Secondary multilevel mixed-effects modelling of seroprevalence trends of Crimean–Congo haemorrhagic fever

Seyyed AY Ahmadi[1], Mohammad S Baghi[2], Razieh Shirzadegan[3] and Hassan Nasirian[4,5]

[1]Preventive Medicine and Public Health Research Center, Psychosocial Health Research Institute, Iran University of Medical Sciences, Tehran, Islamic Republic of Iran. [2]Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Islamic Republic of Iran. [3]Nursing Department, Doroud Branch, Islamic Azad University, Doroud, Islamic Republic of Iran. [4]Department of Medical Entomology and Vector Control, School of Public Health, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran (Correspondence to H Nasirian: hanasirian@yahoo.com). [5]Institute for Environmental Research (IER), Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran.

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

Citation: Ahmadi SAY, Baghi MS, Shirzadegan R, Nasirian H. Secondary multilevel mixed-effects modelling of seroprevalence trends of Crimean–Congo haemorrhagic fever. East Mediterr Health J. 2024;30(1):68–76. https://doi.org/10.26719/emhj.24.006

Received: 08/02/23, Accepted: 04/10/23

Copyright: © Authors 2024; Licensee: World Health Organization. EMHJ is an open access journal. All papers published in EMHJ are available under the Creative Commons Attribution Non-Commercial ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

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:

$$Ln(Y) = \beta 1X1 + \beta 2X2 + \beta 0 + e + \varepsilon$$

$$Y = e^{\beta 1X1+\beta 2X2+\beta 0+e+\varepsilon}$$

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%

Table 1 Summary of the data source studies and the new variables

Country	Cases	Sample size	Year	PL	Location	Weight	CP	Refs
Afghanistan	36	320	2009	40	Local	1.317	0.112	(11)
Bulgaria	21	751	2011.5	50	Across	12.433	0.028	(12)
Bulgaria	56	1500	2015	50	Across	18.600	0.037	(13)
Cameroon	6	137	2008.5	10	Local	1.448	0.044	(14)
China	42	2454	2004.5	50	Across	66.375	0.017	(15)
China	56	1657	2008	50	Local	22.697	0.034	(16)
Georgia	27	905	2014	50	Local	14.043	0.030	(17)
Ghana	6	109	2011	10	Local	0.917	0.057	(18)
Greece	68	1611	2009.5	50	Across	17.669	0.042	(19)
Greece	7	207	2012	50	Across	2.834	0.034	(20)
Greece	6	277	2010.5	50	Across	5.920	0.022	(21)
Greece	120	3152	2011	50	Across	38.327	0.038	(22)
Iran	4	100	1970.5	40	Across	1.157	0.040	(23)
Iran	7	297	2002	40	Local	5.833	0.024	(24)
Iran	18	285	2003.5	40	Local	2.089	0.063	(25)
Iran	12	100	2008	40	Local	0.386	0.120	(26)
Kosovo	44	1105	2012	50	Across	12.847	0.040	(27)
Kuwait	20	502	1980.5	30	Across	5.833	0.040	(28)
Madagascar	10	1995	2008.5	-10	Across	184.246	0.005	(29)
Malaysia	1	682	2012	10	Across	215.311	0.001	(30)
Mozambique	8	300	2015.5	-20	Local	5.208	0.027	(31)
Nigeria	7	297	2011.5	20	Local	5.833	0.024	(32)
Nigeria	126	1189	2012	20	Local	5.194	0.106	(33)
Oman	1	41	1995.5	30	Across	0.778	0.024	(34)
Saudi Arabia	3	354	1997	30	Local	19.337	0.008	(35)
Saudi Arabia	6	1024	2010	30	Local	80.901	0.006	(36)
Tunisia	5	181	2014	40	Across	3.033	0.027	(37)
Tunisia	2	38	2014	40	Across	0.334	0.052	(37)
Turkey	100	782	2006	40	Across	2.831	0.128	(38)
Turkey	356	3557	2009	40	Across	16.452	0.100	(39)
Turkey	85	625	2012	40	Across	2.127	0.136	(40)
Turkey	25	1066	2013	40	Across	21.042	0.023	(41)
Turkey	45	322	2015	40	Local	1.067	0.140	(42)
Turkey	12	324	2012	40	Local	4.050	0.037	(43)
Turkey	53	368	2012	40	Local	1.183	0.144	(44)
United Arab Emirates	12	291	1994.5	30	Across	3.267	0.040	(45)

CP, calculated prevalence and PL, parallel of latitude.

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 (R^2 = 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

Table 2 Fixed-effect model for prediction of CCHF seropositivity (Model 1)

Covariate (unite)	IRR	*P*	95% CI
Time (year)	1.025	< 0.001	1.021–1.030
Location (local vs across)	1.026	0.177	0.988–1.065
Constant	4.62×10^{-24}	< 0.001	

CCHF = Crimean–Congo haemorrhagic fever; CI = confidence interval; IRR, incidence rate ratio.

Table 3 Multilevel mixed-effects model for prediction of CCHF seropositivity using a random intercept of country (Model 2)

Covariate (unite)	IRR	*P*	95% CI
Time (year)	0.899	< 0.001	0.892–0.906
Location (local vs. across)	2.476	< 0.001	2.319–2.642
Constant	9.34×10^{90}	< 0.001	
Random part			
Country			
Variance (constant)	1.501		0.781–2.883

CCHF = Crimean–Congo haemorrhagic fever; CI = confidence interval; IRR, incidence rate ratio.

Table 4 Multilevel mixed-effects model for prediction of CCHF seropositivity using a random intercept of country nested within parallel of latitude (Model 3)

Covariate (unite)	IRR	*P*	95% CI
Time (year)	0.899	< 0.001	0.891–0.907
Location (local vs. across)	2.477	< 0.001	2.316–2.649
Constant	1.21×10^{91}	< 0.001	
Random part			
Parallel of latitude			
Variance (constant)	0.503		0.075–3.365
Parallel of latitude ? country			
Variance (constant)	0.995		0.454–2.180

Number of iterations, 125. CCHF = Crimean–Congo haemorrhagic fever; CI = confidence interval; IRR, incidence rate ratio.

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.

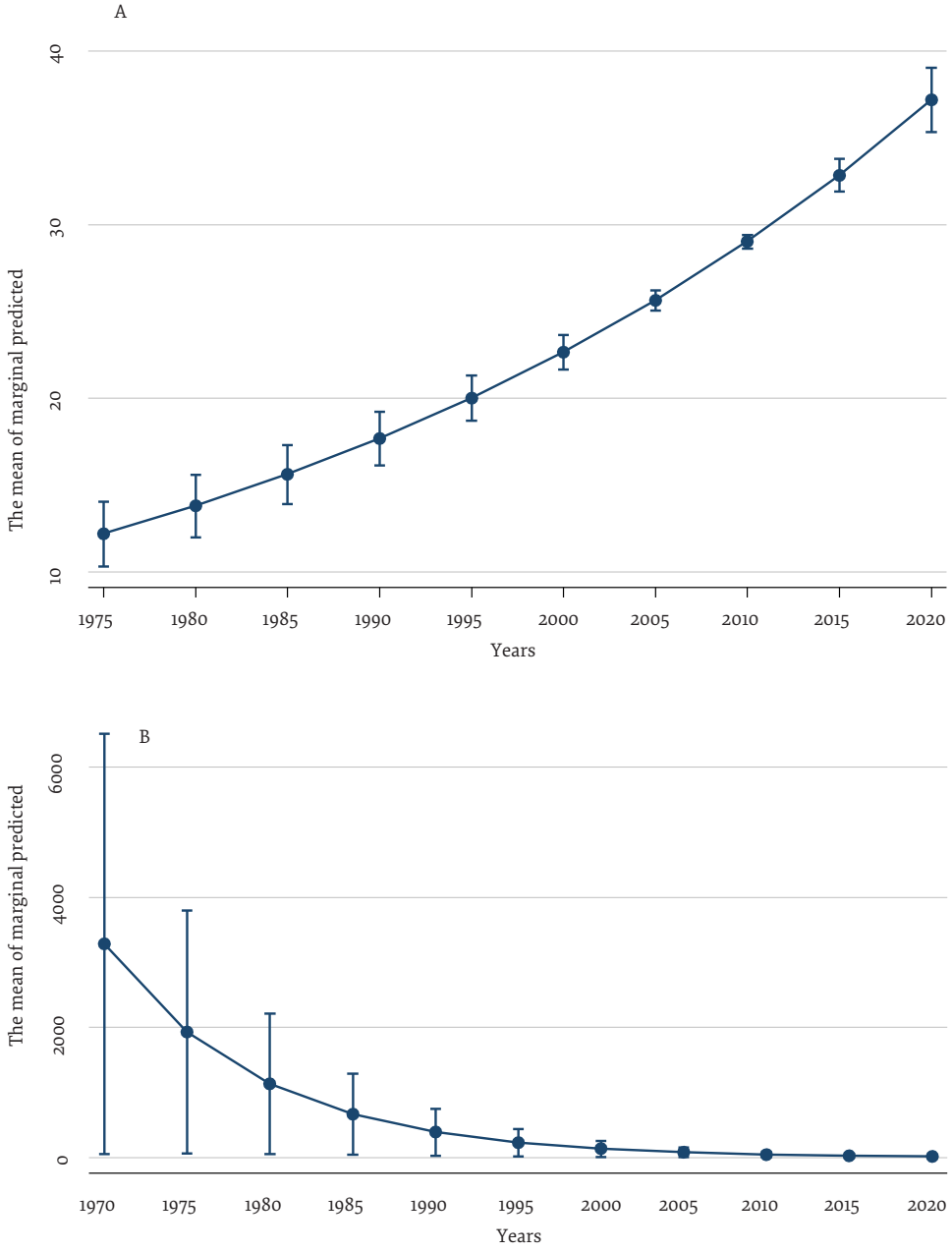
Many modelling studies have been conducted worldwide because of the global importance of CCHF and necessity of disease monitoring. Vescio et al. used Poisson regression to study environmental factors affecting CCHF incidence in Bulgaria (*46*). They found that the significant risk factors were: mean 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 (< 50 km) from endemic zones were the risk factors.

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.

Figure 1 (A) Marginal prediction of Crimean–Congo haemorrhagic fever (CCHF) seropositive cases per study populations (regression predicted number of cases) based on time according to Model 1. Error bars indicate 95% confidence interval (CI). (B) Marginal prediction of CCHF seropositive cases per study populations (regression predicted number of cases) based on time according to Model 3. The error bars indicate 95% CI.



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.

Acknowledgement

We kindly acknowledge the researchers of the primary studies summarized in this paper. We are grateful to the publisher of the previous meta-analysis (*9*) for permission to use the data (copyright available from: https://www.elsevier.com/about/policies/copyright).

Funding: None.

Competing interests: None declared.

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.

هل يزداد الانتشار المَصْلي لِحُمَّى القرم- الكونجو النزفية؟

سيد أمير ياسين أحمدى، محمد صالح باقي، راضيه شيرزادگان، حسن نصيريان

الخلاصة

الخلفية: استقصت بعض البحوث الاستعراضية والتحليلات التلوية اتجاهات الانتشار المَصْلي والإماتة لِحُمَّى القرم-الكونجو النزفية، ولكن ليس من الواضح هل الانتشار المَصْلي لهذه الحمى في ازدياد.

الأهداف: هدفت هذه الدراسة الى تحرِّي اتجاه الانتشار المَصْلي لِحُمَّى القرم-الكونجو النزفية.

طرق البحث: أجرينا تحليلاً ثانويًّا لنتائج تحليل تلوي للانتشار المَصْلي لِحُمَّى القرم-الكونجو النزفية نُشر في عام 2019. واستخدمنا تأثيرات مختلطة متعددة المستويات لنموذج انحدار بواسون لإيجاد العوامل التنبؤية للإيجابية المَصْلية. ولشرح تأثير الجسامة، أبلغنا عن نسبة معدل حدوث الإصابة بفاصل ثقة ٪95. وأجرينا نمذجة متعددة المستويات باستخدام برنامج Stata 14 لتحليل البيانات.

النتائج: في نموذج التأثيرات الثابتة، ارتبط الزمن ارتباطًا كبيرًا بزيادة الإيجابية المَصْلية (نسبة معدل حدوث الإصابة = 1,025، فاصل الثقة 95٪ = 1,021–1,030)، ولم يُعثر على ارتباط يُعتد به لأخذ العينات المحلية (نسبة معدل حدوث الإصابة = 1,026، فاصل الثقة 95٪ = 0,988–1,065). وفي نموذج التأثيرات المختلطة، طُبقت التقاطعات العشوائية للبلد ومتوازية خطوط العرض بوصفها 3 مستويات للنموذج (معدل الانتشار لكل دراسة، المتداخل مع البلدان وخطوط العرض المتوازية). وبناءً على ذلك، ارتبط الزمن ارتباطًا كبيرًا بانخفاض الإيجابية المَصْلية (نسبة معدل حدوث الإصابة = 0,899، فاصل الثقة 95٪ = 0,891–0,907)، وارتبط أخذ العينات المحلي ارتباطًا كبيرًا بزيادة الإيجابية المَصْلية (نسبة معدل حدوث الإصابة = 2,477، فاصل الثقة 95٪ = 2,316–2,649).

الاستنتاجات: رغم الإبلاغ عن تزايد اتجاهات الانتشار المَصْلي لحُمَّى القرم-الكونجو النزفية في الاستعراضات السابقة ونموذج التأثيرات الثابتة للدراسة الماثلة، أظهرت نمذجة التأثيرات الثانوية المختلطة اتجاهًا تنازليًا. ويُوصَى باستخدام نماذج مُعمَّمة متعددة المستويات لهذه التصاميم الزمنية والمكانية في المستقبل.

References

1. Rugarabamu S, Mwanyika GO, Rumisha SF, Sindato C, Lim H-Y, Misinzo G, et al. Seroprevalence and associated risk factors of selected zoonotic viral hemorrhagic fevers in Tanzania. Int J Infect Dis. 2021 Aug;109:174–81. https://doi.org/10.1016/j.ijid.2021.07.006 PMID:34242761
2. Fillâtre P, Revest M, Tattevin P. Crimean-Congo hemorrhagic fever: an update. Med Mal Infect. 2019 Nov;49(8):574–85. https://doi.org/10.1016/j.medmal.2019.09.005 PMID:31607406
3. Kassiri H, Nasirian H. New insights about human tick infestation features: a systematic review and meta-analysis. Environ Sci Pollut Res. 2021 Apr;28(14):17000–28. https://doi.org/10.1007/s11356-021-13102-6. PMID:33641105
4. Nasirian H. Ticks infected with Crimean-Congo hemorrhagic fever virus (CCHFV): a decision approach systematic review and meta-analysis regarding their role as vectors. Travel Med Infect Dis. 2022 May–Jun;47:102309. https://doi.org/10.1016/j.tmaid.2022.102309. PMID:35318129
5. Nasirian H. Detailed new insights about tick infestations in domestic ruminant groups: a global systematic review and meta-analysis. J Parasit Dis. 2022 Jun;46(2):526–601. https://doi.org/10.1007/s12639-021-01460-4. PMID:35692485
6. Nasirian H. Monitoring of hard tick parasitism in domestic ruminants: a scale evidence for policymakers. Vet Parasitol. 2023 Jun;41:100878. https://doi.org/10.1016/j.vprsr.2023.100878. PMID:37208083
7. Nasirian H. New aspects about Crimean-Congo hemorrhagic fever (CCHF) cases and associated fatality trends: a global systematic review and meta-analysis. Comp Immunol Microbiol Infect Dis. 2020 Apr;69:101429 https://doi.org/10.1016/j.cimid.2020.101429. PMID:32062190
8. Javanian M, Roudsari JM, Ebrahimpour S. Immune responses and pathogenesis of Crimean–Congo hemorrhagic fever: an overview. Crescent J Med Biol Sci. 2018 Apr;5(2):166–7. https://www.cjmb.org/uploads/pdf/pdf_CJMB_172.pdf
9. Nasirian H. Crimean-Congo hemorrhagic fever (CCHF) seroprevalence: a systematic review and meta-analysis. Acta Tropica 2019 Aug;196:102–20. https://doi.org/10.1016/j.actatropica.2019.05.019 PMID:31108083
10. Atim SA, Ashraf S, Belij-Rammerstorfer S, Ademun AR, Vudriko P, Nakayiki T, et al. Risk factors for Crimean-Congo Haemorrhagic Fever (CCHF) virus exposure in farming communities in Uganda. J Infect. 2022 Dec;693–701. https://doi.org/10.1016/j.jinf.2022.09.007. PMID:36108783
11. Mustafa ML, Ayazi E, Mohareb E, Yingst S, Zayed A, Rossi CA, et al. Crimean-congo hemorrhagic fever, Afghanistan, 2009. Emerging Infect Dis. 2011 Oct;17(10):1940–1. https://doi.org/10.3201/eid1710.110061 PMID:22000377
12. Gergova I, Kamarinchev B. Seroprevalence of Crimean-Congo hemorrhagic fever in southeastern Bulgaria. Jpn J Infect Dis. 2014;67(5):397–8. PMID:25241694
13. Christova I, Panayotova E, Trifonova I, Taseva E, Hristova T, Ivanova V. Country-wide seroprevalence studies on Crimean-Congo hemorrhagic fever and hantavirus infections in general population of Bulgaria. J Med Virol. 2017 Oct;89(10):1720–5. https://doi.org/10.1002/jmv.24868 PMID:28561377
14. Sadeuh-Mba SA, Yonga Wansi GM, Demanou M, Gessain A, Njouom R. Serological evidence of rift valley fever Phlebovirus and Crimean-Congo hemorrhagic fever orthonairovirus infections among pygmies in the east region of Cameroon. Virol J. 2018 Apr 6;15(1):1–5. https://doi.org/10.1186/s12985-018-0977-8 PMID:29625611
15. Sun S, Dai X, Aishan M, Wang X, Meng W, Feng C, et al. Epidemiology and phylogenetic analysis of crimean-congo hemorrhagic fever viruses in Xinjiang, China. J Clin Microbiol. 2009 Aug;47(8):2536–43. https://doi.org/10.1128/JCM.00265-09 PMID:19553586
16. Xia H, Li P, Yang J, Pan L, Zhao J, Wang Z, et al. Epidemiological survey of Crimean-Congo hemorrhagic fever virus in Yunnan, China, 2008. Int J Infect Dis. 2011 jul;15(7):e459–63. https://doi.org/10.1016/j.ijid.2011.03.013 PMID:21546303
17. Greiner AL, Mamuchishvili N, Kakutia N, Stauffer K, Geleishvili M, Chitadze N, et al. Crimean-Congo hemorrhagic fever knowledge, attitudes, practices, risk factors, and seroprevalence in rural Georgian villages with known transmission in 2014. PLoS One 2016 Jun23;11(6):e0158049. https://doi.org/10.1371/journal.pone.0158049 PMID:27336731
18. Akuffo R, Brandful J, Zayed A, Adjei A, Watany N, Fahmy N, et al. Crimean-Congo hemorrhagic fever virus in livestock ticks and animal handler seroprevalence at an abattoir in Ghana. BMC Infect Dis. 2016 Jul 8;16(1):1–5. https://doi.org/10.1186/s12879-016-1660-6 PMID: 27392037 PMCID: PMC4939019
19. Sidira P, Maltezou H, Haidich AB, Papa A. Seroepidemiological study of Crimean-Congo haemorrhagic fever in Greece, 2009–2010. Clin Microbiol Infect. 2012 Feb;18(2):E16–9. https://doi.org/10.1111/j.1469-0691.2011.03718.x PMID:22192082
20. Sargianou M, Panos G, Tsatsaris A, Gogos C, Papa A. Crimean-Congo hemorrhagic fever: seroprevalence and risk factors among humans in Achaia, western Greece. Int J Infect Dis. 2013 Dec;17(12):e1160–5. https://doi.org/10.1016/j.ijid.2013.07.015 PMID:24084247

21. Sidira P, Nikza P, Danis K, Panagiotopoulos T, Samara D, Maltezou H, et al. Prevalence of Crimean-Congo hemorrhagic fever virus antibodies in Greek residents in the area where the AP92 strain was isolated. Hippokratia 2013 Oct;17(4):322. PMID:25031510

22. Papa A, Sidira P, Tsatsaris A. Spatial cluster analysis of Crimean-Congo hemorrhagic fever virus seroprevalence in humans, Greece. Parasite Epidemiol Control 2016 Aug 5;1(3):211–8. https://doi.org/10.1016/j.parepi.2016.08.002 PMID:29988220

23. Saidi S. Viral antibodies in preschool children. Iran J Public Health 1974;3(2):89–91.

24. Izadi S, Holakouie-Naieni K, Majdzadeh SR, Chinikar S, Nadim A, Rakhshani F, et al. Seroprevalence of Crimean-Congo hemorrhagic fever in Sistan-va-Baluchestan province of Iran. Jpn J Infect Dis. 2006 Oct;59(5): 326–8. PMID:17060701

25. Chinikar S, Ghiasi S, Hewson R, Moradi M, Haeri A. Crimean-Congo hemorrhagic fever in Iran and neighboring countries. J Clin Virol. 2010 Feb;47(2):110–4. https://doi.org/10.1016/j.jcv.2009.10.014 PMID:20006541

26. Chinikar S, Ghiasi SM, Naddaf S, Piazak N, Moradi M, Razavi MR, et al. Serological evaluation of Crimean-Congo hemorrhagic fever in humans with high-risk professions living in enzootic regions of Isfahan Province of Iran and genetic analysis of circulating strains. Vector-Borne Zoonotic Dis. 2012 Sep;12(9):733–8. https://doi.org/10.1089/vbz.2011.0634 PMID:22217167

27. Fajs L, Humolli I, Saksida A, Knap N, Jelovšek M, Korva M, et al. Prevalence of Crimean-Congo hemorrhagic fever virus in healthy population, livestock and ticks in Kosovo. PLoS One 2014 Nov 13;9(11):e110982. https://doi.org/10.1371/journal.pone.0110982 PMID:25393542

28. Al-Nakib W, Lloyd G, El-Mekki A, Platt G, Beeson A, Southee T. Preliminary report on arbovirus-antibody prevalence among patients in Kuwait: evidence of Congo/Crimean virus infection. Trans R Soci Trop Med Hyg. 1984;78(4):474–6. https://doi.org/10.1016/0035-9203(84)90065-8 PMID:6435292

29. Andriamandimby SF, Marianneau P, Rafisandratantsoa J-T, Rollin PE, Heraud J-M, Tordo N, et al. Crimean-Congo hemorrhagic fever serosurvey in at-risk professionals, Madagascar, 2008 and 2009. J Clin Virol. 2011 Dec;52(4):370–2. https://doi.org/10.1016/j.jcv.2011.08.008 PMID:21889395

30. Lani R, Rahim NM, Hassan H, Yaghoobi R, Chang L, AbuBakar S, et al. First report on the seroprevalence of the Crimean-Congo haemorrhagic fever virus, a tick-borne virus, in Malaysia's Orang Asli population. Eur Rev Med Pharmacol Sci. 2015;19(3):461–6. PMID:25720719

31. Muianga AF, Watson R, Varghese A, Chongo IS, Ali S, Monteiro V, et al. First serological evidence of Crimean-Congo haemorrhagic fever in febrile patients in Mozambique. Int J Infect Dis. 2017 Sep;62:119–23. https://doi.org/10.1016/j.ijid.2017.07.024 PMID:28782604

32. Bukbuk DN, Fukushi S, Tani H, Yoshikawa T, Taniguchi S, Iha K, et al. Development and validation of serological assays for viral hemorrhagic fevers and determination of the prevalence of Rift Valley fever in Borno State, Nigeria. Trans R Soci Trop Med Hyg. 2014 Dec;108(12):768–73. https://doi.org/10.1093/trstmh/tru163 PMID:25344695

33. Bukbuk DN, Dowall SD, Lewandowski K, Bosworth A, Baba SS, Varghese A, et al. Serological and virological evidence of Crimean-Congo haemorrhagic fever virus circulation in the human population of Borno State, northeastern Nigeria. PLoS Neglected Trop Dis. 2016 Dec 7;10(12):e0005126. https://doi.org/10.1371/journal.pntd.0005126 PMID:27926935

34. Williams R, Al-Busaidy S, Mehta F, Maupin G, Wagoner K, Al-Awaidy S, et al. Crimean-Congo haemorrhagic fever: a seroepidemiological and tick survey in the Sultanate of Oman. Trop Med Int Health 2000 Feb;5(2):99–106. https://doi.org/10.1046/j.1365-3156.2000.00524.x PMID:10747269

35. Hassanein K, El-Azazy O, Yousef H. Detection of Crimean-Congo haemorrhagic fever virus antibodies in humans and imported livestock in Saudi Arabia. Trans R Soci Trop Med Hyg. 1997 Sep–Oct;91(5):536–7. https://doi.org/10.1016/s0035-9203(97)90014-6 PMID:9463660

36. Memish ZA, Albarrak A, Almazroa MA, Al-Omar I, Alhakeem R, Assiri A, et al. Seroprevalence of Alkhurma and other hemorrhagic fever viruses, Saudi Arabia. Emerging Infect Dis. 2011 Dec;17(12):2316. https://doi.org/10.3201/eid1712.110658 PMID:22172587

37. Wasfi F, Dowall S, Ghabbari T, Bosworth A, Chakroun M, Varghese A, et al. Sero-epidemiological survey of Crimean-Congo hemorrhagic fever virus in Tunisia. Parasite 2016;23:10. https://doi.org/10.1051/parasite/2016010 PMID:26956221

38. Turabi Gunes AE, Poyraz O, Elaldi N, Kaya S, Dokmetas I, Bakir M, et al. Crimean-Congo hemorrhagic fever virus in high-risk population, Turkey. Emerging Infect Dis. 2009 Mar;15(3):461–4. https://doi/org/10.3201/eid1503.080687 PMID:19239765

39. Bodur H, Akinci E, Ascioglu S, Öngürü P, Uyar Y. Subclinical infections with Crimean-Congo hemorrhagic fever virus, Turkey. Emerging Infect Dis. 2012;18(4):640. https://doi.org/10.3201/eid1804.111374 PMID:22469474

40. Koksal I, Yilmaz G, Aksoy F, Erensoy S, Aydin H. The seroprevalance of Crimean-Congo haemorrhagic fever in people living in the same environment with Crimean-Congo haemorrhagic fever patients in an endemic region in Turkey. Epidemiol Infect. 2014 Feb;142(2):239–45. https://doi.org/10.1017/S0950268813001155 PMID:23688370

41. Yagci-Caglayik D, Korukluoglu G, Uyar Y. Seroprevalence and risk factors of Crimean–Congo hemorrhagic fever in selected seven provinces in Turkey. J Med Virol. 2014 Feb;86(2):306–14. https://doi.org/10.1002/jmv.23699 PMID:24037814

42. Cikman A, Aydin M, Gulhan B, Karakecili F, Kesik OA, Ozcicek A, et al. Seroprevalence of Crimean–Congo Hemorrhagic fever virus in Erzincan province, Turkey, relationship with geographic features and risk factors. Vector Borne Zoonotic Dis. 2016 Mar;16(3):199–204. https://doi.org/10.1089/vbz.2015.1879 PMID:26808904

43. Gazi H, Özkütük N, Ecemis T, Atasoylu G, Köroglu G, Kurutepe S, et al. Seroprevalence of West Nile virus, Crimean-Congo hemorrhagic fever virus, Francisella tularensis and Borrelia burgdorferi in rural population of Manisa, western Turkey. J Vector Borne Dis. 2016 Apr–Jun;53(2):112–7. PMID:27353580

44. Bayram Y, Parlak M, Özkaçmaz A, Çıkman A, Güdücüoğlu H, Kılıç S, et al. Seroprevalence of Crimean-Congo hemorrhagic fever in Turkey's Van province. Jpn J Infect Dis. 2017 Jan 24;70(1):65–8. https://doi.org/10.7883/yoken.JJID.2015.675 PMID:27169950

45. Khan AS, Maupin GO, Rollin PE, Noor AM, Shurie H, Shalabi A, et al. An outbreak of Crimean-Congo hemorrhagic fever in the United Arab Emirates, 1994-1995. Am J Trop Med Hyg. 1997 Nov;57(5):519–25. https://doi.org/10.4269/ajtmh.1997.57.519 PMID:9392589

46. Vescio FM, Busani L, Mughini-Gras L, Khoury C, Avellis L, Taseva E, et al. Environmental correlates of Crimean-Congo haemorrhagic fever incidence in Bulgaria. BMC Public Health 2012 Dec27;12:1116. https://doi.org/10.1186/1471-2458-12-1116 PMID:23270399

47. Mostafavi E, Haghdoost AA, Doosti IA, Bokaei S, Chinikar S. Temporal modeling of Crimean-Congo hemorrhagic fever in Iran. J Med Microbiol Infec Dis. 2014;2(1):28–34. https://jommid.pasteur.ac.ir/article-1-45-en.pdf

48. Lysholm S, Lindahl JF, Dautu G, Johansson E, Bergkvist PK, Munyeme M, et al. Seroepidemiology of selected transboundary animal diseases in goats in Zambia. Prev Vet Med. 2022 Sep;206:105708. https://doi.org/10.1016/j.prevetmed.2022.105708 PMID:35835047

49. Molla W, Jemberu WT, Mekonnen SA, Tuli G, Almaw G. Seroprevalence and risk factors of contagious bovine pleuropneumonia in selected districts of North Gondar Zone, Ethiopia. Front Vet Sci. 2021 Feb 26;8:626253. https://doi.org/10.3389/fvets.2021.626253 PMID:33718469

50. Mohammadi H, Kaabar MK, Alzabut J, Selvam AGM, Rezapour S. A complete model of Crimean-Congo Hemorrhagic Fever (CCHF) transmission cycle with nonlocal fractional derivative. J Funct Spaces 2021;2021:1–12. https://doi.org/10.1155/2021/1273405

51. Telford C, Nyakarahuka L, Waller L, Kitron U, Shoemaker T. Spatial prediction of Crimean Congo hemorrhagic fever virus seroprevalence among livestock in Uganda. One Health 2023 Jun 12;17:100576. https://doi.org/10.1016/j.onehlt.2023.100576 PMID:38024282