Estimating The Seasonally Varying Effect of Climatic Factors On The District-Level Incidence of Acute Watery Diarrhea Among Under-Five Children of Iran, 2014-2018: A Bayesian Hierarchical Spatiotemporal Model

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Research

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Estimating the seasonally varying effect of climatic factors on the district-level incidence of acute watery diarrhea among under-five children of Iran, 2014-2018: A Bayesian hierarchical spatiotemporal model

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Abstract:

Background: Under-five years old acute watery diarrhea (U5AWD) accounts for most diarrheal diseases' burden due to rotavirus infection. It is claimed that many climatic and socioeconomic factors are associated with U5AWD. However, little information is available about the occurrence of U5AWD in Iran and the adjusted effect of potential determinants.

Methods: We collected a dataset containing the seasonal numbers of U5AWD cases at the district level of Iran through MOHME. We calculated the district level Standardized Incidence Ratio and Moran's I values to detect the significant clusters of U5AWD over sixteen seasons from 2014 to 2018. In addition, we examined twelve Bayesian hierarchical models to recognize the strongest in predicting the seasonal number of incidents.

Results: Iran has many hotspots of U5AWD, especially in southeast areas. An extended spatiotemporal model with seasonally varying coefficients and space-time interaction outperformed other models, becoming our proposal in modeling U5AWD. Temperature had a global positive relationship with seasonal U5AWD in districts (IRR: 1.0497, 95% CrI: 1.0254-1.0748), due to its varying effects in winter (IRR: 1.0877, 95% CrI: 1.0408-1.1375) and fall (IRR: 1.0866, 95% CrI: 1.0405-1.1357) seasons. Also, elevation (IRR: 0.9997, 95% CrI: 0.9996-0.9998), piped drinking water (IRR: 0.9948, 95% CrI: 0.9933-0.9964), public sewerage network (IRR: 0.9965, 95% CrI: 0.9938-0.9992), years of schooling (IRR: 0.9649, 95% CrI: 0.944-0.9862), Infrastructure-to-Household Size Ratio (IRR: 0.9903, 95% CrI: 0.986-0.9946), wealth index (IRR: 0.9502, 95% CrI: 0.9231-0.9781) and urbanization (IRR: 0.9919, 95% CrI: 0.9893-0.9944) of districts were negatively associated with seasonal U5AWD incidence.

Conclusions: The development of specific alert systems could be a strategy to predict high-risk areas of U5AWD using climatic inputs. Also, the study anticipates a higher incidence of U5AWD in districts with weaker hygiene and socioeconomic status. Therefore, policymakers should take appropriate preventive actions in such areas.

Keywords: Acute diarrhea; Children under-five; Climate change; Socioeconomic determinants; Seasonality; Spatiotemporal modeling; Time-varying coefficients; Bayesian hierarchical modeling; INLA

1. Background

Diarrheal diseases are among fatal causes of death, ranking second for children younger than five years old[1]. World Health Organization (WHO) and the Institute for Health Metrics and Evaluation (IHME) respectively estimate more than 1.7 billion and 947 million incidents of diarrheal diseases, killing more than 500,000 children each year[2, 3]. Under-five years old acute watery diarrhea (U5AWD) has more responsibility for the burden of diarrheal diseases than other clinical types, even though interventions such as rotavirus vaccine have dramatically reduced the morbidity and mortality caused by U5AWD. However, a limited number of 70 countries have taken such immunization programs into account till 2014, revealing the underuse of the vaccine in Asia and Africa[4]. If the dullness of vaccinations persists, U5AWD will inevitably remain an intensive issue, especially for the developing countries of these regions.

Iran is known as a seriously affected country by U5AWD, despite recent progress in rotavirus immunization programs[5]. According to the Global Burden of Disease (GBD) Study in 2019, diarrheal diseases account for more than 11.9 million incidents and 238 deaths in under-five children of Iran[2]. However, to date, no national study has focused on the district-level incidence of U5AWD in Iran. Hence, it is vital to recognize the geographical locations undergoing U5AWD outbreaks, especially in small areas with lower quality of life, to help the health officials meet Sustainable Development Goal 3 (SDG 3) by 2030.

Assessing the risk of U5AWD, a great number of determinants have been looked over in literature consisting: cumulative rainfall[6-18], temperature[6, 8, 10, 12-24], wind speed[12, 13, 17], elevation[25], traveling history[26], drinking water source[9-11, 27-35], disposal system[11, 29, 31, 36-38], household size[30, 39, 40], caregivers' education[10, 28, 29, 32-35, 39-41], economic status[11, 29, 33, 35, 41, 42] and urbanization[41, 43] have been investigated as the potential determinants of diarrheal diseases. Abandoned suppression of significant risk factors can activate severe epidemics affecting millions of lives of children around the globe. Thus, it is crucial to distinguish these factors to prevent such catastrophes. However, so far, no study has included a set of all the items above in a thorough statistical model to derive conclusions about the adjusted effect of risk factors on U5AWD.

Small-area studies are generating widespread interest in terms of the methodology required to perform such studies. Herein, spatiotemporal models attract considerable attention since they can presume the simultaneous dynamic trends inherent in space and time and take space-time interactions into account[44]. Another advantage is that they allow us to quantify the nonlinear effect of the suspicion factors on U5AWD. Walking on this path, we believe critical attention should be paid to the potential nonstationary effect of environmental variables. For example, climatic factors (e.g. rainfall, temperature) are recognized as time-varying determinants of viral infectious diseases elsewhere[45].

Implementing such complex models is plausible in a Bayesian hierarchical modeling (BHM) setting, but there is still a tough numerical challenge. Markov chain Monte Carlo (MCMC) methods used for BHM often impose an unendurable burden working with large datasets[46]. In 2009, Rue et al.[47] introduced a relatively fast and accurate approach to do BHM named integrated nested Laplace approximation (INLA), which researchers broadly utilize as an appropriate surrogate for MCMC. They also developed a statistical tool for INLA in R Statistical Software which is downloadable via <https://www.r-inla.org/download-install>.

The present paper aims to: 1) demonstrate the spatial and temporal patterns of U5AWD in Iran; 2) locate the statistically significant hotspots in the area; 3) infer about the association of the mentioned determinants with U5AWD, and 4) propose an efficacious easy-to-use model with solid predictive ability.

2. Methods

2.1. Study area

From Apr 2014 to Mar 2018, the Ministry of Health and Medical Education (MOHME) reported a total of 1,552,255 children <5 years old who were confirmed to have diarrhea in Iran. Based on the latest divisions, Iran consists of 429 districts that define our study's geographical framework. We followed every district for sixteen seasons (spring: Apr-Jun, summer: Jul-Sep, fall: Oct-Dec, winter: Jan-Mar), demonstrating the study's timeline.

2.2. Data collection

We used average cumulative rainfall, temperature, wind speed, elevation, the prevalence of traveling history, piped drinking water, public sewerage network, Infrastructure-to-Household Size Ratio (IHSR), years of schooling (YOS), wealth index and urbanization as the independent variables. We calculated the rainfall, temperature and wind speed in each district-month by aggregating over the hourly reported data of Iran Meteorological Organization (IRIMO) stations. The 2016 Iran National Population and Housing Census supplied us with the district-level population data necessary to control for the population effect in subsequent analyses. The prevalence of remaining socioeconomic variables are taken from Households Income and Expenditure Survey (HIES). A full list of variables, data sources and the temporal domain is provided in Table 1.

2.3. Standardized Incidence (Morbidity) Ratio (SIR)

To illustrate the U5AWD risks, we notably used SIR [48], which is an adequate descriptive measure in estimating disease risks in different district-seasons and defined it as follows:

$$SIR_{it} = \frac{O_{it}}{E_{it}} \quad (1)$$

where O_{it} is the observed number of U5AWD cases in district i , season t and E_{it} is the expected number of U5AWD cases in district i , season t . E_{it} can be simplified as:

$$E_{it} = \frac{pop_{it}}{\sum_{i,t} pop_{it}} \sum_{i,t} O_{it} \quad (2)$$

where pop_{it} is the population in district i , season t . The maps on SIRs are presented in section 3.3 of the results.

2.4. Spatial autocorrelation analysis

Anselin outlined the term Local Indicators of Spatial Association (LISAs)[49] to decompose the global indicators used to test for spatial autocorrelation in a geographic area. Using LISAs, we can distinguish which areal units play a more/less important role in the global indices. The most famous LISA is the Local form of the Moran's I statistics (called 'Local Moran's I') which we applied to detect the seasonal hotspots of U5AWD among 429 districts of Iran. It can be defined as:

$$I_{it} = \frac{y_{it} - \bar{y}_t}{S_{it}^2} \sum_{j=1, j \neq i}^n w_{ij}(y_{jt} - \bar{y}_t) \quad (3)$$

$$S_{it}^2 = \frac{\sum_{j=1, j \neq i}^n (y_{jt} - \bar{y}_t)^2}{n - 1} \quad (4)$$

where I_{it} is the Local Moran's I value in district i , season t ; y_{it} is the observed number of U5AWD cases in district i ; $\bar{y}_t$ is the average number of U5AWD cases in season t ; w_{ij} denotes the corresponding spatial weight between district i and j ; S_{it}^2 is the sample variance of the district i observation among other observations in season t .

Positive I_i signifies the homogeneity of U5AWD incidence with neighbors in district i , whereas negative I_i has an unlikely interpretation, revealing a heterologous pattern. Besides, the scaled incidence values in district i and surrounding neighbors can also get positive or negative values. Taken together, Local Moran's I value can fit into four groups: 1) high incidence clusters with high incidence neighbors (High-High); 2) low incidence clusters with low incidence neighbors (Low-Low); 3) high incidence clusters with low incidence neighbors (How-Low); 4) low incidence clusters with high incidence neighbors (Low-High). We will display the significant clusters at three confidence levels (90%, 95%, and 99%) in section 3.3. The package used to detect the clusters was "spdep" in R Statistical Software (version 4.0.5) [50].

2.5. Bayesian hierarchical modeling

Using a Bayesian hierarchical structure, we aim to model the incidence rates of U5AWD, which is believed to have a seasonal trend:

$$IR_{it} = \frac{O_{it}}{pop_{it}} \quad (5)$$

$$\log(IR_{it}) \sim \text{Normal}(\mu_{it}, \sigma^2) \quad (6)$$

where O_{it} is the observed number of U5AWD cases in district i , season t ; pop_{it} is the population in district i , season t . We used the logarithmic transformation of incidence rates in equation 6 to facilitate the running process by assuming the normal distribution for the response variable. We will compensate for this by reversing the transformations on predicted posterior samples to report case numbers.

We will display the national trend of incidence rates ($IR_t \times 10.000$) in results (section 3.2).

Among different options, we evaluated twelve candidate models. We should note that we adopted the same notations to shorten the explanations and streamline the comparison between models:

- **Model 1:** The ordinary multivariate regression model (non-spatial and non-temporal) as:

$$\mu_{it} = \beta_0 + \sum_{k=1}^{11} \beta_k X_{k,it} \quad (7)$$

where β_0 is the intercept; $X_{k,it}$ is the value of k -th covariate in district i , season t and β_k is the estimated coefficient of k -th covariate, showing its linear fixed effect through space and time.

- **Model 2:** The spatial ecological regression model as:

$$\mu_{it} = \beta_0 + \sum_{k=1}^{11} \beta_k X_{k,it} + u_i + v_i \quad (8)$$

$$u \sim \text{Normal}(0, \sigma_u^2 I_u^{-1}) \quad (9)$$

$$v_i | v_{j \neq i} = \text{Normal}\left(\frac{1}{N_i} \sum_{j=1}^{N_i} v_j, \frac{\sigma_i^2}{N_i}\right) \quad (10)$$

where u_i and v_i are the spatial unstructured and structured random effect in district i , respectively; N_i is the number of districts sharing boundaries with i -th district and σ_i^2 is the variance between i -th district's effect and neighbors. In every model, we selected an independent and identically distributed (iid) Gaussian distribution as diffuse prior for u_i and the intrinsic conditional autoregressive (ICAR) structure as the prior distribution of v_i (equation 9-10). $u_i + v_i$ togetherly construct a prominent convolution model known as Besag York Mollié (BYM) [51].

- **Model 3:** The time series regression model as:

$$\mu_{it} = \beta_0 + \sum_{k=1}^{11} \beta_k X_{k,it} + \gamma_t + \phi_t \quad (11)$$

$$\gamma \sim \text{Normal}(0, \sigma_\gamma^2 I_\gamma^{-1}) \quad (12)$$

$$\pi(\phi_t | \sigma_\phi^2) \propto \exp\left(-\frac{1}{2\sigma_\phi^2} \sum_{t=1}^{13} (\phi_t + \phi_{t+1} + \phi_{t+2} + \phi_{t+3})^2\right) \quad (13)$$

where γ_t and ϕ_t are the temporal unstructured and structured random effect in year t , respectively. In every model, we selected an iid Gaussian distribution as non-informative prior for γ_t (equation 12). We utilized the *seasonal* latent model available in R-INLA as the prior of ϕ_t , assuming $\sum_{t=1}^4 \phi_t = 0$. We formulated the density for seasonal prior in equation 13.

- **Model 4:** A seasonally varying coefficients model containing nonstationary random effects for climatic variables,

$$\mu_{it} = \beta_0 + \sum_{k=1}^{11} \beta_k X_{k,it} + \sum_{k=1}^3 f(\xi_{k,t} X_{k,it}) \quad (14)$$

which can be stated more straightforwardly as follows:

$$\mu_{it} = \beta_0 + \sum_{k=1}^3 (\beta_k + \xi_{k,t}) X_{k,it} + \sum_{k=4}^{11} \beta_k X_{k,it} \quad (15)$$

$$\xi_t | \xi_{t-1} \sim \text{Normal}(\xi_{t-1}, \sigma_\xi^2) \quad (16)$$

$$\sum_{t=1}^4 \xi_{k,t} = 0, \quad k = 1, 2, 3 \quad (17)$$

$$\pi(\xi_t | \sigma_\xi^2) \propto \exp\left(-\frac{1}{2\sigma_\xi^2} \sum_{t=2}^T (\xi_t - \xi_{t-1})^2\right) \quad (18)$$

where $X_{1,it}$, $X_{2,it}$ and $X_{3,it}$ represent rainfall, temperature and wind speed of district i in season t ; $\{X_{4,it}, \dots, X_{11,it}\}$ are the remaining covariates that are just linear predictors having fixed effects; $\{\xi_{1,t}, \xi_{2,t}, \xi_{3,t}\}$ are the variable-specific seasonally varying structured random effects for which we specified cyclic first-order random walk (RW1) priors (equation 16-17).

- **Model 5:** A spatiotemporal model (combining Model 2 and Model 3),

$$\mu_{it} = \beta_0 + \sum_{k=1}^{11} \beta_k X_{k,it} + u_i + v_i + \gamma_t + \phi_t \quad (19)$$

- **Model 6:** The spatial ecological regression with seasonally varying coefficients for climatic variables (combining Model 2 and Model 4),

$$\mu_{it} = \beta_0 + \sum_{k=1}^3 (\beta_k + \xi_{k,t}) X_{k,it} + \sum_{k=4}^{11} \beta_k X_{k,it} + u_i + v_i \quad (20)$$

- **Model 7:** The time series regression model with seasonally varying coefficients for climatic variables (combining Model 3 and Model 4),

$$\mu_{it} = \beta_0 + \sum_{k=1}^3 (\beta_k + \xi_{k,t}) X_{k,it} + \sum_{k=4}^{11} \beta_k X_{k,it} + \gamma_t + \phi_t \quad (21)$$

- **Model 8:** The spatiotemporal model with seasonally varying coefficients for climatic variables (combining Model 2-4),

$$\mu_{it} = \beta_0 + \sum_{k=1}^3 (\beta_k + \xi_{k,t}) X_{k,it} + \sum_{k=4}^{11} \beta_k X_{k,it} + u_i + v_i + \gamma_t + \phi_t \quad (22)$$

- **Model 9:** Model 8 + space-time interaction between spatially unstructured (u) and temporally unstructured (γ) random effects (referred to as interaction type I[44]),

$$\mu_{it} = \beta_0 + \sum_{k=1}^3 (\beta_k + \xi_{k,t}) X_{k,it} + \sum_{k=4}^{11} \beta_k X_{k,it} + u_i + v_i + \gamma_t + \phi_t + \delta_{it} \quad (23)$$

$$\delta \sim \text{Normal}(0, \sigma_\delta^2 (I_u \otimes I_\gamma)^{-1}) \quad (24)$$

where δ_{it} is the mentioned interaction term in district i , season t ; I_u and I_γ are 429×429 and 16×16 identity matrices, respectively and $\otimes$ is the Kronecker product operator used to build a block matrix out of I_u and I_γ .

Model 9-12 have the same formulation for μ_{it} and only the distribution of δ_{it} differs.

- **Model 10:** Model 8 + space-time interaction between spatially unstructured (u) and temporally structured (ϕ) random effects (interaction type II) as:

$$\delta \sim \text{Normal}(0, \sigma_\delta^2 (I_u \otimes R_\phi)^{-1}) \quad (25)$$

where R_ϕ is a 16×16 matrix with RW1 structure.

- **Model 11:** Model 8 + space-time interaction between spatially structured (v) and temporally unstructured (γ) random effects (interaction type III),

$$\delta \sim \text{Normal}(0, \sigma_\delta^2 (R_v \otimes I_\gamma)^{-1}) \quad (26)$$

where R_v is a 429×429 matrix with ICAR proximity structure which we specified the prior in equation 10.

- **Model 12:** Model 8 + space-time interaction between spatially structured (ν) and temporally structured (ϕ) random effects (interaction type IV),

$$\delta \sim \text{Normal}(0, \sigma_\delta^2 (R_\nu \otimes R_\phi)^{-1}) \quad (27)$$

We performed the required Bayesian computations using "R-INLA" (<https://www.r-inla.org/home>) [47].

2.6. Model validation

As theorized in the last section, we considered twelve models that seemed to fit right in modeling such data. In an effort to select the best model among the candidates, we considered a few model selection criteria which are commonly used to evaluate Bayesian models: Deviance Information Criterion (DIC); effective number of parameters for DIC (P_{DIC}); Watanabe-Akaike Information Criterion (WAIC); effective number of parameters for WAIC (P_{WAIC}); Logarithmic score (LS). The lowest values of these criteria suggest the best mixture of fitness and parsimony. To also give a frequentistic vision, we computed some classic tools such as the coverage gained by 95% credible interval (CrI), mean length of 95% CrI, mean absolute error (MAE) and the elapsed time for fit to evaluate these models. We did the software implementation using a computer with an Intel (R) Core (TM) i7-4820K CPU @ 3.70GHz and a RAM of 16.00 GB.

3. Results

3.1. Descriptive Characteristics

The mean cumulative rainfall, temperature, wind speed, elevation, usage of piped drinking water, public sewerage network, traveling history, YOS, IHSR and urbanization were 69.74 mm, 18.7 °C, 2.74 km/h, 1042.58 m, 96.9%, 21.67%, 4.16%, 6.59 years, 27.26 m² and 71.56% respectively. We have prepared a summary of other measures, including standard deviation (SD), 95% confidence interval (CI) and interquartile range (IQR) in Table 2.

The SIRs show that the number of cases in districts with lowest values of elevation, piped drinking water prevalence, public sewerage network prevalence, YOS, IHSR, wealth index, and urbanization is respectively 1.38, 1.84, 1.35, 1.6, 1.36, 1.78, and 2.03-fold higher than expected. On the other hand, the cases in hottest districts are 1.87-fold more than the expected count. A detailed description is available in Supplementary Table 1.

3.2. Observed trends

Figure 1a shows seasonal boxplots for district-level incidence rate measurements of U5AWD. The seasonal medians of U5AWD incidence rates ranged from 47.61 to 191.84 cases (per 10,000 <5 children). Besides, the first and third quantiles of district-level values ranged 12.97-97.87 and 115.3-343.9 cases (per 10,000 <5 children), respectively. Each year's lowest and highest values were recorded in winter (Jan-Mar) and summer (Jul-Sep) seasons. Also, U5AWD incidence rate peaked in the summer of 2015 and had the least value in winter of the same year. Besides, we demonstrated the seasonal patterns of district-level cumulative rainfall,

temperature and wind speed in Figure 1c-e. They show us the ranges that 10%, 25%, 50%, 75% and 100% of the district-level measurements fall in. As expected, all three factors confirm the existence of seasonal patterns in districts.

We depicted a single map to show the heterogeneity in the geographical distribution of the cumulative number of U5AWD cases during this period in Iran (Figure 1b). Hamadan reported the highest incident value with 57379 cases and Simorgh reported the lowest (44 cases). It seems that the central parts have much lower incident cases than the southeast, where too many cases were reported. We will rigorously examine the clustering possibilities and find the anomaly areas in section 3.3.

3.3. Hotspot analysis

Before following LISAs, we presented the subnational estimates of SIRs. As illustrated in Figure 2, there is an explicit spatial dependency in SIR's values warning us about potential seasonal outbreaks in many districts. We revealed a total of 185 significant High-High (HH) clusters of U5AWD by computing district-specific Moran's I in each year-season. Nevertheless, no Low-Low, High-Low, and Low-High cluster was detected. We should point out that HH clusters are hotspot districts also surrounded by high-risk neighbors. Figure 3 displays significant HH clusters' locations at three confidence levels (90-94%, 95-99%, and $\geq 99\%$). Ijrud and Khoramdareh were the most frequent HH clusters, followed by Jask and Mahneshan. Like Figure 2, the southeast of Iran overlays more HH clusters than other parts. A complete list of cluster names is provided in Supplementary Table 2.

3.4. Model selection

We listed the values of the mentioned selection criteria for all twelve models in Table 3. Model 9 and Model 12 show the ability to outperform others, having lower DIC, WAIC and LS and higher 95% coverage and MAE values. Choosing between the two, Model 12 seems to fit more considering DIC, P_{DIC} , P_{WAIC} and LS as the main criteria and Model 9 has better performance in terms of WAIC, 95% coverage and MAE. Finally, we picked up Model 12 as the best since it is preferred based on Bayesian model validation tools.

3.5. Modelled trends

Considering Model 12, Figure 4 shows the modeled time trend of U5AWD on a national scale during sixteen seasons from 2014 to 2018. Visually, the seasonal variations in the raw case numbers seem to be well-covered by the fitted values. As described before, every four years' high and low incident peaks occurred in summer (July to September) and winter (January to March), respectively. Moreover, the 95% credible interval has a perfect coverage overlaying all the observed national values, though the district level coverage is around 65.7%.

3.6. Bayesian inference

Lying under a Bayesian framework, we illustrated the marginal posterior distribution of the best model's coefficients (described in section 2.5: Model 12). We accordingly reported the exponentiated form of posterior samples of coefficients, named incidence rate ratio (IRR) in Table 4. We then estimated the combined IRR

effects for climatic variables by multiplying the global and seasonally varying effects in every season ($\exp(\beta_k + \xi_{k,t}) = \exp(\beta_k) \exp(\xi_{k,t})$).

Based on combined IRR values, the incidence rate would increase by 4.97% for 1°C increase in mean temperature of districts. This amount would rise to 8.77% in winter and 8.66% in fall. In contrast, the incidence rate would decrease by 1.17% and 4.41% in spring and summer, resulting in subtle effects of temperature in this period (3.74% and 0.34%). The incidence rate would decrease by 0.03% for 1 meter increase of elevation; 0.52% for 1% increase of piped drinking water availability; 0.35% for 1% increase of public sewerage network prevalence; 3.51% for 1 year increase of average YOS; 0.97% for 1 m² increase in IHSR; 4.98% for 1 score upgradations of wealth index and 0.81% for 1% increase of urbanization in districts. We should note that coefficients and IRRs have the same inference expressed in different words. However, IRRs are more straightforward in terms of interpretations. It is also worthwhile noting that we only interpreted important effects (based on 95% CrIs).

4. Discussion

It is plain to see that an apparent seasonal pattern exists in the temporal trend of U5AWD incidence in Iran, like trends in other countries[17, 23]. This variation has also been observed elsewhere, focusing on various diarrheagenic *Escherichia coli* pathotypes[52]. We observed a decreasing trend from summer (Jul-Sep) to winter (Jan-Mar), which is in complete agreement with the diarrhea trend in Afghanistan[23], the eastern neighbor of Iran. However, Our overall trend is different from the observed seasonal trends in Australia[20], India[8] and Nepal[53], which could be due to the differences in the classification of seasons in these countries. Unlike the Nepalese study mentioned above, some districts of Iran are significantly and spatially clustered in terms of U5AWD rates. Again, the significance of spatial autocorrelation in Iran concurs with the study in Afghanistan[23]. As displayed in Figure 2-3, the southeast of Iran has a worse situation than other parts. The first potential reason might be the immigrants and travelers who convey the rotavirus coming from eastern neighbors of Iran (e.g. Pakistan and Afghanistan). However, traveling history had a subtle global effect and did not show any remarkable association with U5AWD in this study.

Our results do not show any global or seasonal association between rainfall and U5AWD, being consistent with studies in Indonesia[12], Rwanda[7] and Afghanistan[23]. On the other side, our findings on rainfall do not fit several studies in Fiji[6], Taiwan[15], India[8], China[13, 17], Ethiopia[16] and Senegal[11]. In 2014, Carlton et al.[9] found heavy rainfall as a key risk factor of diarrhea incidence, especially in periods of low rainfall. Iran is experiencing an unprecedented drought period, receiving less than a third of the global average precipitation[54]. From 2014 to 2018, we estimated that the average annual precipitation of Iran is equal to 69.74 mm. Our estimate is 183 mm lower than the mean annual precipitation from 1980 to 2004, showing a dramatic reduction. Meanwhile, Iran has recorded significant flood events during this period. It is predicted that flood events will increase in southern parts[54], where we detected significant HH clusters of U5AWD.

Over recent decades, Iran's warming trend has also been exacerbated as a consequence of global warming[54]. We quantified the risk of U5AWD to increase by 4.97% for 1 °C increase in temperature (Table 4). In 2003, WHO estimated that 1 °C increase in temperature is associated with 5% growth in global incidence of diarrhea[55]. After a decade, the influence of temperature on U5AWD in Iran is quite close to the global

effect in 2003, recording 0.03% risk difference. Globally, there has been an extensive discussion about the link between temperature and the incidence of diarrheal diseases through decades. We found temperature positively and importantly associated with U5AWD, fitting with studies in Fiji[6], Bangladesh[10], Taiwan[15], Australia[22], China[13], South Africa[21], Ethiopia[16, 18], Afghanistan[23], India[14], Senegal[11] and Peru[24].

In the case of U5AWD, extremely high temperatures in districts can be harmful in three main ways. First, diarrhea-related pathogens have prolonged survival and faster replication in warm areas, where habitants (of Iran) usually struggle with low-quality drinking water sources. Second, high temperatures may hinder the food processing industries from providing uncontaminated food for consumers, accelerating the transmission of U5AWD. Third, the functionality of under-five children's immune systems may decrease under scorching weather due to probable dehydration situations, becoming more vulnerable against rotavirus infections. In 2014, Xu et al.[19] investigated Brisbane's satellite remote sensing data and observed the significant effect of extremely high temperature on emergency department visits for childhood diarrhea. Therefore, our explanations appear to be well supported. As a solution, exclusive alert systems could be developed based on meteorological predictions to spatiotemporally locate infectious outbreaks before they cause severe damage to the district-level public health. Such systems could also shield against the deteriorating effect of extreme temperature on under-five children's morbidity. Nevertheless, some other studies in Australia[20], India[8], Indonesia[12] and China[17] found either a negative or an insignificant positive association between temperature and diarrheal disease.

We did not find a serious relationship between wind speed and U5AWD corroborating the findings of an Indonesian study[12] concentrating on hospital admissions of under-five years old children. Luckily, both studies share similarities in terms of the clinical type of infection (rotavirus) and the time interval. According to another study in Shanghai of China, the Spearman correlation between the weekly number of infectious diarrhea and average wind speed was statistically significant and insignificant with type I error of 0.05 and 0.01, respectively[13]. Also, Wang et al.[17] found significant correlations between infectious diarrhea incidence in Guangzhou of China and all meteorological factors except wind velocity. Therefore, observing a subtle effect for wind speed does not seem haphazard.

We found high elevation a protective variable for U5AWD in districts of Iran which is somehow following what is discussed about diarrhea incidence in the Guinea Highlands and the Bangiagara Escarpment in Mali[25]. As Dunn et al.[25] declared, this effect could be due to the lower possibility of storms and floods in highly elevated areas.

Among hygiene-related indicators in literature, intermittency of safe drinking water supplies is distinguished as a protective one for under-five children in getting diarrheal diseases[11, 30-33]. Herein, We looked at the availability of piped drinking water as a proxy for safe drinking water. We inferred that a 1% increase in coverage of piped drinking water is associated with 0.52% decline in U5AWD, corroborating previous studies. United Nations (UN) has determined safe water as an undoubtful right for individuals worldwide[56]. At the same time, we estimate that around 3.1% of under-five children are deprived of piped

water for drinking in Iran, making it crucial to fill the gap. However, our inference contrasts the study in India[35], where improved drinking water had no significant impact on the prevalence of diarrhea.

Our results revealed that districts with higher public sewerage network coverage are less prone to U5AWD. The observed relationship is seen in another study in Gaza Strip[36], where acute diarrhea is discussed, and other clinical types are excluded. A Bayesian study in Senegal[11] has also approached this topic and observed a positive relationship between diarrhea and unsafe wastewater disposal. Other related indicators e.g., living close to dirty sewage[38] and improper solid waste disposal[31], have also been identified as risk factors of diarrhea in children aged <5 years. There are dangerous pathogens in children's feces and wastewater that can trigger U5AWD if not correctly disposed of. Surprisingly, only 21.67% of Iranian children live in an environment with public sewerage network for waste disposal. Most residents of rural areas in Iran deal with open sewerage channels, whereas extending (or renewing) public sewerage networks can secure the food chain and water supplies of the residents against these pathogens and obstruct the spread of U5AWD.

We used a continuous measure known as years of schooling (YOS) to address the educational variability in districts of Iran. The mean YOS of Iranians is about 6.59 years nationally, while one year increase of district-level YOS could cut U5AWD by 3.51%. Knowledge of water, sanitation, and hygiene (WASH) instructions could help people take sanitary actions (e.g. handwashing) more seriously. Thus, we expect highly educated people to be more likely to practice WASH interventions, having less chance of experiencing U5AWD. However, almost all previous studies work on individual data where personal information is available. As a result, mostly mother/caregivers' education is examined instead of aggregated YOS in literature and ascertained as a determinative factor for diarrheal diseases incidence in under-five children[29, 33, 34, 41, 43].

At the end of 2019, we introduced the so-called Infrastructure-to-Household Size Ratio (IHSR)[57], a continuous measure indicating the mean housing space per household member in districts of Iran. We believe IHSR has an advantage over typical indicators (like household size, house size, room per capital) in measuring the house crowdedness by differentiating districts with quite intimate features. After all, IHSR had an intensive positive association with U5AWD in our study. Our results consensus with studies in Nigeria[40], northwest Ethiopia[39], and northern Uganda[30], where significant positive effects of household size are seen. One reason could be the easier transmission of rotavirus infection between adults and children younger than five years old under household crowding circumstances.

As quoted by Statistical Center of Iran (SCI) officials, 31% of Iranian households lived below the poverty line in 2014[58]. Hereby, we used the categorical version of the wealth index (with five scores, each representing one quantile) to take the economic status of districts' households into account. On average, we expect the district-level risk of developing U5AWD to increase by 4.98% for one score decline of the wealth index. Our interpretation seems to be well-supported since recent studies from Ethiopia[42], India[35], and Kenya[29] generated wealth indices with the same instruction and found them rigorously impactful on diarrhea prevalence among under-five children. Likewise, other studies in Asia and Africa[11, 33] have acknowledged that a lower incidence of diarrhea accompanies better economic status. The community-level effect of wealth status on the incidence of infectious diseases has made many global institutions (e.g., IHME) present the burden estimates by economic strata.

Urbanization was also another important predictor of U5AWD. Based on a systematic review and meta-analysis[43], Ethiopian under-five children living in urban areas were more likely to have diarrhea than those inhabiting rural areas, completely agreeing with what we found in Iran. The underlying reason might be the exceedance allocation of healthcare facilities to urban areas. Beyond that, the incompleteness of registered case numbers is more common in rural areas than urban areas due to the lower number of public health sectors. Also, a study in Ghana[41] found rural areas at higher risk of childhood diarrhea, considering interaction terms between urban-rural residence and wealth quintile of households.

We found the best blend of simplicity and effectiveness in Model 12, followed by Model 9. The most critical aspect that discriminates Model 12 is the inclusion of interaction type IV. This term assumes that the temporal trend of U5AWD in every district is correlated with the average time trends of adjacent districts[44]. The observed superiority of interaction type IV lends support to the findings of a similar small-area study watching other infection dynamics[57]. On the other side, interaction type I considers an unstructured space-time relationship. We constructed a matrix of size 16×16 (Instead of 4×4) in both models to consider maximum long-term temporal variations placing year-season combinations on the rows and columns.

This study contains several strengths in both methodology and application. This study investigates the etiology of seasonal U5AWD incidence in an extensive geographical area, while most studies are restricted to local areas and cross-sectional time frames. The study also considers small areas (districts) as the study units, unlike most previous studies where individuals and their sociodemographic characteristics are assessed. The study tried to meet the recommended requirements for a reliable small-area study at the data cleaning stage as surveillance data should be dealt with and many design issues are likely to happen[59]. In this case, the misclassification of disease counts to districts is corrected by uniting the dataset and updating the older administrative divisions to the present. In addition, this study simultaneously discusses the spatial and seasonal distribution of U5AWD and the adjusted seasonally varying climatic effects by including the information of available socioeconomic determinants.

Certain limitations deserve to be mentioned. First, Iran's surveillance system for communicable diseases suffers from incompleteness. For example, it does not cover private health centers and self-medicated patients are not counted. To address this issue, MOHME should re-establish the surveillance system and improve the data gathering procedure. Second, stational data may not express all the heterogeneity of climatic variables in districts as a limited number of them collect the climatic data under the supervision of IRIMO. Third, we were forced to define a community-level frame because we had permission only to use the aggregated incident counts of U5AWD. Thus, any individual-level inference by the readers might be perplexing or inappropriate. Fourth, our results are not entirely immune against many forms of ecological fallacy since we assumed a monotone distribution for U5AWD within districts. Lastly, we failed to access the U5AWD data after the January of 2018, and further studies are required to provide us with an up-to-date picture of U5AWD in Iran.

5. Conclusions

Taken together, the current study provided strong evidence about the spatiotemporal dynamics of U5AWD in Iran applying novel geospatial methodologies. U5AWD showed a decreasing trend from summer to winter, and by utilizing spatial autocorrelation analysis, most hotspots of U5AWD were found in southeast areas. A

Bayesian hierarchical spatiotemporal model consisting of seasonally varying coefficients (for climatic variables) and space-time interaction (type IV) outperformed the other eleven choices in predictive ability and flexibility. In this model, the estimated seasonal coefficients of meteorological factors suggested temperature as a critical factor in explaining U5AWD, especially in winter and fall. The selected model proposed elevation, piped drinking water, public sewerage network, IHSR, YOS, wealth index, and urbanization as deep-rooted community-level predictors of U5AWD. The development of specific alert systems could be a strategy to predict high-risk areas of U5AWD using climatic inputs. Also, the study anticipates a higher incidence of U5AWD in districts with weaker hygiene and socioeconomic status. Therefore, policymakers should take appropriate preventive actions in such areas.

List of abbreviations: WHO, World Health Organization; IHME, Institute for Health Metrics and Evaluation; U5AWD, Under-five acute watery diarrhea; GBD, Global Burden of Disease; SDG 3, Sustainable Development Goal 3; BHM, Bayesian hierarchical modeling; MCMC, Markov chain Monte Carlo; INLA, integrated nested Laplace approximation; MOHME, Ministry of Health and Medical Education; IHSR, Infrastructure-to-Household Size Ratio; YOS, Years of Schooling; IRIMO, Iran Meteorological Organization; HIES, Households Income and Expenditure Survey; SCI, Statistical Center of Iran; PCA, Principal Component Analysis; DHS, Demographic and Health Surveys; SIRs, Standardized Incidence Ratios; LISAs, Local Indicators of Spatial Association; IR, incidence rate; iid, independent and identically distributed; ICAR, intrinsic conditional autoregressive; BYM, Besag-York-Mollié; RW1, first-order random walk; DIC, Deviance Information Criterion; P_{DIC} , effective number of parameters for DIC; WAIC, Watanabe-Akaike Information Criterion; P_{WAIC} , effective number of parameters for WAIC; LS, Logarithmic score; CrI, credible interval; MAE, mean absolute error; SD, standard deviation; CI, confidence interval; IQR, interquartile range; HH, High-High; IRR, incidence rate ratio

Declarations

Ethics approval: The Iranian Ministry of Health and Medical Education (MOHME) waives the need for approval in analyses where only aggregated surveillance data are provided.

Consent for publication: Not applicable.

Availability of data and materials: Climatic data is accessible at IRIMO meteorological data request system: <https://data.irimo.ir/login/login.aspx>. Elevation data can be obtained from <https://www.calcmaps.commap-elevation/>. The raw data of different stages of Iran National Population and Housing Census and the Households Income and Expenditure Survey (HIES) is available at: <https://www.amar.org.ir/english>. The data that support the findings of this study are available from MOHME but restrictions apply to the availability of these data, and so are not publicly available. Data may however be available from the authors upon reasonable request and with permission of MOHME.

Competing interests: The authors declares that he has no competing interests.

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Authors' contributions: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Review & Editing, Visualization: Masoud Masinaei

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Figure legends and tables

Figure 1. The seasonal trend of national (a) U5AWD incidence rates (per 100,000 children); (c) cumulative rainfall; (d) temperature; (e) wind speed. (b) shows the geographical distribution of U5AWD cases from April 2014 to March 2018.

Figure 2. The geographical map of measured Standardized Incidence Ratios (SIRs) for U5AWD in every season and district of Iran.

Figure 3. The geographical location of significant High-High (HH) clusters of U5AWD in every season with 90-94%, 95-99%, and $\geq 99\%$ confidence levels in Iran.

Figure 4. Seasonal trend of U5AWD case numbers in Iran from April 2014 to March 2018. Black points are the observed numbers of cases; the brown line represents the fitted values and grey lines show the bounds of 95% credible interval.

Table 1. The list of variables, data sources and the temporal domain used in the study.

Table 2. Descriptive statistics of district-level estimates of climate and socioeconomic variables in Iran from April 2014 to January 2018.

Table 3. Model selection criteria values for twelve comparative Bayesian models accounting for model fitness, parsimony, predictive performance and time-efficiency.

Table 4. Estimated posterior mean values of global and time-varying random effects for environmental and socioeconomic variables in Model 12.

Supplementary Table 1. Standardized Incidence Ratios (with 95% confidence interval) of U5AWD in districts with different characteristics based on five quantiles of every variable.

Supplementary Table 2. High-High (HH) clusters of U5AWD at different levels of significance.

Figures

Figure 1

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Supplementary Files

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