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Original Article

Seasonal Models of Herpangina and Hand-Foot-Mouth Disease to Simulate Annual Fluctuations in Urban Warming in Tokyo

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SUMMARY: In order to investigate the effects of global warming, we attempted to establish seasonal models to predict fluctuations in rates of herpangina (HA) and hand-foot-mouth disease (HFMD) associated with weather conditions and calendar months in Tokyo, Japan. Surveillance data tracking HA/HFMD incidences in Tokyo was retrieved from the Infectious Agents Surveillance Report, published by the National Institute of Infectious Diseases in Japan. From the Meteorological Agency, we obtained data for 54 weather condition parameters. The annual fluctuations in reported HA cases comprising start, peak, and end weeks almost exactly matched the model, although peak levels for each fluctuation did not always match in HFMD. Furthermore, for the HA model, 88% of the variations among observed HA cases were explained by the linear relationship with the seasonal parameters investigated, which was higher than the 64% observed for the HFMD model. The HA and HFMD models were applied to data from the years 1999 to 2002, and demonstrated correlations of 86% and 64%, respectively. These models predicted that warmer climate conditions would lead to an increased number of HA and HFMD cases. These results suggest that our seasonal models may quantify the dependency of infectious diseases on seasonal parameters and simulate the impact of global warming.

INTRODUCTION

The coxsackie-, echo-, and polioviruses are all enteroviruses, and are widely distributed throughout human populations. Enterovirus infections may be asymptomatic or may cause diarrhea, rashes, vesicular lesions on the hands, feet, and oral mucosa (hand-foot-mouth disease: HFMD), herpangina (HA), aseptic meningitis, encephalitis, myocarditis, or a combination of these conditions. The majority of infections caused by non-polio enteroviruses are asymptomatic or result in undifferentiated febrile illnesses (1), while the clinical manifestations of HFMD and HA are clinically distinct. A variety of enteroviruses have been identified, and some are quite prevalent, such as echoviruses 4, 6, 9, 11, and 30, coxsackieviruses A9, A16, and B2-B5, and enteroviruses 70 and 71. Coxsackievirus A16 is the major cause of HFMD, an infection displaying typical enteroviral features, including a short incubation period and a summer and fall seasonal pattern (2,3).

Enterovirus 71 has recently been revealed to be the etiologic agent in several outbreaks of HFMD. In Japan, Ishimaru et al. (4) reported outbreaks of HFMD in 1970, 1973, 1975, and 1978, and two of these outbreaks (1973 and 1978) involved complications of the central nervous system. Illnesses caused by this virus are frequently more severe than those due to coxsackievirus A16 (5). In Taiwan, between April and December 1998, 405 children were hospitalized as a result of complications from HFMD/HA, and 78 of these patients died (6). Both large and small outbreaks due to enterovirus 71 have previously been reported around the world including Malaysia (7, 8). Aseptic meningitis due to echovirus 30 has also been reported worldwide (9-12). Therefore, although HFMD and HA are generally considered to be benign diseases, we must pay close attention to disease trends.

Enteroviruses have a worldwide distribution. In tropical and semitropical areas, they are found year-round, whereas in temperate climates, they are detectable during winter and spring but are more common during summer and fall. Such strong seasonality of HFMD and HA suggests a climatic contribution to disease prevalence. Over the course of this century, the Earth has warmed by about 0.5°C, and mid-range estimates of future temperature change suggest an increase of 2.0°C by the year 2100 (13). Particularly in Tokyo, it has been noted that the ambient temperature during the summer months has been increasing dramatically (14). In this study, we attempted to establish nonlinear mathematical models in order to simulate the incremental effects of global warming on HA/HFMD incidences.

PATIENTS AND METHODS

In Tokyo, there were an average of 129 clinics acting as sentinel points between 1987 and 1997. The number of sentinel points increased to 250 after 1999. Almost all of these points were pediatric clinics. Thus, most patients reported to have HA/HFMD were younger than 15 years. Pediatricians at the sentinel points diagnosed HA/HFMD based on the presence of typical clinical symptoms, with or without laboratory confirmation. They reported the number of patients with HA/HFMD to the nearby health center on a weekly basis. The total number of cases in Tokyo was compiled for each week. We then retrieved surveillance data from the Infectious Agents Surveillance Report published by the National Institute of Infectious Diseases of Japan (15).

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We obtained weekly measurements of 54 weather parameters from the Meteorological Agency (Appendix I). We then collected data for the one-week periods prior to the reported cases of HA/HFMD.

Multiple regression analysis and model building were performed using STATA 7.0 software (STATA Corporation, College Station, Tex., USA) using 54 weather parameters listed in appendix I and 12 calendar moths as dummy variable using the stepwise approach with backward elimination (cut off: $P < 0.05$).

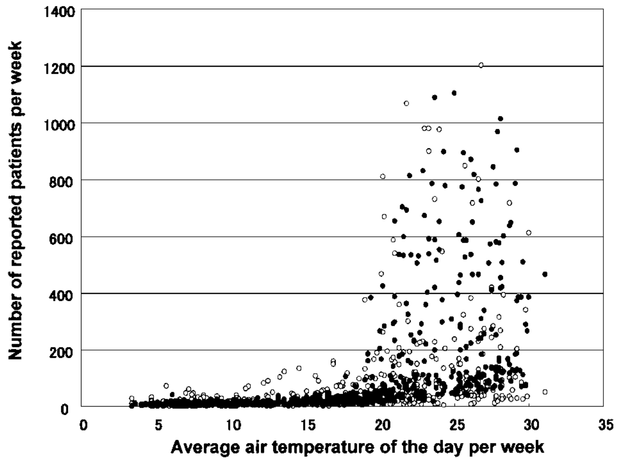
RESULTS

Simple associations between the reported number of HA/HFMD cases in Tokyo and average air temperature/vapor pressure are shown in Figure 1. The reported number of HA/HFMD cases increased sharply when the average temperature exceeded a threshold value of 19°C, and when vapor pressure increased to a threshold of 15 hPa, although no clear linear relationships were demonstrated between air temperature/vapor pressure and disease incidence. Because all weather parameters showed strong correlations (average air temperature had a strong correlation with vapor pressure; $\gamma = 0.97$), we used as many seasonal parameters as possible in order to build best fit models using multi-regression analysis, and then filtered important and independent parameters by means of a stepwise approach.

Significance testing was conducted using 54 weather parameters as continuous variables and 12 months as dummy variables. In HA model building, higher average air temperatures (AVET) and more days per week of maximum air temperature less than 25°C (M25) were positively correlated with reported HA cases per week, whereas more days per week of relative humidity less than 90% (S90), more days per week of minimum temperature below 20°C (N20), and higher levels of precipitation were negatively correlated with reported HA cases per week (Table 1). This model indicated that 88% of the variation in reported HA cases could be explained by linear relationships with these weather parameters and calendar months. In the HFMD model, vapor pressure, days per week of minimum temperature less than or equal to 25°C (N25), and days per week of maximum temperature less than or equal to 30°C (M30) were positively correlated, whereas duration of sunshine, days per week of average temperature greater than or equal to 30°C (A30), and days per week of average temperature greater than or equal to 25°C (A25) had a positive association after adjusting for calendar month (Table 2). This model indicated that 64% of the variation among the observed number of HFMD cases was explained by linear relationships with these weather parameters and calendar months.

Regression equations were formulated using the coefficients of variables created by multiple regression analysis, as described above (Appendices II and III). With these equations, the number of HA/HFMD cases was predicted and compared to the reported number of HA/HFMD cases from 1987 to 1997. The annual oscillation of predicted HA cases at the start, peak, and end weeks nearly matched the actual number of reported

(A)



(B)

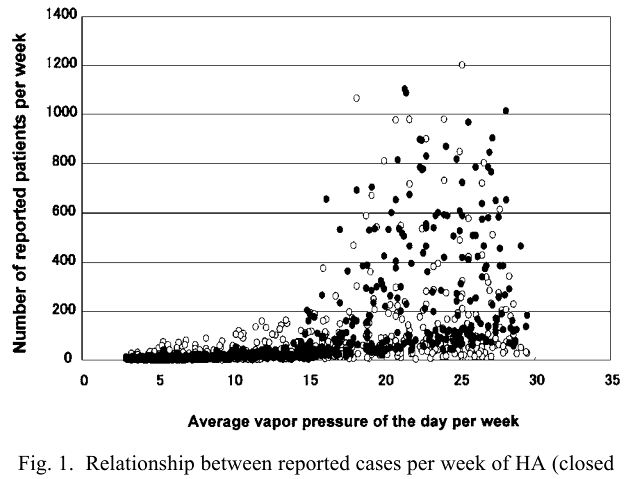


Fig. 1. Relationship between reported cases per week of HA (closed circle) / HFMD (open circle) and average air temperature (A) or vapor pressure (B) in Tokyo during the preceding week.

Table 1. Weather parameters associated with incidence of herpangina[5)]

	Coefficiency	t	P	95% CI
AVET[1)]	2.62	2.32	0.02	0.41 to 4.83
M25[2)]	11.88	2.48	0.013	2.47 to 21.3
S90[3)]	−33.96	−3.65	0.000	−52.2 to −15.7
N20[4)]	−23.44	−5.29	0.000	−32.1 to −14.7
Precipitation	−0.23	−2.04	0.042	−0.44 to −0.008

[1)] average air temperature (AVET)
[2)] days of maximum air temperature <25°C per week (M25)
[3)] days of relative humidity <90% per week (S90)
[4)] days of minimum temperature <20°C per week (N20)
[5)] adjusted by calendar months of May, June, July, August, September

Table 2. Weather parameters associated with incidence of hand-foot-mouth disease[7)]

	Coefficiency	t	P	95% CI
VP[1)]	4.83	4.11	0.000	22.52 to 7.13
N25[2)]	19.82	2.28	0.023	2.77 to 36.9
M30[3)]	25.96	−2.86	0.004	−42.7 to −7.93
SS[4)]	−3.37	−2.46	0.014	−6.06 to −0.68
A30[5)]	−27.23	−2.21	0.028	−51.5 to −2.98
A25[6)]	−25.33	−2.86	0.004	−42.7 to −7.93

[1)] vapor pressure (VP)
[2)] days per week of minimum temperature ≤25°C (N25)
[3)] days per week of maximum temperature ≤30°C (M30)
[4)] duration of sunshine (SS)
[5)] days per week of average temperature ≥30°C (A30)
[6)] days per week of average temperature ≥25°C (A25)
[7)] adjusted by calendar months of June and July

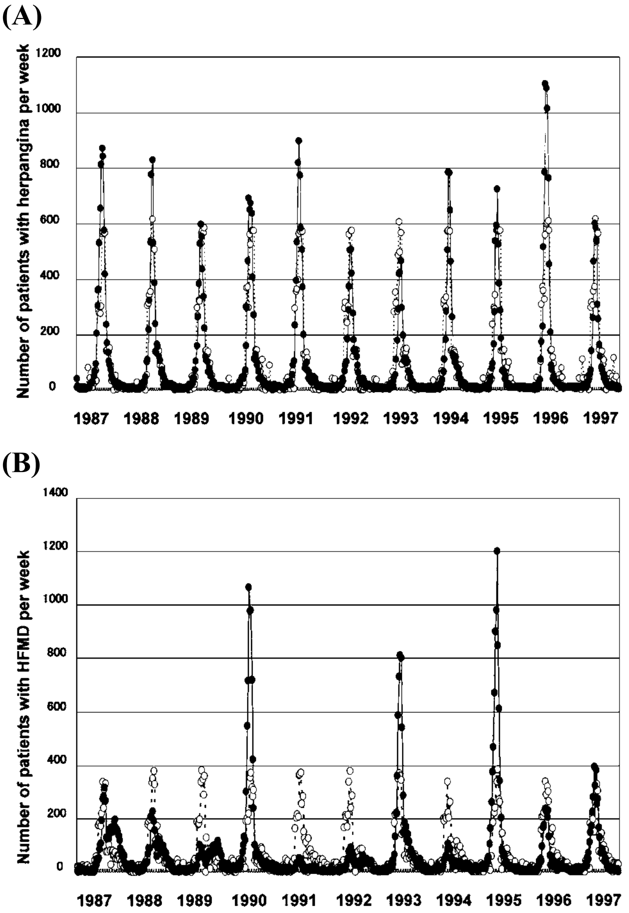


Fig. 2. Comparison of epidemic curves of weekly reported cases in Tokyo and predicted numbers based on the model between 1987 and 1997 for HA (A) and for HFMD (B). Solid lines show reported data and dotted lines show predicted data.

cases (Fig. 2A). In contrast, predicted peak numbers of HFMD did not always match with reported numbers of HFMD (Fig. 2B).

The validity of these seasonal models was examined using data gathered between March 1999 and February 2002. The predicted fluctuation of HA rates nearly matched those that were reported, although peak numbers differed slightly from the observed peaks (Fig. 3A). In contrast, for HFMD, predicted and observed peaks differed greatly (Fig. 3B).

We then simulated the impact of global warming on the incidence of HA (Fig. 4A). According to the HA seasonal model, when AVET increased by 1°C and N20/S90 decreased by 1 day per week between June and September, the number of HA cases increased by 22%. Moreover, when the parameters changed by 2°C and 2 days, HA cases increased by 43%. Although the accuracy and validity of the HFMD seasonal model were lower, we also simulated the impact of global warming on the incidence of HFMD (Fig. 4B). When vapor pressure increased by 1 hPa and A30/S90 decreased by 1 day per week between June and September, the number of HFMD cases increased by 7%. Furthermore, when the parameters changed by 2 hPa and 2 days, HFMD cases increased by 14%.

DISCUSSION

In this study, we examined important weather parameters that might affect the fluctuation of patterns and peaks of HA

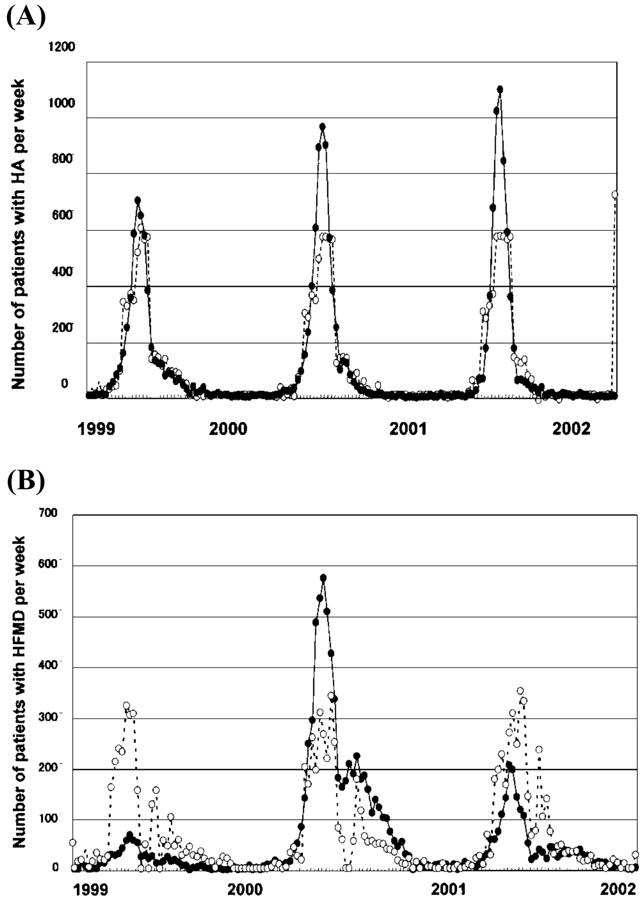


Fig. 3. Comparison of epidemic curves between March 1999 and December 2000 of weekly reported cases in Tokyo and predicted numbers based on the model built by data from 1987 to 1997 for HA (A) and for HFMD (B). Solid lines show observed data and dotted lines show predicted data.

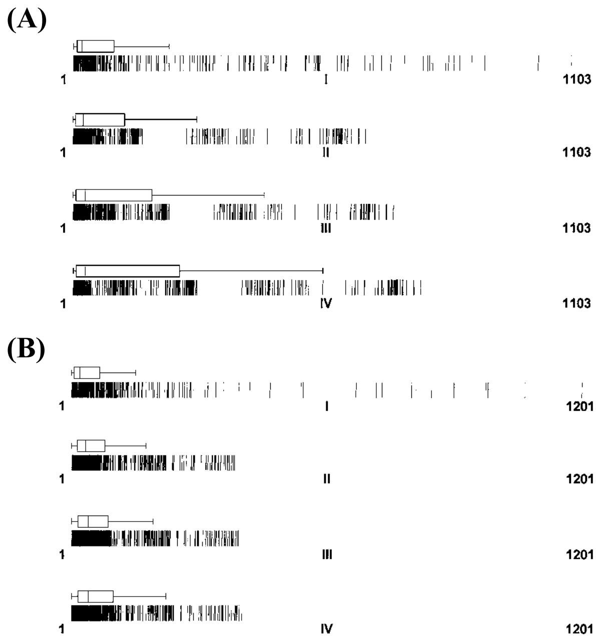


Fig. 4. Simulation for incidence of influenza by seasonal model for HA (A) and HFMD (B). I: Reported numbers of patients. II: Predicted numbers of patients based on weather parameters between 1987 and 1997. III: Simulation with warmer weather conditions between June and September. IV: Simulation with greater warming between June and September for HA and for HFMD.

and HFMD incidences, at least in part. The seasonal variability of some infectious diseases is quite clear, but very few studies on the relationship between infectious disease and climate have been reported in the literature (16). We found that higher air temperature and humidity/vapor pressure, and lower precipitation and duration of sunshine increased the incidence of HA/HFMD; particularly strong associations were found between higher air temperature and HA, and higher vapor pressure and HFMD. The stability of the enteric viruses was generally influenced by environmental factors such as relative humidity, temperature, and type of surface contaminated (13). A more rapid virus decline was observed during dry seasons than during wet seasons. This characteristic of the enteroviruses may partially explain their seasonality. In addition, prevalent types of enteroviruses and levels of neutralizing antibodies against them in the population of small children may also be major modifiers for endemics of HA and HFMD. Moreover, the population dynamics of small children may also be contributors affecting them. In turn, these various factors can affect the peak of HA and HFMD in each year.

However, annual fluctuation patterns were relatively regular in HA, but were slightly irregular in HFMD. The majority of HA fluctuations were explained by seasonal parameters, whereas in this study only 64% of HFMD were associated with seasonal parameters. During the past 8 years, a total of 3,974 viruses from HA cases were reported from 47 participating laboratories; coxsackie A viruses accounted for the vast majority, 3,055 (76.9%). However, these differential annual fluctuation patterns between HA and HFMD cannot always be explained by homogeneity of causative enteroviruses, since coxsackievirus A16 and enterovirus 71 may contribute to the regular annual fluctuation patterns of HFMD (a diagram is available at http://idsc.nih.go.jp/prompt/graph/et7.gif), whereas HA is caused by multiple serotypes of enterovirus (a diagram is available at http://idsc.nih.go.jp/prompt/graph/etb.gif).

Annual fluctuations in HA and HFMD rates were closely predicted by seasonal models. Hamer postulated that the course of an epidemic depends on the rate of contact between susceptible and infectious individuals (17). This has been extensively studied by Anderson and May as the SEIR (susceptible/exposed/infectious/removed) model (18-20). Although we initially applied the SEIR model to track fluctuations in HA and HFMD cases using average air temperature or vapor pressure as a modifier of transmission rate, we could not identify a closer association than that revealed by our seasonal model. However, we would continue to apply this SEIR model using more information such as neutralizing antibodies and prevalence of virus types for future research directions.

Global warming is evident (21,22), and its deleterious effects have been revealed through increases in heat-related deaths in Tokyo (14). The number of patients with HA/HFMD will increase if summer and autumn get warmer. Our study simulated the temperature/humidity increases that would result in increased numbers of patients by HA/HFMD in Tokyo. Judging from our model, during a hotter summer and warmer autumn, the number of patients with HA could increase dramatically, while those with HFMD would increase only slightly.

In conclusion, most of the fluctuation in the number of HA and HFMD cases was explained by our seasonal model, although each of these infections displayed its own unique association with seasonal parameters. This tool may enable us to simulate and quantify the impact of global warming on the incidence of season-dependent diseases.

ACKNOWLEDGMENTS

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APPENDIX

Appendix I. List of weather parameters and their means/min/max between 1987 and 1997

No.	Weather parameter average of the week	unit	mean	Min to Max	
1	Average temperature of the day	°C	16.3	3.4	31.1
2	Difference between Maximum and Minimum temperature of the day	°C	7.0	3.4	10.7
3	Days of Max temperature <0°C	days	0	0	0
4	Days of Max temperature <5°C	days	0.04	0	2
5	Days of Max temperature <10°C	days	0.8	0	7
6	Days of Max temperature <15°C	days	2.2	0	7
7	Days of Max temperature <20°C	days	3.4	0	7
8	Days of Max temperature <25°C	days	5.0	0	7
9	Days of Max temperature <30°C	days	6.1	0	7
10	Days of Max temperature <35°C	days	6.9	3	7
11	Days of Min temperature <−5°C	days	0	0	0
12	Days of Min temperature <0°C	days	0.07	0	5
13	Days of Min temperature <5°C	days	1.6	0	7
14	Days of Min temperature <10°C	days	2.8	0	7
15	Days of Min temperature <15°C	days	4.0	0	7
16	Days of Min temperature <20°C	days	5.3	0	7
17	Days of Min temperature <25°C	days	6.5	0	7
18	Days of Min temperature <30°C	days	7.0	6	7
19	Days of Ave temperature ≥0°C	days	7	7	7
20	Days of Ave temperature ≥5°C	days	6.7	1	7
21	Days of Ave temperature ≥10°C	days	5.1	0	7
22	Days of Ave temperature ≥15°C	days	3.9	0	7

Appendix I.-Continued

No.	Weather parameter average of the week	unit	mean	Min to Max	
23	Days of Ave temperature ≥20°C	days	2.5	0	7
24	Days of Ave temperature ≥25°C	days	1.1	0	7
25	Days of Ave temperature ≥30°C	days	0.1	0	6
26	Days of Ave temperature ≥35°C	days	0	0	0
27	Days of Ave temperature <0°C	days	0	0	0
28	Relative humidity	%	62.5	36.3	86.9
29	Days of relative humidity <10%	days	0	0	0
30	Days of relative humidity <20%	days	0	0	0
31	Days of relative humidity <30%	days	0.04	0	2
32	Days of relative humidity <40%	days	0.6	0	6
33	Days of relative humidity <50%	days	1.6	0	7
34	Days of relative humidity <60%	days	2.8	0	7
35	Days of relative humidity <70%	days	4.5	0	7
36	Days of relative humidity <80%	days	6.0	1	7
37	Days of relative humidity <90%	days	6.8	4	7
38	Station atmospheric pressure	hPa	1009.7	997.6	1023.1
39	Sea level atmospheric pressure	hPa	1013.9	1001.6	1027.5
40	Vapor pressure	hPa	13.3	2.9	29.1
41	Days of Max wind speed ≥10 m/s	days	0.5	0	4
42	Days of Max wind speed ≥25 m/s	days	0	0	0
43	Days of Max wind speed ≥29 m/s	days	0	0	0
44	Wind speed	m/s	3.4	2.2	5.4
45	Cloud cover		6.5	1.2	10
46	Days of Ave cloud cover <2.5	days	1.1	0	6
47	Days of Ave cloud cover ≥7.5	days	3.4	0	7
48	Days of Ave cloud cover <1.5	days	0.8	0	5
49	Days of Ave cloud cover ≥8.5	days	2.7	0	7
50	Duration of sunshine	hour	36.4	0.2	74.3
51	Number of sunless days	days	44.4	0.2	93.9
52	Rate of sunshine	%	0	0	0
53	Mean flux of global solar radiation	MJ./m^2	11.7	2.7	23.6
54	Amount of precipitation	mm	28.8	0	310.5

Appendix II. Calculation for predicting number of patients with HA per week in Tokyo.

Predicted number of patients with HA = 11.88 × [more days of maximum temperature less than 25°C per week (M25)] + 2.62 × (average temperature) − 33.96 × [more relative humidity less than 90% per week (S90)] − 23.44 × [more days of minimum temperature less than 20°C per week (N20)] − 0.23 × (precipitation) + 31.45 × (May) + 253.119 × (June) + 442.18 × (July) − 26.55 × (September) + 304.81

Appendix III. Calculation for predicting number of patients with HFMD per week in Tokyo

Predicted number of patients with HFMD= 4.83 × (vapor pressure) + 19.82 × [days per week of minimum temperature less than or equal to 25°C (N25)] + 25.96 × [days per week of maximum temperature less than or equal to 30°C (M30)] − 3.37 × (duration of sunshine) − 27.23 × [days per week of average temperature more than or equal to 30°C (A30)] − 25.33 × [days per week of average temperature more than or equal to 25°C (A25)] + 123.33 × (June) + 241.39 × (July) + 64.65

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