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Quantifying the influence of climate, host and change in land-use patterns on occurrence of Crimean Congo Hemorrhagic Fever (CCHF) and development of spatial risk map for India

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A B S T R A C T

Crimean Congo Hemorrhagic Fever (CCHF), is an emerging zoonosis globally and in India. The present study focused on identifying the risk factors for occurrence of CCHF in the Indian state of Gujarat and development of risk map for India. The past CCHF outbreaks in India were collated for the analyses. Influence of land use change and climatic factors in determining the occurrence of CCHF in Gujarat was assessed using Bayesian spatial models. Change in maximum temperature in affected districts was analysed to identify the significant change points over 110 years. Risk map was developed for Gujarat using Bayesian Additive Regression Trees (BART) model with remotely sensed environmental variables and host (livestock and human) factors. We found the change in land use patterns and maximum temperature in affected districts to be contributing to the occurrence of CCHF in Gujarat. Spatial risk map developed using CCHF occurrence data for Gujarat identified density of buffalo, minimum land surface temperature and elevation as risk determinants. Further, spatial risk map for the occurrence of CCHF in India was developed using selected variables. Overall, we found that combination of factors such as change in land-use patterns, maximum temperature, buffalo density, day time minimum land surface temperature and elevation led to the emergence and further spread of the disease in India. Mitigation measures for CCHF in India could be designed considering disease epidemiology and initiation of surveillance strategies based on the risk map developed in this study.

1. Introduction

Crimean Congo Hemorrhagic fever (CCHF) is a tick-borne viral zoonosis caused by Crimean Congo hemorrhagic fever virus (CCHFV) (an arbovirus), a member of the family *Nairoviridae* and genus *Orthonairovirus*. The first CCHFV outbreak was recognized in 1944 when Soviet troops re-occupying areas of the Crimean Peninsula developed an acute febrile illness with symptoms like shock and bleeding [1]. In 1969, this agent was found identical to that isolated in Belgian Congo in 1956 [2], leading to the disease being named Crimean Congo Hemorrhagic Fever. At the global scale, CCHFV seroprevalence was found to be 4.7% for humans and 24.6% for animals [3]. Based on an analysis of complete or partial sequences of the viral S-segment of CCHFV, six virus lineages/clades have been identified which are circulating in the region: Africa 3 (clade I) and Europe 1 (clade V) in Iran, Africa 1 (clade III) in the UAE, and Asia 1 and Asia 2 (clade IV) in Iran, Pakistan, Afghanistan, UAE, Oman, and Iraq [4] .CCHVF is commonly transmitted to humans through bites of infected *Hyalomma* ticks or *via* direct contact with blood and tissues of viremic livestock and infected patients [5,6].

In India, the first clinical case was reported from a tertiary care hospital in Ahmedabad in the western state of Gujarat, in 2011. Later, it was also reported from Sirohi from the neighboring state of Rajasthan, in 2014 and 2015 as a nosocomial outbreak recorded in a private hospital [7]. The disease was detected in the south Indian state of Kerala in January 2016, linked to the travel history of a slaughterhouse worker visiting from Oman [8]. Human seroprevalence studies from Gujarat showed a gender predisposition towards males and a several-fold increase in the risk for a CCHF case neighbor [9].

There is a need to pragmatically estimate and discuss the importance of climate with respect to other critical factors affecting the spatio-

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temporal dynamics of infectious diseases [10]. CCHF has been an emerging neglected zoonosis in India with a direct threat to public health and national security. The study aimed to investigate the epidemiology of CCHF in Gujarat and identification of factors such as change in land use patterns, climate and hosts responsible for its emergence and spread. The findings of this paper are based on the retrospective data collected from December 2010 to December 2021 for CCHF outbreak occurrences in Gujarat. The study was performed with the following key questions in understanding the epidemiology of CCHF

1. What are the climatic and land use change factors influencing the occurrence of CCHF in Gujarat?
2. Whether risk map for Gujarat and further extended to India can be developed to help in future surveillance strategies?

2. Materials and methods

2.1. CCHF occurrence data

Information like village affected, district name, month and year of outbreak, number of cases and mortality, age and gender of index cases and number of contacts affected from index case were obtained from reports available on the Integrated Disease Surveillance Programme (IDSP) webpage (mohfw.gov.in). For this analysis, data was restricted to only lab-confirmed CCHF cases. The coordinates of each village (latitude and longitude) were extracted for further analysis.

2.2. Environmental and hosts data

MODIS (Moderate Resolution Imaging Spectroradiometer) derived data was used for extraction of information regarding environmental risk factors like day time land surface temperature, night time land surface temperature, NDVI (Normalized Difference Vegetation Index), EVI (enhanced vegetation index) where parameters like their minimum, maximum and variance values were considered [11]. Livestock densities of cattle, buffalo, duck, sheep, goat, and pigs were obtained from Food and Agriculture Organization (FAO) [12]. Land cover rasters were obtained from the European Space Agency (ESA) land cover products for the year 1992 and 2015 at 300 m resolution [13].

2.3. Climate data

Monthly minimum temperature, mean temperature, maximum temperature, rainfall, and wet day frequency estimates from 1911 to 2020 for all the districts of Gujarat were extracted from the CRU TS4.05 dataset at a 0.5° x 0.5° spatial resolution from the Climatic Research Unit (CRU) (http://www.cru.uea.ac.uk/data), University of East Anglia [14] and average values were used for spatial analysis. Yearly average from the years 1911 to 2020 was used in temporal analysis to detect significant change in maximum temperature.

2.4. Descriptive epidemiological analysis of CCHF cases

Disease prevalence was estimated as the number of cases per 10 million populations using the 2011 Human census data (*https: //www.census2011.co.in*). The population at risk comprised the total population from all the affected districts where CCHF cases had been reported over the years. The prevalence of CCHF cases was calculated for each district where cases had been reported and across years from 2011 to 2020.

2.5. Bayesian spatial model details

There were a total of 16 variables for fitting the spatial model. We used the glmulti package in R [15] to narrow the change in land use and climate variables to be used in final spatial model because it would have been computationally prohibitive to calculate all possible combinations of variables in candidate model sets. We used genetic algorithm (GA) approach with CCHF outbreaks as response variable and land use change and climate variables as independent variables. This best model was selected based on the lowest AICc (corrected Akaike's Information Criterion) as this gives the estimated importance of the variables selected in the top models. The AICc is computed as the sum of the relative evidence weight of all the models in which the particular variable appears. District level spatial models were fitted using Bayesian Poisson generalised linear model at district level for Gujarat and implemented in INLA-R [16] using variables selected in the above mentioned variable selection step. Deviance Information Criteria (DIC) [17] was used to compare different models. The INLA (Integrated Nested Laplace Approximation) is a method for approximate Bayesian inference and this method was implemented in R [16].

2.6. Change in land use in affected and unaffected districts

Difference in 13 classes of land use pattern namely artificial surface, herbaceous crops, woody areas, multiple or layered crops, grassland, tree cover areas, mangrove, shrub cover areas, shrubs or herbaceous areas, sparsely natural vegetated areas, terrestrial barren land, permanent snow cover and glacier and inland water bodies were calculated between the years 1992 and 2015 among districts reporting CCHF cases and those that did not report any case of the disease.

2.7. Segmented analysis (Piece wise regression analysis) of maximum temperature for 100 years for affected districts

Yearly average of maximum temperature from 1911 to 2020 was used in piecewise regression analysis to identify significant year of change. Piecewise regression models for maximum temperature were fitted to estimate long-term trends (increasing or decreasing) for districts of Ahmedabad, Amreli, Bhavnagar, Rajkot, Kachchh and Surendranagar. There are two steps in fitting piece wise regression models. In the first step, a standard Poisson regression model was fitted to each district level yearly maximum temperature from 1911 to 2020 with year as independent variable and maximum temperature as dependent variable. In second step, the model was refitted using the segmented function in segmented package [18]. This method identified piecewise linear relationships between year and maximum temperature, and provided estimate of approximate change points/break points, for example years marked by increasing or decreasing trend. This was done to know change in maximum temperature over the years in selected districts where CCHF was reported.

2.8. Hyalomma habitat map

Hyalomma distribution records were obtained from the literature at district level as described [19]. The district coordinates (latitude and longitude) were extracted for all the districts where *Hyalomma* species were recorded. The data has limitations, as all the districts were not surveyed in the studies, and the data is from published literature only.

2.9. Risk mapping of CCHF

Bayesian Additive Regression Trees (BART) model was used to develop risk map for *Hyalomma* in R [20]. Similarly, BART was used to develop risk map for Gujarat using livestock hosts and remotely sensed variables. Further, the selected variables were also used to predict all India risk map for CCHF.

3. Results

The study consisted of 55 IDSP reported CCHF cases from 38 different villages of Gujarat out of which 20% outbreak cases (11/55) were reported from the districts of Amreli and Bhavnagar each and nearly 11% of CCHF outbreak reports (6/55) from Kutch and Rajkot each which was followed by 9% outbreaks being reported (5/55) from Surendra Nagar district (Fig. S1 for district names shown on map). There were 27 reported deaths during this time period. CCHF reporting were observed to be maximum during the month of September followed by November and August. The year 2019 showed the maximum number of disease outbreak reporting ($n = 24$). Overall, CFR was estimated as 49% (27/55). Highest case fatality was observed in cases reported in the months of March and May (100%) followed by February, June, October, and December (50% each). Months of January and April reported no case fatality. Year 2014 showed the highest fatality rate (100%) followed by year 2011 (60%) where the first case of disease was reported in India. Districts of Anand and Kheda showed 100% CFR while Sabarkantha and Jamnagar reported no fatality. Disease prevalence was highest in Amreli district followed by the prevalence in Bhavnagar. The prevalence was recorded lowest in Sabarkantha district. Year 2019 showed the maximum incidence in CCHF cases whereas least was observed for 2014 and 2015.

3.1. Spatial model results

Five land use variables and one climatic variable were selected in variable selection. These variables were used to fit the spatial model and the results are shown in Table 1. Change in herbaceous crops, grassland, shrub cover areas, shrubs and/or herbaceous areas and average maximum temperature were significant in determining the spatial variation in occurrence of CCHF in Gujarat along with random effects (Table 1).

3.2. Distribution of significant risk factors in affected versus unaffected districts

The difference between case and non-case districts for herbaceous crops was quite high, with the land class increasing for case districts. Grasslands have decreased to a greater extent in affected districts compared to unaffected districts. Grasslands were also found to be significantly associated with CCHF outbreaks in the spatial model. Shrub/herbaceous areas have greatly increased for districts with CCHF outbreaks than for districts with no CCHF outbreaks. A comparative figure between the CCHF affected districts and districts not affected with CCHF have been given in a graphical representation (Fig. 1).

3.3. Segmented model analysis

3.3.1. Year as dependent variable from 1911 to 2020

Piecewise regression analysis to identify break points with year as independent variable for different districts is shown in Fig. 2a-f. Districts like Surendranagar, Kachchh and Rajkot show significant increase in maximum temperature from year 1993–94, whereas Amreli, Bhavnagar, Ahmedabad and Banas Kantha show year 2001–2002 for significant increase in the maximum temperature.

3.3.2. Risk map for Gujarat and projected risk map for India

Three variables namely buffalo density, day time minimum land surface temperature and elevation were identified as important and significant risk factors for the occurrence of CCHF in Gujarat in the BART model. The risk map developed indicated high disease risk probability in the districts of Amreli, Bhavnagar and Surendranagar (Fig. 3). The projected risk map for India shows risk of CCHF in southern parts of Madhya Pradesh, northern parts of Maharashtra, few areas in Chattisgarh, Orissa, Jharkhand, parts of Andhra Pradesh and many areas in Tamil Nadu (Fig. 4A). The suitability of *Hyalomma* vector is shown in Fig. 4B. Environmental suitability of *Hyalomma* is shown in northern and southeastern regions of Gujarat, western parts of Rajasthan, regions of Punjab, Haryana, Uttar Pradesh, Bihar, few areas in north-eastern states, parts of Maharashtra, Karnataka, Andhra Pradesh, Tamil Nadu and Kerala.

The response plots developed shows the ranges at which the risk of disease is highest for each individual risk factor with uncertainty plotted (Fig. 5a). The 2-Dimension partial dependent plots of selected variables and the risk of CCHF is shown in Fig. 5b.

Table 1
Spatial model with selected land use change variables and mean maximum temperature. Deviance Information Criteria (DIC) for the model is 79.79. Mean and credible intervals are presented. The variables are considered as significant if the credible intervals do not bridge zero in Bayesian analysis. Grassland, shrub cover areas, shrubs and or herbaceous areas, average maximum temperature were significant.

Variable	Mean (credible interval)
Intercept	24.56 (10.67, 38.24)
Fixed effects	
Herbaceous crop	0.059 (−0.224, −0.225)
Grassland	−0.24 (−0.35, −0.13)
Shrub cover areas	−2.52 (−3.80, −1.25)
Shrubs and or herbaceous areas	−0.75 (−1.29, −0.21)
Sparsely natural vegetated areas	0.000 (−62.017, 62.017)
Average maximum temperature	−0.77 (−1.20, −0.77)
Random effects	
Precision for ID (iid component)	1831.73 (117.98, 6724.66)
Precision for ID (spatial component)	1808.70 (112.24, 6662.76)

4. Discussion

Crimean Congo Hemorrhagic Fever is an emerging zoonotic disease with high case fatality rate and spreading to different countries ever since its first outbreak. Although, the disease in India was first reported in a single district in the year 2011, it subsequently spread to 11 districts of Gujarat. There are many studies to understand the influence of climate, change in land use patterns on occurrence of diseases, but not conducted for India. In the present study we found that change in land use patterns, maximum temperature, density of buffalo population, elevation determine the occurrence and variation of CCHF in India. Further, the study also developed an all India spatial risk map for CCHF and habitat suitability map for *Hyalomma* vector.

The results from this study provide an understanding that though the vectors of CCHF are widely distributed throughout India (Fig. 4B) yet there are some factors that limit the disease occurrence to a few districts in the state of Gujarat. During 2012-2015, CCHF cases were documented from the following six districts of Gujarat – Ahmedabad, Amreli, Patan, Surendranagar, Kutch and Aravalli; and Sirohi, a district of Rajasthan bordering Gujarat [21] indicating fast spread of the disease within Gujarat.

In the spatial model, we found that change in land use patterns of five classes were significant in occurrence of CCHF in Gujarat. Change in herbaceous crops, grassland, shrub cover areas, shrubs and/or herbaceous areas were found to be associated with disease incidence in the different districts of Gujarat meaning that a change in land use of these classes over the years had favoured disease incidence and spread within the geography of Gujarat. Several studies have indicated that changes in land use patterns play a significant role in expansion of geographical spread of ticks and, in turn the disease. There was a major change in grassland in affected districts compared to unaffected districts. A reduction in grassland covers for agricultural or urbanization purposes for growing population had significantly affected disease patterns of CCHF in Gujarat. Similar results were found during previous studies done in other regions of the world which had identified evapotranspiration [22], altitude, the land cover type, and the transitional woodland/shrub land, as well as the number of livestock, and specifically the number of goats, sheep, and cattle [23]. Wooded habitat-grassland, which is linked to grassland cover, was negatively associated with abundance of *Ixodes* nymphs and are considered as not suitable for ticks

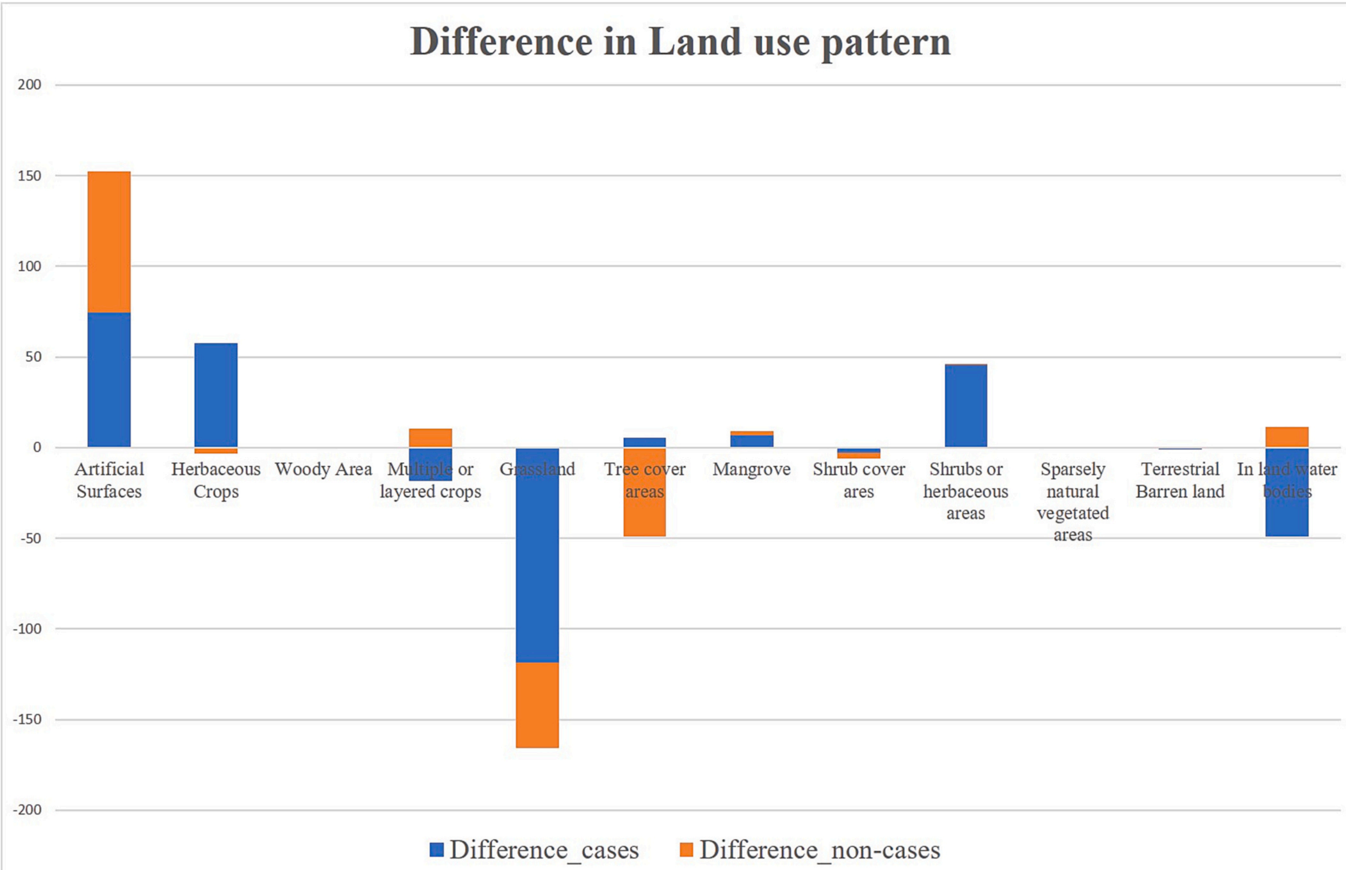

Fig. 1. District level analysis of difference in Land use pattern between affected and unaffected districts with CCHF. The land use change in all the affected districts and land use change in all the unaffected districts is compared. The proportion of change in particular land use above zero are positive changes (increase in proportion of that particular land use) and below zero are negative changes (decrease in proportion of that particular land use). The Grassland, in land water bodies is decreased more in affected districts compared to not affected districts. Herbaceous crops and shrubs is increased in affected districts compared to unaffected districts.

[24]. In our study, we found that there was drastic reduction of grassland and increase in herbaceous crops in affected districts compared to unaffected districts (Table S1 and Fig. S10).

Deforestation may also increase the risk of re-emergence of disease from areas where disease has not been reported for long [25]. The source of infection of a single human occurrence after nearly 50 years of disease reporting in Congo seemed to be associated with forest areas undergoing deforestation [25]. In most of the studies the proportion of land cover was used to identify association between the land use and occurrence of CCHF, however, in our study we used change in land use between 1992 and 2015 to identify the association.

Along with change in land use patterns, we also found that the maximum temperature is significant in determining spatial variation in occurrence of CCHF in Gujarat and most districts showing increasing trend in temperature (Fig. 2a-f) indicating that the influence of climate change on the affected districts which might have led to occurrence and establishment of CCHF in Gujarat. Change in climatic conditions and absence of vaccination is projected to result in further geographical spread of CCHFV [26]. It is established that rainfall, temperature, and moisture affect the habitat and life cycle of the ixodid ticks [10]. Climate change significantly affects the reproduction rate of *Hyalomma* ticks [27]. In addition, climate change is likely to influence anthropogenic factors like changes in agricultural practices and access to forest for hunting activities that may serve as important factors for disease emergence/ reemergence [27]. In other studies, temperature, moisture, and precipitation indices like mean temperature (°C), accumulated rainfall (mm), maximum relative humidity (%) [28] were found to be important drivers of CCHF infections.

The risk map developed identifies areas in districts of Amreli, Bhavnagar and Surendra Nagar as high risk for the occurrence of CCHF in Gujarat. In one study, it was found that Amreli had highest animal seropositivity for CCHF followed by Aravalli, Kutch and Rajkot [9]. Buffalo density, elevation and daytime land surface temperature were identified as important variables in the spatial risk map analysis (Fig. 5A & B). Identification of buffalo density as significant risk factor is important considering the host preference of *Hyalomma* species for this host. There is evidence that ticks like *Hyalomma* prefer thick skinned and less hairy hosts [29]. There are also reports of seroprevalence (6%) of CCHF in bovines of Gujarat [21]. CCHFV infection rate in livestock was found to be a strong positive predictor of CCHF incidence in humans [30]. The role of buffalo and other livestock species is important in occurrence of CCHF in Gujarat and hence, surveillance must be carried out in livestock and ticks associated with livestock. The day time LST may play role in the life history parameters of *Hyalomma* species resulting in higher abundance of vectors for efficient transmission. Studies in the past identified that the seroprevalence of CCHF and disease incidence in humans were significantly affected by altitude, the land cover type, number of goats, sheep, cattle and NDVI [31]. The habitat map developed using past occurrences of *Hyalomma* distribution will be helpful in planning vector surveillance in these areas and to plan systematic vector control in high-risk areas.

In addition to Gujarat, the other states which showed the risk of CCHF in all India risk map (Fig. 4) are parts of southern Madhya Pradesh and northern Maharashtra, parts of Andhra Pradesh, Tamil Nadu, Chattisgarh and Orissa. Notably, these states also showed seroprevalence of CCHF [21]. In a study to know the seroprevalence of CCHF in

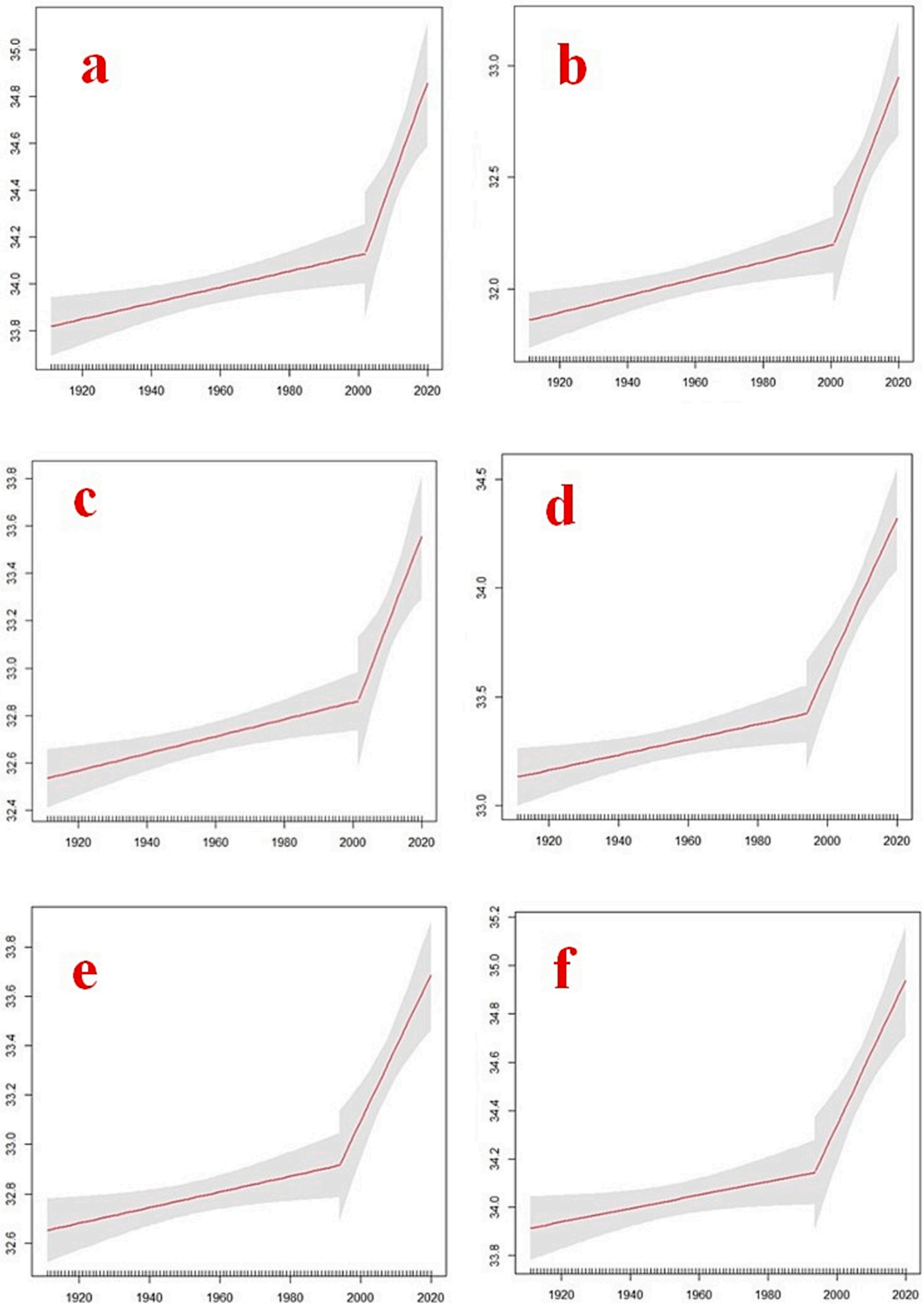

Fig. 2. Change point detection using piece wise regression analysis for maximum temperature in (a) Ahmedabad (b) Amreli (c) Bhavnagar (d) Kachchh (e) Rajkot and (f) Surendarnagar using year as dependent variable from 1911 to 2020. X-axis is the year and Y-axis is the maximum temperature. There is significant increase in temperature for all the six districts around the year 2000.

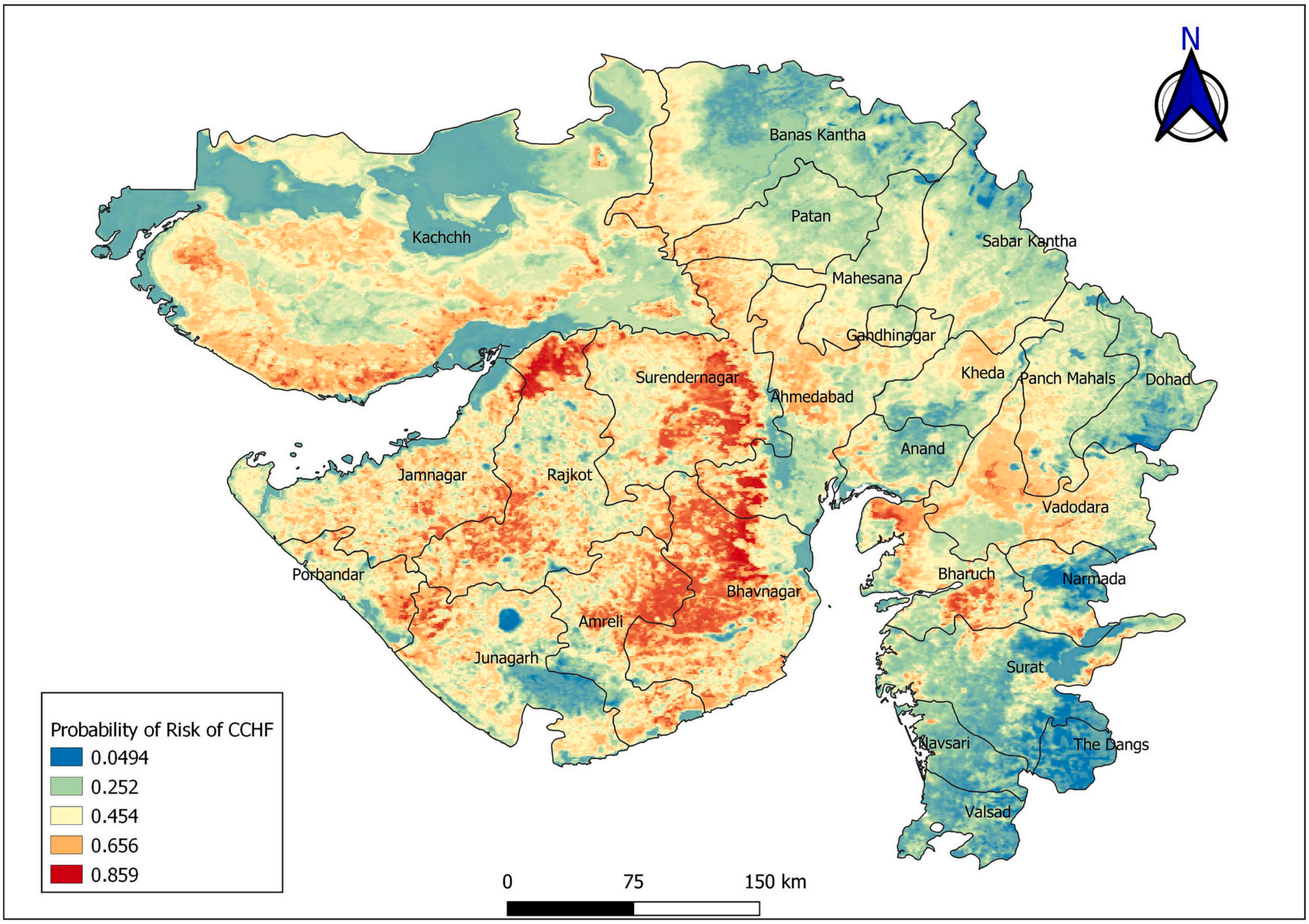

Fig. 3. Risk map developed using remotely sensed variables and hosts for occurrence of CCHF in Gujarat. The risk is shown on the probability scale of 0 to 1. The risk of CCHF is more in districts of Kachchh, Jamnagar, Rajkot, Amreli, Surendernagar and Bhavnagar.

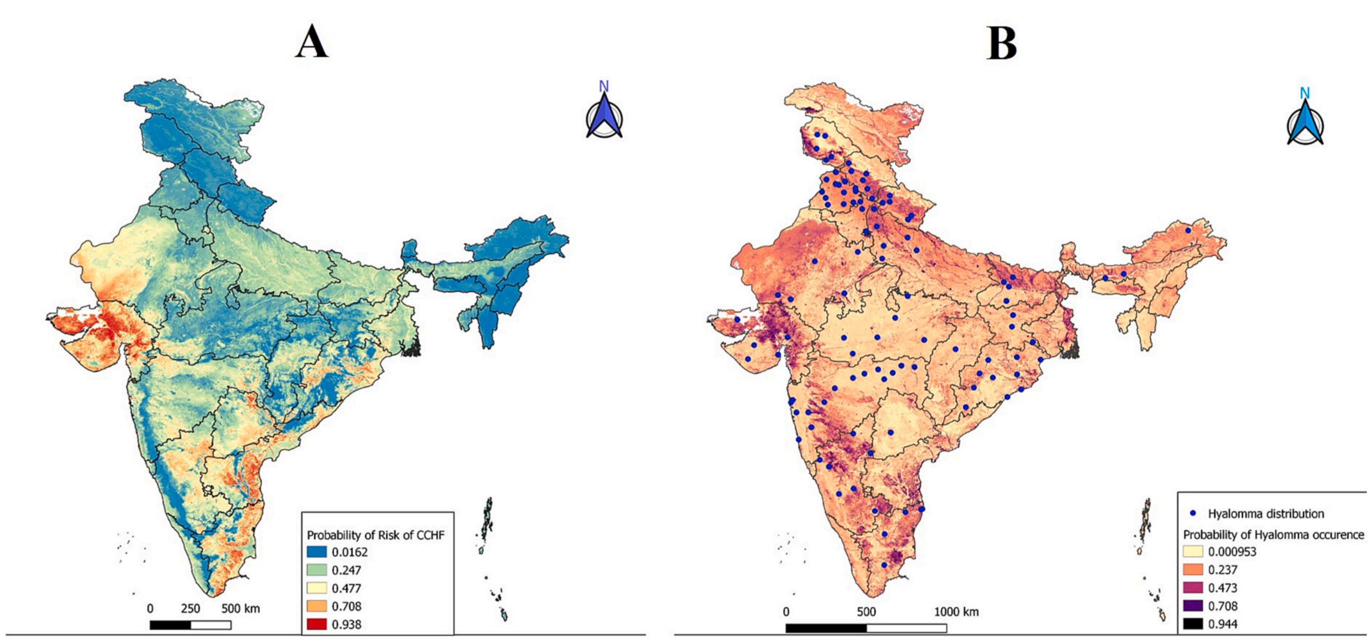

Fig. 4. (A) Projected risk map developed using selected variables for occurrence of CCHF in India. The risk is shown on the probability scale of 0 to 1. The risk of CCHF is high in southern states of Tamil Nadu, Andhra Pradesh along with Gujarat compared to other states. (B) *Hyalomma* habitat suitability map developed. The probability of habitat suitability is shown on the probability scale of 0 to 1.

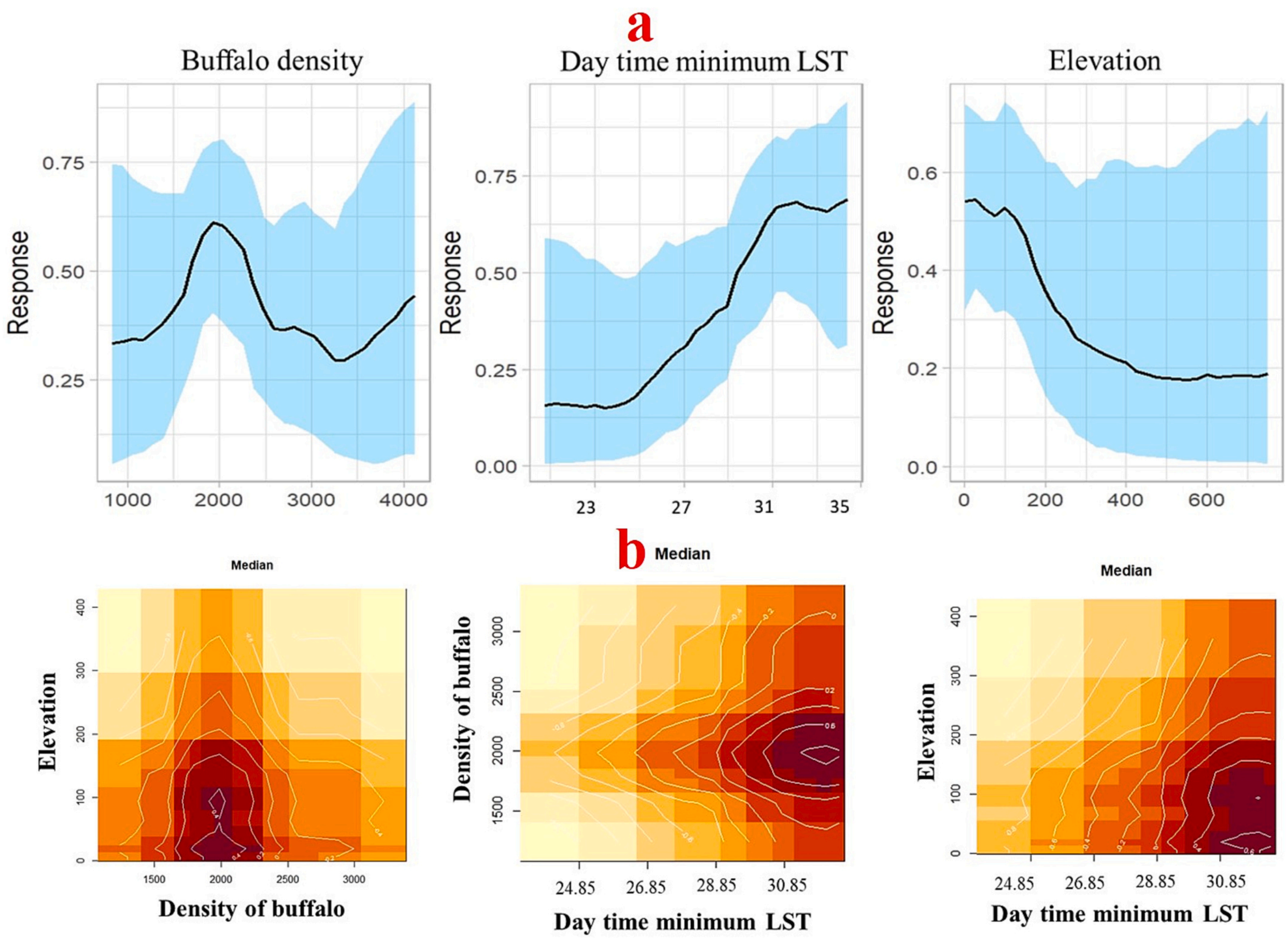

Fig. 5. (a) Response curve of selected variables; Buffalo density, Day time minimum land surface temperature and elevation. The relationship with occurrence of CCHF is non-linear with Buffalo density, increases with increase in day time LST and decreases with increase in elevation. (b) 2-Dimension partial dependent plots to show the interaction between optimum condition of variables and risk of CCHF. (a) Interaction between density of buffalo and elevation. (b) Interaction between day time minimum LST and density of buffalo. (c) Interaction between day time minimum LST and elevation. The x-axis and y-axis gives the values of a particular variable and values indicate the risk probability on a 0 to 1 scale.

animals, it was found that 5.43% of bovine samples and 10.99% of sheep and goat samples were IgG positive from samples from all over India in 2013–14 [21]. Among bovine samples, Orissa showed the maximum seropositivity of 31.3% and for sheep and goat samples, maximum IgG positivity was seen in Himachal Pradesh (53.1%) [21]. The viremia in livestock is short lived and of low intensity, hence the animals do not visibly develop clinical disease but are still able to transmit it to other animals and humans [21]. The role of different livestock hosts and other reservoir hosts in maintenance and transmission of CCHF is poorly studied in India.

5. Conclusion

Crimean congo hemorrhagic fever is endemic in many countries and in India the disease is mainly reported from Gujarat. Currently, work on CCHF is mainly focussed on providing diagnosis to suspected clinical cases. There are no efforts to understand the factors responsible for occurrence of CCHF in Gujarat and the risk of disease in other states. We highlight the importance of quantifying the role of land use change, climate and other host factors driving the occurrence of CCHF in Gujarat and predict the occurrence of the disease in other states of India for developing effective surveillance strategies. In our study, we identified the importance of land use change, climatic and host factors in determining spatial variation in occurrence of CCHF. We found that there was an increase in maximum temperature in mainly affected districts using more than 100-year climate data. We predicted the risk of CCHF in Gujarat and further predicted the all-India risk of the disease which is valuable for planning surveillance in high-risk areas. The importance of livestock hosts, especially buffalo, needs more field studies on host preference to understand the role of this species in dynamics of disease transmission. It is hitherto not known how the disease entered India for the first time. Whether the disease has become endemic only in Gujarat or every time the disease enters India from other countries is also not yet known. There are many critical gaps in understanding the ecology and epidemiology of disease in India such as role of birds (including migratory birds), vector competence of different tick species involved in the transmission and reservoirs (animal hosts) for the disease. Hence, it warrants immediate strategy for vector surveillance and pertinent efforts to better understand the disease ecology with One health approach.

5.1. *Limitations of the study*

The outbreaks of CCHF were mainly reported from Gujarat state of India and there may be underreporting from other states. However, our all-India risk map and habitat map for *Hyalomma* can be valuable for policy makers to plan active surveillance in these areas. We used Climate Research Unit (CRU) [14] climate data for our analysis as we could not get access to the Indian Meteorological Department (IMD) data.

Author contribution

MMC designed the study with inputs from AP, YR, BRS, MD and SBS. MMC collated the disease data and environmental data and performed all the statistical analyses. MMC and PK wrote the first draft of the manuscript with inputs from MD, AP, YR, BRS and SBS. All the authors contributed to subsequent revisions of the manuscript.

CRediT authorship contribution statement

Mohammed Mudassar Chanda: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Visualization, Writing – original draft. **Priyanka Kharkwal:** Investigation, Methodology, Writing – original draft. **Meera Dhuria:** Visualization, Writing – review & editing. **Awadesh Prajapathi:** Data curation. **Revanaiah Yogisharadhya:** Investigation. **Bibek Ranjan Shome:** Resources. **Sathish Bhadravati Shivachandra:** Project administration, Writing – review & editing.

Declaration of Competing Interest

None**.**

Data availability

Data will be made available on request.

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Appendix B. Supplementary information

The point map of the distribution of CCHF cases (Fig. S2), other descriptive data analysis on year wise CFR, district wise CFR and prevalence is provided in the supplementary (Fig. S3-S6). A comparative table between the case and non-case districts have been given in table (Table S1). The map depicting land use patterns in affected districts and unaffected districts in the years 1992 & 2015 is shown (Fig. S9). The land use change in selected affected districts is shown in figs. S10-S15.

Three variables namely buffalo density, day time minimum land surface temperature and elevation were selected as important and significant risk factors for the occurrence of CCHF in Gujarat. The distribution of the selected variables in Gujarat is shown (Fig. S7, S8 & S9). Supplementary data to this article can be found online at [https://doi.org/10.1016/j.onehlt.2023.100609].

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