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Review

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Abstract

Background: Some review papers and meta-analyses have investigated seroprevalence and fatality trends of the Crimean-Congo hemorrhagic fever (CCHF), but it is not clear if its seroprevalence is increasing.

Aim: To investigate the trend in the seroprevalence of CCHF.

Methods: We conducted a secondary analysis of the results of a meta-analysis of the seroprevalence of CCHF published in 2019. We used a multilevel mixed effects Poisson regression to find the predictors of seropositivity. To explain the magnitude effect, we reported an incidence rate ratio (IRR) with a 95% confidence interval (CI). We conducted multilevel modeling using Stata 14 for data analysis.

Results: In the fixed effects model, time was significantly associated with increased seropositivity (IRR = 1.025, 95% CI = 1.021–1.030), and no significant association was found for local sampling (IRR = 1.026, 95% CI = 0.988–1.065). In the mixed effects model, random intercepts of the country and parallel of latitude were applied as 3 levels of the model (prevalence rate of each study, nested within countries and latitude parallel). Accordingly, time was significantly associated with a reduction of seropositivity (IRR = 0.899, 95% CI = 0.891–0.907), and local sampling was significantly associated with increased seropositivity (IRR = 2.477, 95% CI = 2.316–2.649).

Conclusion: Despite reporting increasing trends for seroprevalence of CCHF in previous reviews and the fixed effects model of the present study, the secondary mixed effects modeling showed a decreasing trend. The multilevel generalized model is recommended for such temporal and spatial designs in the future.

Keywords: Poisson distribution, Crimean–Congo haemorrhagic fever, multilevel analysis, statistical modelling

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Background

Haemorrhagic fever is caused by many types of viruses, including Ebola, Marburg, Rift Valley fever, Yellow fever, and Crimean–Congo haemorrhagic fever (CCHF) viruses (1). CCHF is a tick-born disease that presents as an acute haemorrhagic fever. CCHF virus is an arbovirus (arthropod-borne virus) belonging to the Bunyaviridae family and the Nairovirus genus (with some controversies). Different mammals can act as asymptomatic hosts of CCHF virus, which can be transmitted to humans through tick bites and contact with animal blood. The disease is common in Africa, Asia (especially the Middle East), and South-east Europe. The incubation period is short and signs and symptoms begin to appear within a week. Primary symptoms are similar to those of other viral diseases, and include fever, headache, myalgia, and gastrointestinal symptoms, with haemorrhagic symptoms appearing in the second phase of the disease. CCHF can cause bleeding in mucosal membranes as well as the skin. The disease can be confirmed by polymerase chain reaction in the first few days, followed by determination of virus-specific IgM (2–6).

CCHF is of epidemiological importance because of the lack of specific treatment and vaccination and its high case fatality rate (7, 8). Several reviews and meta-analyses have investigated its seroprevalence and fatality trends in recent decades (7, 9). In addition to time trends, the seroprevalence of CCHF is affected by demographic and local factors. For example, in a study of 800 people in Uganda, 221 (27.6%) were seropositive for CCHF-specific IgG, which was related to livestock farming, age, and collecting/eating engorged ticks (10).

The main objective of this study was to determine whether the seroprevalence of CCHF increased over the period of the studies covered by the reviews. A multilevel mixed-effects model was constructed, with adjustment for possible confounding or random effects, to analyse the time trend in CCHF seropositivity. This was a secondary study based on the seroprevalence data in prior studies. It was expected that the random effects of countries would have influenced the trends in CCHF seropositivity.

Methods

Study design

A secondary analysis was conducted on a summary of the results of a meta-analysis published by Nasirian in 2019 about the seroprevalence of CCHF (9). The meta-analysis was performed on Google Scholar, PubMed, ScienceDirect, Scopus, and Web of Science. There were 36 studies with reports of CCHF seroprevalence in humans between 1944 and 2017. Multilevel modelling with an ecological approach was conducted on the collected data. Appropriate data were retabulated based on the objectives of our study. No human or nonhuman case was directly involved as it was a secondary study.

Variables

The outcome variable was CCHF seropositivity, expressed as the count per number of patients evaluated (statistically referred to as count per exposure). To reach the raw counts, each seroprevalence was multiplied by each study sample size, and the obtained number was rounded. The independent variables were study time (as a time trend) and sampling location (across a country or localized). For the time variable, if the samples were collected for > 1 year, the mean time range was taken (in years). The levelling variables were the country and the parallel of latitude of each country. For the parallel of latitude, the classification was from the 90th parallel south to the 90th parallel north increasing 10° by 10° (during analysis, deviation from the equator was regarded as positive without considering south or north). During multilevel analysis, the parallel of latitude was considered the main level, and the country was considered a level nested within the parallel of latitude.

Statistical methodology

Dataset preparation and multilevel modelling were conducted using Stata version 14. The prevalence rates were mostly low; therefore, a Poisson distribution was regarded as the outcome variable. After data collection, the weight of each study was calculated using the following steps: (1) standard error (SE) for Poisson distribution was calculated by the -cii- command based on the imported seropositive cases per sample size of each study; (2) inverse variance was calculated as 1 divided by the square of SE; (3) relative weights were calculated by division of each inverse variance by the sum of inverse variances; (4) the mean of sample sizes was calculated (802.917); the reason for not using the sum of sample size was to prevent over-powering of analysis; and (5) the relative weights were multiplied by the above mean to reach individual study weights.

Multilevel Poisson regression was performed by the -mepoisson- command. To explain the magnitude effect, an incidence rate ratio (IRR) was reported, as the exponential form of β coefficient with a 95% confidence interval (CI). The significance level was regarded as 0.05. The predicted values of the model equation were then reported by the -predict- post estimation command.

The template of the mixed-effects model equation and definitions of each term were as follows:

β1, β2: regression coefficient of each independent variable

β0: fixed part intercept

X1, X2: independent variables of the fixed part, including time (unit: years) and location (unit: local = 1, across country = 0)

e: random part including a random intercept of countries nested within parallel of latitude.

ε: residual variance

Y: count outcome with Poisson distribution (number of seropositive cases considering the sample size as the exposure variable).

Ethical considerations

As a secondary study, there was no requirement for ethical approval. The collected information was newly tabulated along with further variables; therefore, no plagiarism occurred. The sources of primary data were cited and acknowledged. Copyright of the publisher was respected (https://www.elsevier.com/about/policies/copyright). Access to the data was institutional.

Results

A total of 1412 seropositive cases from 28 905 individuals were investigated. The data from the individual studies (11–45) along with the collected variables and calculated new variables are summarized in Table 1 . The time range was 1970.5–2015.5, sample size was 38–3557, and calculated prevalence was 0.001–0.144.

A fixed-effects model was constructed to determine the effect of time trend and location (local vs countrywide) on the seropositivity of CCHF (Model 1). Time was significantly associated with increased seropositivity (IRR = 1.025 per year, 95% CI = 1.021–1.030), but no significant association was found for location (IRR = 1.026, 95% CI = 0.988–1.065) (Table 2).

A multilevel mixed-effects model was constructed for prediction of CCHF seropositivity using country as a random intercept (Model 2). Time was significantly associated with a reduction in seropositivity (IRR = 0.899 per year, 95% CI = 0.892–0.906), but local investigation was significantly associated with increased seropositivity (IRR = 2.475, 95% CI = 2.319–2.642) (Table 3).

A multilevel mixed-effects model was constructed for prediction of CCHF seropositivity using a random intercept of country nested within parallel of latitude (Model 3). Time was significantly associated with a reduction of seropositivity (IRR = 0.899 per year, 95% CI = 0.891–0.907), but local investigation was significantly associated with increased seropositivity (IRR = 2.477, 95% CI = 2.316–2.649) (Table 4). Marginal prediction based on time is also shown in Figure 1 . Accordingly, the trend was increasing in the marginal prediction of the fixed-effects model (Figure 1A), while the trend was decreasing in the marginal prediction of the mixed-effects model (Figure 1B).

The mean of the predicted prevalence rates was 1.86% (95% CI = 1.67–2.04%) based on Model 3. The mean of the observed prevalence rates was 1.65% (95% CI = 1.49–1.81%) using the individual study weights and the symmetric of 95% CI. In other words, the number of predicted cases was associated linearly with the number of real cases (R2 = 0.947).

Discussion

This study investigated the role of the random effects of country and parallel of latitude on the association of time trend with seroprevalence of CCHF. The previous meta-analysis showed that the time trend was significantly associated with increased seroprevalence of CCHF (9). However, in this study, there was a negative association after weighting the studies and adjusting for the random intercepts of country and parallel of latitude. This trend change after applying random effects may have resulted from heterogeneity in CCHF seroprevalence among different countries and latitudes. In other words, large random effects affected the estimation of regression coefficients. The role of sampling location was adjusted in Model 3 as a possible confounder, which was associated with increased seroprevalence.

Many modelling studies have been conducted worldwide because of the global importance of CCHF and necessity of disease monitoring. Vescio et al. used Poisson regression to study environmental factors affecting CCHF incidence in Bulgaria (46). They found that the significant risk factors were: mean temperature (IRR = 1.055); mean normalized vegetation index (IRR =

1.018); habitat fragmentation level (medium vs low, IRR = 1.402; high vs low, IRR = 1.558); and proportion of areas covered by grassland, scrub, and herbaceous vegetation (medium vs low, IRR = 3.994; high vs low, IRR = 4.260). However, they did not investigate the time trend. Mostafavi et al. conducted temporal modelling in the Islamic Republic of Iran to predict the future occurrence of CCHF (47). According to their logistic regression modelling, the risk factors were districts with a history of CCHF reports in previous years, population size, altitude, seasonal variation, relative humidity with a 2-month time lag, and maximum temperature with a 3-month time lag. The protective factors were a year of CCHF reports and latitude of the region. The negative association found for the time trend was consistent with our findings. Additionally, we used the Poisson model instead of the logistic model with an ecological approach. Lysholm et al. conducted multilevel modelling analyses in Zambia to find predictors of the seroprevalence rates of some infectious agents, including CCHF in goats (48). They found that keeping pigs was associated with an increased seroprevalence of CCHF. Multilevel modelling is effective for such ecological approaches used in seroprevalence studies.

Multilevel modelling has been used for the seroprevalence of other infectious agents. Molla et al. (2021) used multilevel modelling to study the risk factors for Mycoplasma mycoides seroprevalence in Ethiopia (49). They used herds as the random part of their model and found that trekking from/through endemic zones, endemic and epidemic borders, and adjacent distances (

Some studies on CCHF epidemiology have used other modelling methods. Mohammadi et al. (2021) performed mathematical modelling of the CCHF transmission cycle (50). According to their numerical simulation, to control CCHF spread, the transmission rate should be reduced by reducing contact between different groups. Telford et al. (2023) conducted spatial modelling of the seroprevalence of CCHF among livestock in Uganda (51). They used a generalized linear geostatistical model on the logit-transformed seroprevalence rates of CCHF. The risk factors were sheep/goat species (vs cattle), sand content of the soil, and land surface temperature, while the protective factor was the distance to croplands. In contrast to our study, they used a logit-transformed model, but a similarity was that they considered the random effects in their model.

Our study had some limitations. First, it was a secondary study and we did not have access to the individual participant data. Second, we did not have access to other potential confounding variables. Third, there was a wide range of 95% CIs of random variances, which showed the heterogeneity of the primary studies. Finally, the study was sensitive to ecological fallacies as the analyses were performed on the aggregate data. The multilevel modelling was a strength of the study as it is an increasingly used statistical method worldwide.

Conclusion

Despite reporting increasing trends for seroprevalence of CCHF in previous reviews and our fixed-effects model, the secondary mixed-effects modelling showed a decreasing trend after adjustment for local sampling as a covariate and country and parallel of latitude as random intercepts. The results of this study show the importance of the random effects in ecological approaches and aggregate data analysis. Therefore, the main recommendation is that multilevel generalized models should be used further for such temporal and spatial designs in the future to adjust for any potential random effect.

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Modélisation secondaire multiniveau à effets mixtes de la tendance de la séroprévalence de la fièvre hémorragique de Crimée-Congo

Résumé

Contexte : Plusieurs articles de synthèse et méta-analyses ont examiné la séroprévalence et les tendances en matière de létalité de la fièvre hémorragique de Crimée- **Congo**. Cependant, il n'est pas certain que sa séroprévalence soit en augmentation.

Objectif : Étudier l'évolution de la séroprévalence de la fièvre hémorragique de Crimée-Congo.

Méthodes : Nous avons procédé à une analyse secondaire des résultats issus d'une méta-analyse sur la séroprévalence de la fièvre hémorragique de Crimée-Congo publiée en 2019. Nous avons recouru à la régression de Poisson à effets mixtes à plusieurs niveaux afin de déterminer les facteurs prédictifs de séropositivité. Pour expliquer l'ampleur de l'effet, nous avons établi un rapport du taux d'incidence (IRR) avec un intervalle de confiance (IC) à 95 %. Nous avons réalisé une modélisation multiniveau à l'aide du logiciel STATA version 14 pour l'analyse des données.

Résultats : Dans le modèle à effets fixes, le temps était associé de manière significative à une augmentation de la séropositivité (IRR = 1,025 ; IC à 95 % : 1,021-1,030), et aucune association notable n'a été observée pour l'échantillonnage local (IRR = 1,026 ; IC à 95 % : 0,988-1,065). Dans le modèle à effets mixtes, les intercepts aléatoires du pays et la latitude ont été appliqués pour constituer les trois niveaux du modèle (taux de prévalence de chaque étude, niché dans les pays et la latitude). Ainsi, le temps était significativement associé à une réduction de la séropositivité (IRR = 0,899 ; IC à 95 % : 0,891-0,907) et l'échantillonnage local était fortement associé à une augmentation de la séropositivité (IRR = 2,477 ; IC à 95 % : 2,316-2,649).

Conclusion : Malgré une tendance à la hausse de la séroprévalence de la fièvre hémorragique de Crimée-Congo constatée dans les analyses précédentes et dans le modèle à effets fixes réalisé au cours de la présente étude, la modélisation secondaire à effets mixtes a montré une tendance à la baisse. Les modèles multiniveaux généralisés sont recommandés pour de telles conceptions spatiales et temporelles à l'avenir.

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