

## Ribavirin for patients with Crimean–Congo haemorrhagic fever: a systematic review and meta-analysis

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**Background:** Crimean–Congo haemorrhagic fever (CCHF) is a potentially fatal tick-borne infection. The virus is widely distributed around the world and reports of sporadic cases and outbreaks have recently increased significantly. Some authors have proposed that ribavirin improves survival in CCHF and this view appears to be widely accepted.

**Methods:** We evaluated the efficacy of ribavirin in reducing mortality by conducting a systematic review and meta-analysis. We included randomized controlled trials and observational studies that compared the outcomes of CCHF patients who were treated with ribavirin with those of patients that were not treated. The main endpoint we assessed was survival. We also evaluated secondary endpoints, i.e. adverse events, length of stay in the hospital, time taken for laboratory values to return to normal and requirement for blood products. A pooled estimate of the relative risks for survival from each study was obtained by using random effects models.

**Results:** One randomized controlled trial and seven observational studies met our inclusion criteria. Most observational studies suffered from different types of bias due to inappropriate selection of controls. Compilation of data from all included studies showed that ribavirin did not improve survival in CCHF (relative risk 1.06, 95% confidence interval 0.97–1.16). Analysis of secondary endpoints did not suggest a clinically significant beneficial effect either.

**Conclusions:** Our systematic review and meta-analysis revealed that the available data in the literature are inadequate to support a claim of efficacy of ribavirin in CCHF. We believe a real uncertainty exists over the benefit of ribavirin in the treatment of CCHF, which necessitates the urgent conduct of a randomized placebo-controlled trial.

**Keywords:** haemorrhagic fever, antiviral therapy, mortality

### Introduction

Crimean–Congo haemorrhagic fever (CCHF) is a tick-borne viral infection. The virus is a member of the genus *Nairovirus* in the family *Bunyaviridae*. Infection can cause a wide range of symptoms, from mild febrile illness to severe haemorrhagic fever, for which the reported mortality rate is up to 80%.<sup>1–3</sup> The virus is widely distributed around the world and CCHF is known to occur in parts of Africa, Asia, Southern and Eastern Europe and the Middle East.<sup>1–4</sup> During the last decade, reports of sporadic cases and outbreaks have increased substantially.<sup>5–10</sup> Particularly in Iran and Turkey, the annual number of diagnosed cases has increased to an outbreak level since the recognition of the infection.<sup>11,12</sup>

As with all haemorrhagic fever syndromes, the mainstay of treatment for CCHF is supportive, including replacement of blood and blood products and providing intensive care for severe cases who develop organ failure.<sup>13,14</sup> The efficacy of ribavirin in the treatment of CCHF is debatable. Ribavirin is a broad-spectrum antiviral nucleoside with *in vitro* activity against both DNA and RNA viruses.<sup>15</sup> Although the exact antiviral mechanism of ribavirin has not been fully characterized, due to its broad-spectrum activity there have been attempts to use it in the treatment of many different viral infections, particularly those with no proven therapeutic options,<sup>16,17</sup> but almost none has shown a therapeutic effect.<sup>18–23</sup> On the basis of its *in vitro* activity and a single clinical trial in haemorrhagic fever with renal syndrome,<sup>24</sup> which is also caused by a bunyavirus, ribavirin is widely advocated for the treatment of CCHF.<sup>16,25</sup> Some reports have suggested its

efficacy<sup>25–28</sup> but it has not been approved for use in CCHF by any rigorous regulatory agency, such as the US FDA or European Medicines Agency (EMA). However, ribavirin is mentioned as being effective in CCHF-related documents at the WHO website<sup>29</sup> and it is included in the WHO Essential Medicines List. Furthermore, a statement in a report by European Centre for Disease Control and Prevention (ECDC) argues that a randomized placebo-controlled trial of ribavirin for CCHF would be unethical.<sup>30</sup>

Recently, there have been reports that cast doubt on this widely accepted conviction about the efficacy of ribavirin in CCHF. One of them was a population-level study that showed that the use of ribavirin for CCHF dropped from 68% to 12% in Turkey between 2004 and 2007 while the mortality rate stayed the same, at around 5%.<sup>11</sup> Another report, which had the largest sample size to date, failed to show any survival benefit<sup>31</sup> and the first randomized trial, published recently, supported these findings.<sup>32</sup> In this study, our aim was to critically evaluate the information available in the literature and assess whether ribavirin offers a survival benefit in CCHF.

## Methods

### Search strategy

We searched The Cochrane Library, Current Controlled Trials Register, PubMed, EmBase and ISI Citation Indexes until April 2010, without language restriction. The following search terms were used with (OR): ‘hemorrhagic fever virus, Crimean–Congo [MeSH]’, ‘hemorrhagic fever, Crimean [MeSH]’, ‘Crimean–Congo hemorrhagic fever’, ‘Crimean–Congo haemorrhagic fever’, ‘Crimean–Congo’, combined with (AND) ‘ribavirin’. We also searched the bibliographies of published studies and abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Infectious Diseases Society of America (IDSA) and European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) starting from 2001, and investigated whether relevant abstracts were later published in full. We searched local journals on the internet, from Pakistan (<http://www.pakmedinet.com>), Iran (<http://www.iranmedex.com>) and Turkey (<http://medline.pleksus.com.tr>) and the Russian language internet. Google Scholar was also used for searching the internet. All titles and abstracts were examined by two authors (S. A. and H. L.) and full-text articles were retrieved if they included information on the use of ribavirin in patients with CCHF.

### Inclusion criteria and outcomes

We considered randomized controlled trials (RCTs) and observational studies that compared the outcomes of CCHF patients who were treated with ribavirin with the outcomes of those who were not treated. We required a defined control group of patients who were not treated with ribavirin in an observational study to differentiate it from a case series. Studies were included irrespective of case confirmation, age of the study population, setting (hospital or outpatient) or formulation and dose of ribavirin used. We excluded case reports and case series and studies with missing outcome data (mortality rate) for all or part of the study population.

A patient was defined as a confirmed case as defined by the authors of the study, and either specific CCHF immunoglobulin M or a real-time PCR test positivity was required. Since patients who recover from CCHF infection do not experience any long-term morbidity, our primary outcome was survival at any timepoint during follow-up. We also defined secondary outcome measures, which were adverse events, length of stay (LOS) in the hospital, time taken for laboratory values to

return to normal, and the requirement for blood products, i.e. fresh frozen plasma (FFP), platelet suspension and erythrocyte suspension.

### Evaluation of bias

Observational studies of treatment effects may be subject to various types of bias, and guidelines for the meta-analyses of observational studies therefore recommend thorough assessment and explicit reporting of study quality.<sup>33–35</sup> We assessed study quality issues related to the design, conduct, analysis and reporting of each study. Bias was assessed in the four domains of (i) selection bias, (ii) performance bias, (iii) detection bias and (iv) attrition bias, since these are the most important threats to validity.<sup>33,36,37</sup> Owing to lack of agreement and validated scoring systems for observational studies,<sup>33,36</sup> we did not use a scoring system. Evaluations of different types of bias were done independently by the two reviewers (S. A. and K. A. C.) according to standard definitions<sup>33,36,37</sup> and the results reported were unanimously agreed upon.

### Data extraction and analysis

From each eligible study, we recorded data on study populations, settings, diagnosis and treatment details, survival rates, adverse events and study design items. Data were extracted independently by two investigators (S. A. and H. L.) and discrepancies between independent search results were resolved by a third investigator (H. V.). Authors of two studies<sup>38,39</sup> provided the numbers of confirmed cases. One author<sup>31</sup> provided data for calculations of standard deviations of the mean for transfused blood products and LOS. We received information about the randomization procedure of the RCT from the authors.<sup>32</sup>

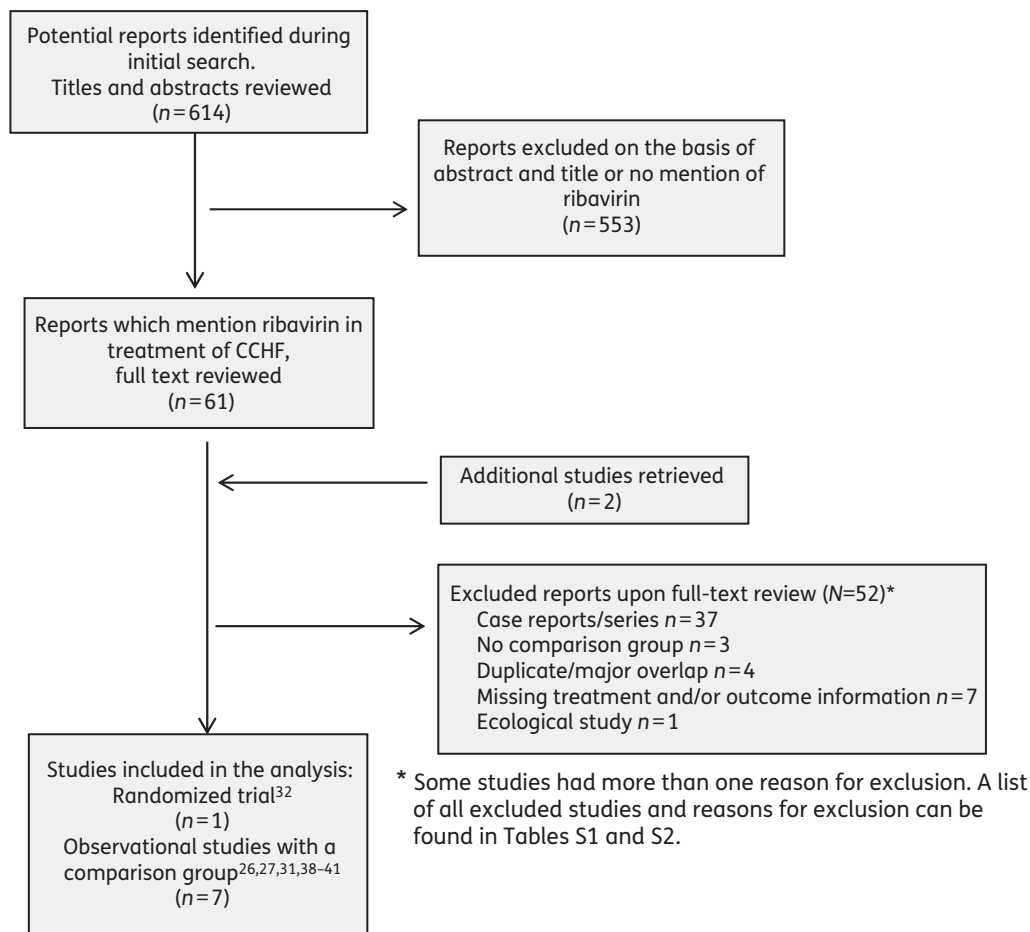
To assess whether using ribavirin increased survival, cumulative survival rates among ribavirin users were divided by the cumulative survival rates among the non-users to estimate the relative risk for survival (RR); 95% confidence intervals (CIs) were calculated for each estimate. A pooled estimate of these RRs was obtained by using random effects models. For our primary analysis we included all cases, and we also did a sensitivity analysis by including only the confirmed cases. Heterogeneity was assessed by using statistical tests (the Q-test and  $\tau^2$ ) and the  $I^2$  method was used to assess the magnitude of variation secondary to heterogeneity (considered significant for  $I^2 > 50\%$ ). A stratified analysis by the country of origin was performed to explore heterogeneity. For continuous secondary outcome measures (LOS, blood product transfusions and time taken for laboratory values to return to normal), we subtracted the mean value of the ribavirin group from the mean value of the control group to estimate whether the amount was decreased on average by the use of ribavirin. Therefore, a positive result shows a favourable effect of ribavirin and a negative result the opposite.

Publication bias could not be evaluated due to the small number of studies. All analyses were performed using STATA version 9 (Stata, College Station, TX, USA). For the conduct and reporting of this systematic review, we used the guidance of the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statements.<sup>34,35</sup>

## Results

### Eligible studies

Our search yielded a total of 614 potential references (Figure 1). After we had examined all titles and abstracts, we retained 61 studies that mentioned ribavirin in the treatment of CCHF. We identified two more studies through reference lists. We read the full texts of 63 articles and excluded 52 of them; a list of excluded articles and reasons for exclusion can be found in Tables S1 and S2 (available as Supplementary data at JAC



**Figure 1.** Flow diagram for identification of studies for inclusion in the systematic review and meta-analysis.

Online). We identified one RCT<sup>32</sup> and seven observational studies<sup>26,27,31,38-41</sup> with a control group that met our inclusion criteria. We also identified three studies comparing the outcomes of patients treated early versus late during the course of disease,<sup>28,42,43</sup> one study performed both types of comparison.<sup>40</sup> All these publications were exclusively from two countries, Iran and Turkey. Table 1 shows the key characteristics of the studies included in our analysis.

### Design and quality characteristics

Methodological quality issues of the studies are summarized in Table 2 and detailed explanations can be found in Table S3.

The only RCT evaluating the efficacy of ribavirin did not show a survival benefit.<sup>32</sup> Although it had limitations such as small sample size and insufficient concealment during randomization, it is still the most valid study to date on this subject.

All observational studies suffered from selection bias to different degrees. Three studies<sup>26,39,40</sup> were assessed to harbour major performance and detection biases and two studies<sup>26,39</sup> to harbour major attrition bias. Our assignment of bias was mostly based on inappropriate selection of control groups, which were compiled retrospectively from records of untreated patients. For example, two studies<sup>26,39</sup> chose their control

groups from patients who were reported before recognition of the infection and the availability of ribavirin in the country. No information was provided to illustrate whether ribavirin-treated and untreated patients were similar with regard to important risk factors for mortality, such as severity of disease, adequate supportive treatment or timely admission, which must have been very different during the earliest period of the outbreak and afterwards. Another example of a study design that led to severe bias was the comparison of early with late starters of ribavirin. In that study,<sup>40</sup> patients who did not receive ribavirin or started late were actually the patients admitted to the hospital too late, as reported by the authors elsewhere;<sup>44</sup> so these patients did not have the opportunity for a timely start of supportive treatment. Thus, the difference in the outcomes of these patients cannot confidently be attributed solely to ribavirin, as suggested in these reports.

### Meta-analysis of survival

Eight studies were included in the analysis that reported the outcomes of 968 patients, of whom 731 (75.5%) had confirmed CCHF infection. The average mortality rate was 17% in total and 11% among the confirmed cases. Compilation of data including both confirmed and suspected cases across all eight

**Table 1.** Studies comparing ribavirin-treated patients with a control group of ribavirin-untreated patients in CCHF

Study and publication year	Study period	Location	Study design	Regimen	Mean age (years $\pm$ SD)	Diagnosis confirmed/total no. of patients	Total no of deaths (% CFR)
Mardani <sup>26</sup> 2003	1999–2001	Iran	historical control	oral 30 mg/kg loading 15 mg/kg 4 times/day, 4 days 7.5 mg/kg 3 times/day, 6 days	not reported	81/187	64 (34.2)
Alavi-Naini <sup>39</sup> 2006	1999–2004	Iran	historical control	oral 30 mg/kg loading 15 mg/kg 4 times/day, 4 days 7.5 mg/kg 3 times/day, 6 days	not reported	155/255	49 (19.2)
Ergonul <sup>27</sup> 2004	2002–03	Turkey	retrospective cohort	oral 4 g/day for 4 days 2.4 g/day for 6 days	47 $\pm$ 17	35/35	1 (2.9)
Ozkurt <sup>38</sup> 2006	2002–04	Turkey	retrospective cohort	oral 2 g loading 4 g/day for 4 days 500 mg 4 times/day, 6 days	40 $\pm$ 17	29/60	6 (10)
Cevik <sup>41</sup> 2008	2006	Turkey	retrospective cohort	intravenous 17 mg/kg loading 17 mg/kg 4 times/day, 4 days 8 mg/kg 3 times/day, 6 days	not reported	25/25	12 (48)
Tasdelen Fisgin <sup>40</sup> 2009	2004–07	Turkey	retrospective cohort	not reported	46 $\pm$ 15	52/52	6 (11.5)
Elaldi <sup>31</sup> 2009	2003–04	Turkey	prospective pre-post study	oral 30 mg/kg loading 15 mg/kg 4 times/day, 4 days 7.5 mg/kg 3 times/day, 6 days	44 $\pm$ 19	218/218	20 (9.2)
Koksal <sup>32</sup> 2010	2010	Turkey	randomized controlled trial	oral 30 mg/kg loading 15 mg/kg 4 times/day, 4 days 7.5 mg/kg 3 times/day, 6 days	49 $\pm$ 17	136/136	8 (5.9)

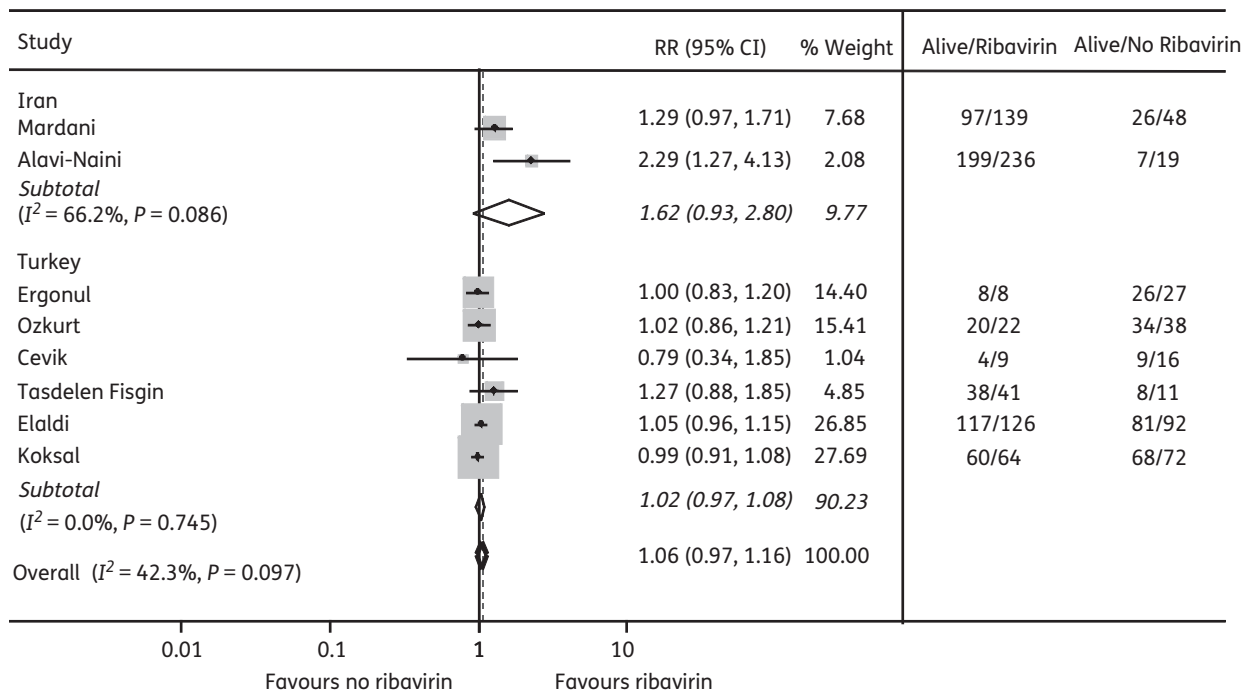
CFR, case fatality rate.

**Table 2.** Quality assessment of the studies included in the systematic review<sup>a</sup>

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Net bias towards	Method to control for confounding
Mardani <sup>26</sup>	major	major	major	major	efficacy of ribavirin	none
Alavi-Naini <sup>39</sup>	major	major	major	major	efficacy of ribavirin	none
Ergonul <sup>27</sup>	insufficient information/ risk of major bias	insufficient information/ risk of major bias	unlikely	unlikely	unknown	none
Ozkurt <sup>38</sup>	moderate	unlikely	unlikely	unlikely	efficacy of ribavirin	none
Cevik <sup>41</sup>	insufficient information <sup>b</sup> / risk of major bias	insufficient information/ risk of major bias	unlikely	unlikely	unknown	none
Tasdelen Fisgin <sup>40</sup>	major	major	major	unlikely	efficacy of ribavirin	none
Elaldi <sup>31</sup>	moderate	unlikely	unlikely	unlikely	efficacy of ribavirin	multivariable regression
Koksal <sup>32</sup>	unlikely	unlikely	unlikely	unlikely	unlikely	randomization

<sup>a</sup>Major, moderate and unlikely show the level of bias in a study caused by problems in design and/or conduct. Detailed explanations of the basis of evaluations can be found in Table S3.

<sup>b</sup>Manuscript does not include enough detail to evaluate bias.



**Figure 2.** Effect of ribavirin on survival in CCHF. Point estimates and 95% confidence intervals are indicated as boxes and whiskers, respectively. The pooled summary estimate is the dark diamond at the bottom. The table on the right shows survival rates according to use of ribavirin in each study.

studies showed that ribavirin did not increase the probability of survival in CCHF (pooled RR for survival 1.06, 95% CI 0.97–1.16,  $P=0.18$ ). Between-study heterogeneity was just statistically significant ( $P=0.097$ ,  $\tau^2=0.005$  and  $I^2=42.3\%$ ). To explore heterogeneity, we analysed the data by stratifying on the country of publication. This analysis revealed that the variation in RR attributable to heterogeneity came from the two Iranian studies (Figure 2). This can be explained by the very similar design of these two studies, which were at high risk of bias due to their way of control selection (Table S3). When we

analysed confirmed cases only, the results were similar, and again did not show any evidence of increased survival with the use of ribavirin (pooled RR for survival 1.03, 95% CI 0.97–1.09,  $P=0.26$ ). In this analysis, heterogeneity was not significant ( $P=0.26$ ,  $\tau^2=0.002$  and  $I^2=21.7\%$ ).

**Length of stay in hospital**

Average LOS in the hospital was reported in four studies.<sup>31,32,38,41</sup> When we combined LOS data from these four studies, the pooled

weighted mean difference (WMD) was only 0.8 h and was non-significant (WMD  $-0.034$  days, 95% CI  $-1.47$  to  $1.54$ ).

### **Time for laboratory values to return to normal**

Four studies<sup>27,32,38,40</sup> reported the time it took for leucocytes, platelets and liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] to return to normal levels. However, two studies<sup>27,40</sup> reported daily mean values of platelets and liver enzymes without showing how many patients' values were used for calculations on each day; this prevented us from pooling their data. When we combined the results of two studies with appropriate reporting, results showed that the time differences were negligible and statistically non-significant (leucocytes, WMD 0.65 days, 95% CI  $-2.83$  to  $4.13$ ; platelets, WMD 0.72 days, 95% CI,  $-1.53$  to  $2.98$ ; ALT/AST, WMD 0.63 days, 95% CI  $-1.67$  to  $2.93$ ).

### **Requirement for blood products**

Three observational studies<sup>31,38,41</sup> compared the amount of blood product transfusions in the ribavirin and control groups. Pooled data showed no evidence for decreased transfusions of platelet suspension or erythrocyte suspension, but ribavirin-treated patients received two units less FFP on average, which was just significant (platelet suspension, WMD 1.88 units, 95% CI  $-0.035$  to  $3.79$ ; FFP, WMD 2.13 units, 95% CI  $0.83$ – $3.42$ ; erythrocytes, WMD  $-0.48$  units, 95% CI  $-1.03$  to  $0.06$ ).

### **Adverse events**

Three studies<sup>32,38,41</sup> reported adverse events. Three cases of severe anaemia were observed among ribavirin users.<sup>32,38</sup> One patient developed allergic rash, and two patients developed nausea and vomiting during intravenous use.<sup>41</sup> None of these events caused discontinuation of treatment. In Elaldi *et al.*<sup>31</sup> no adverse events were reported, but their time-to-event analysis showed a statistically significant time-dependent effect of ribavirin on survival and the authors have speculated that this (crossing of hazards) might have been due to toxicity of ribavirin among the more severe patients.

## **Discussion**

Our study demonstrated the limited evidence available addressing the efficacy of ribavirin. Most observational studies published on this subject lacked a very basic requirement for evaluating a medical intervention, i.e. ensuring the comparability of treated and untreated groups so that the difference in outcome between the groups can be attributed to the treatment given.<sup>45–47</sup> The only proven way of ensuring this is by proper randomization;<sup>46,47</sup> when randomized evidence is unavailable or scarce the potential for bias and uncertainty in the estimates is high. It has been emphasized by many authors that a thorough quality assessment of the observational studies contributing to the evidence should be done.<sup>33,34,48</sup> Our assessment of quality showed that the choice of historical control groups from the initial phase of the outbreak introduced important flaws into the studies. During this period only the most severe cases will be clinically recognized; mild forms of CCHF can easily be misdiagnosed,

even as the common cold. After awareness among the public and the medical community has increased, milder forms of the disease will be diagnosed because patients will start seeking medical care even after a tick bite or a reported tick bite in their history, directing the clinician to the diagnosis.<sup>11</sup> Moreover, interventions such as supportive treatment and early admission will not be similar during the initial and well-established periods of an outbreak. Hence, historical control groups will include more severe patients or patients who could not receive supportive treatment in time. Systematic bias acts consistently in a given direction, leading to biased estimates overall.<sup>33</sup> Our finding of systematic bias in most of the studies favouring the efficacy of ribavirin is consistent with the literature; it has been repeatedly shown that observational studies of medical interventions, especially when the controls are selected from an earlier time period, will weigh the outcome in favour of new therapies.<sup>33,49–51</sup>

We also showed that, even when most of the studies were biased towards finding a beneficial effect of ribavirin, compilation of data from these studies in a meta-analysis did not support the claim that ribavirin is beneficial in CCHF. These observations also cannot refute the possibility that ribavirin may provide benefit; therefore it is essential that a placebo-controlled trial of ribavirin should be conducted. There are repeated statements that a placebo control group in a randomized trial of ribavirin would be unethical.<sup>4,30</sup> However, placebo-controlled trials are only unethical when a treatment is available that has been proved effective, life-saving or at least life-prolonging,<sup>52,53</sup> our study has shown that neither efficacy nor life-saving effect of ribavirin has been proved in CCHF.

Recently, another meta-analysis has been published on this subject,<sup>54</sup> which reported that although some benefit might be possible from ribavirin (RR 0.56, 95% CI 0.35–0.90), the quality of the individual studies was poor and this result might be prone to bias. This study included four additional reports<sup>55–58</sup> that we chose to exclude after a detailed review; one was an abstract of a study not yet completed<sup>58</sup> and the other three were case series (Table S1).

Our study showed that there was no evidence of increased survival with ribavirin in CCHF. In addition, we did not find any suggestion of a benefit that might be implied by a shorter hospital stay, earlier improvement of laboratory values or decreased requirement for blood products among ribavirin-treated patients. We believe a genuine uncertainty exists over whether ribavirin will be beneficial in the treatment of CCHF. This warrants an urgent randomized placebo-controlled trial in the face of an infection that has broadened its geographical distribution rapidly during the last decade. Since this is an acute infection without any long-term sequelae or a definite surrogate of outcome, the only relevant outcome in a trial will be survival and a large sample size will be required. However, this should not discourage us from demanding the best scientific justification for ribavirin treatment. We believe a placebo-controlled randomized trial is achievable using a large, simple trial design<sup>59</sup> and the collaboration of multiple centres.

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## Transparency declarations

None to declare.

## Author contributions

S. A., H. L. and H. V. designed the systematic review. S. A., H. L. and H. V. did literature searches and full-text reviews and collated the studies. S. A. analysed the data and drafted the manuscript. S. A. and K. A. C. critically reviewed the studies. K. A. C., H. L. and H. V. revised and commented on subsequent drafts.

## Supplementary data

Tables S1–S3 are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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