although results obtained by the retrospective analysis of data collected during control programmes activities are known to be burdened by data incompleteness, including missing information about those lost to follow-up, and by irregularity of observations over time, overall, these data are in support that the vast majority of CE cysts either maintain the same cyst stage or evolve along the main natural history path identified from previous observations [2].

THE WATCH-AND-WAIT APPROACH IN CLINICAL PRACTICE: RESULTS FROM HOSPITAL-BASED COHORTS

Four case series [14–17] reported the results of the watch-and-wait approach applied to uncomplicated inactive hepatic CE cysts. Lissandrin *et al.* [14] expanded the cohort described by Piccoli *et al.* [15] to include 53 patients with 66 uncomplicated CE4 ($n = 41$) and CE5 ($n = 25$) cysts without history of previous treatment and followed-up with ultrasound for a minimum of 24 months [median 52 months; interquartile range (IQR) 36.6]. They observed that 98.5% of cysts remained inactive over time and in only one patient (1.9% of patients) and one cyst (1.5% of cysts) a reactivation to CE3b occurred, with no complications observed.

In the case series published by Stojkovic *et al.* [16], the authors evaluated the difference in

reactivation over time between inactive cysts that inactivated spontaneously and those that inactivated as the consequence of medical treatment of active (CE1–2-3b) or transitional (CE3a) stages, drawing from previous observations that the former reactivated rarely while in the latter reactivation was common, provided follow-up was long enough [16,17]. The mean follow-up was 64.8 months for the untreated group and 87.6 months for the group previously treated with benzimidazoles. Among the 30 patients (46 cysts) in the untreated group, no reactivation (and no complication) was observed, while in the 15 patients previously treated, eight out of 17 cysts reactivated within 18 months [16]. Notably, the rate of reactivation is extremely high when CE4 is derived from benzimidazole-induced inactivation of CE3b, as shown by Rinaldi *et al.* [17].

Although the retrospective nature and the loss to follow-up, which ranged from 15% [16] to 70% [14,15], are evident limitations of these studies, taken together, their results show the consistent stability of naturally inactivated cysts, in contrast to those that reached inactivity through treatment. These results support the safety of the watch-and-wait approach for all inactive cysts, sparing treatment to a substantial proportion of asymptomatic patients reaching medical attention, and suggesting the need to implementing a regular follow-up of a few years with ultrasound to detect reactivations. Continuous treatment with albendazole to prevent reactivation of inactive cysts is also not justified, as no marker is currently available that predicts what individual cyst will reactivate and when, and this would imply over-treating a large proportion of patients, with attendant risks of side effects, limitations to patients' lives and costs. This line of conduct is also supported by observations obtained from the Turkana control programme activities [10] and experimental results on the actual target of benzimidazole drugs in the CE cyst [18,19]. Indeed, among individuals with inactive cysts treated with albendazole in the context of the cystic echinococcosis control programme in Turkana, 14% (29/208 of CE4 observations) reactivated to CE3b, suggesting that antiparasitic treatment did not contribute to improve the 'stability' of the inactive stage [10]. The group of Brehm [18,19] investigated *in vitro* the interaction between albendazole and *Echinococcus multilocularis* metacestode stem cells, closely related to *E. granulosus*, which are the only cells able to proliferate and therefore have an evident role in reactivation after treatment. They demonstrated that stem cells might be less sensitive to chemotherapy because they express a beta-tubulin isoform with limited affinity to benzimidazoles.

SPECIAL CONDITIONS: IMMUNOSUPPRESSION AND PREGNANCY

Unlike alveolar echinococcosis [20], caused by infection with the larval stage of *E. multilocularis*, clinicians in referral centres for cystic echinococcosis tend to think that the course of cystic echinococcosis is unaffected by immunosuppression. Although it has been hypothesized that HIV may affect the course of cystic echinococcosis and lead to unusual and potentially more severe clinical disease [21,22], Wahlers *et al.* [23], reviewing cases attended at two teaching hospitals in Johannesburg, found that HIV-positive patients did not seem to develop disseminated cystic echinococcosis more commonly than HIV-negative patients. Unfortunately, no cyst stage information was provided, which weakens their conclusions. In their recent reviews, Russotto *et al.* [24] reported that cystic echinococcosis is a common co-infection in patients with HIV in endemic countries, and Ghasemirad *et al.* [25▪] specifically highlighted the impossibility, from current literature, to draw conclusions on any possible difference in the clinical course of the infection in immunocompromised compared with immunocompetent patients. No longitudinal studies compared the long-term outcome of patients with cystic echinococcosis and concomitant immunosuppressive conditions, which could provide robust data while avoiding the potential bias due to clinical observation and publication of only symptomatic, severe and complicated cases (Supplementary file 2, http://links.lww.com/COID/A49).

Pregnancy affects the immune status of the expecting woman. Preventive surgery for pregnant patients in fear of reactivation or complications is often advocated on the basis of case reports of cystic echinococcosis complications in pregnancy, but this could be biased by the fact that it is mainly complicated clinical cystic echinococcosis cases in pregnant women that come to medical attention and are published. Celik *et al.* [26], in their retrospective case series including 27 pregnant women with cystic echinococcosis, nine of whom with inactive cysts (8/9 spontaneously inactive), found no reactivation during pregnancy and no association between inactive cysts and pregnancy outcome. A recently published case series from a single referral centre in Italy [27▪▪] included seven pregnant women with eight hepatic inactive CE cysts (5/7 spontaneously inactive), followed-up by ultrasound during and after pregnancy. In only one patient with a history of multiple treatments with albendazole and with a CE4 cyst at the start of pregnancy, reactivation of the cyst during pregnancy was observed, in line with what observed in nonpregnant patients.

CONCLUSION

The stage-specific approach advocated by the experts of the WHO-IWGE [1] aims to optimize treatment allocation of patients with cystic echinococcosis, avoiding overtreatment with attendant risks, impact on patients' lives and costs. In this context, the watch-and-wait approach to asymptomatic, uncomplicated CE4 and CE5 cysts is safe and supported by increasing evidence. Although 13 years ago, when the WHO-IWGE Expert Consensus document was published, evidence on the long-term outcome of untreated CE4-CE5 cysts and on the safety of the watch-and-wait approach for these stages was low, studies carried out so far, although mainly retrospective, have increased the strength of recommendation and quality of evidence. Results on the long-term outcome of the watch-and-wait approach for inactive CE cysts from data prospectively collected in a standardized manner will be hopefully available from the activities of the European Register of Cystic Echinococcosis (ERCE) [28▪▪].

It would be extremely difficult to quantify the adoption of the watch-and-wait approach, and of the stage-specific approach recommended in the WHO-IWGE Expert Consensus document [1] more in general, in part because of the still generally scant reporting of the CE cyst stage in cohort studies describing how patients with cystic echinococcosis are managed in different centres [5,29]. Nevertheless, the watch-and-wait approach for asymptomatic, uncomplicated inactive CE cysts seem still poorly adopted and inappropriate treatment of inactive cysts still occurring [26,28▪▪,30–34], exposing patients to unnecessary treatment-derived risks and the health system to unnecessary costs. Strong advocacy of such approach in the medical community is needed, as it is the urgent support of updated WHO guidelines on the management of cystic echinococcosis, being written at the time of writing of this paper. Equally important is the information and education of patients regarding the importance of compliance with ultrasound follow-up even in the presence of asymptomatic, inactive CE cysts. When patients lost to follow-up were re-contacted by telephone to understand the reason for missing regular visits, Lissandrin *et al*. [14] found that 38.2% could not be reached, 37.3% were followed in another hospital, whereas 21.6% reported being in good clinical condition and therefore decided not to attend follow-up visits. Two (2.0%) patients died for causes unrelated to cystic echinococcosis and one (0.9%) patient reported complications, the nature of which and relation to cystic echinococcosis could not be clarified.

Acknowledgements

The authors thank Dr Cristina Mazzi at IRCCS Sacro Cuore Don Calabria Hospital for the meta-analysis of the population-based prevalence of infection.

Financial support and sponsorship

This work was supported by the Italian Ministry of Health 'Fondi Ricerca Corrente' to IRCCS Sacro Cuore Don Calabria Hospital – Linea 2.

Conflicts of interest

There are no conflicts of interest.

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