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# Pityriasis rosea: elucidation of environmental factors in modulated autoagressive etiology and dengue virus infection

Mehak Singh[1], Manoj Pawar[2] ✉, Antonio Chuh[3], Vijay Zawar[2]

## Abstract

**Introduction:** A retrospective epidemiological study was conducted to study seasonal variation in the incidence of pityriasis rosea (PR) and its temporal association with various meteorological variables, and dengue virus infection.
**Methods:** The study was conducted at a tertiary referral center in Guwahati, Assam, India. We searched for and retrieved all medical records of patients diagnosed with PR by dermatologists from December 1st, 2014 to July 31st, 2017. The diagnosis was made only if the patient fulfilled at least three out of the following four clinical features: 1) herald patch, 2) peripheral collaret scales, 3) predominant truncal and proximal limb distribution of the lesions, and 4) orientation of lesions along the lines of cleavage. For each visit by every patient, we retrieved data for the monthly mean air temperature, mean total rainfall, and mean relative humidity. PR patients that had dengue fever with NS1 antigen and/or IgM/IgG antibody positivity were studied along with healthy controls.
**Results:** Overall, PR occurred more frequently in the colder months and months with less rainfall. However, these associations were insignificant ($p = 0.23$, $R = -0.38$, and $R = -0.55$, respectively). Upon further examination of the data, we found that the monthly incidence of PR was significantly lower in March and April than the other months during the study period ($F = 8.31$, $p = 0.002$). A statistically significant higher incidence was detected in September, November, and December ($p < 0.01$ for 2014 and 2017, but not in the 2016 seasonal cohort) and also in January and February ($p < 0.05$ for 2016 and 2017). Interestingly, a retrospective history of dengue fever emerged as a significant correlate.
**Conclusions:** In our setting, there was significant temporal clustering and seasonal variation among patients with PR. The incidence of dengue fever is significantly correlated with PR.

**Keywords:** dengue, pityriasis rosea, seasonal variation

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## Introduction

Pityriasis rosea (PR) is suspected to be associated with an infection. However, an exact cause has not been found. Drago et al. reported human herpesvirus 7 to be the causative agent (1). Other investigators reported findings supporting and refuting such an association. However, the distinct clinical course, a lack of recurrences in most of the patients, and the presence of temporal case clustering support an infectious etiology. Furthermore, seasonal variation, association with respiratory tract infections, and a history of contact with PR patients in some patients do support an infectious etiology (2).

Cluster analysis is a useful approach for elucidating possible infectious etiologies. Several studies have evaluated the presence of clustering in PR (3–12). In 1982, Messenger et al. reported significant spatial-temporal clustering only in female patients with PR and a temporal cluster of 16 patients within a 28-day period (3). However, there was no control and the impact of seasonal variation was not studied. Later on, some studies reported seasonal variation and/or case clustering for patients with PR (4, 8–11), whereas others did not find any significant association with seasonal variation and incidence of PR (6, 12). To the best of our knowledge, no study has reported an association of dengue fever with PR. We thus report here a retrospective study investigating the epidemiology of PR and the incidence of dengue fever and its association with PR at a tertiary referral center in Assam.

## Methods

The study was conducted at a tertiary referral center in Guwahati, Assam, India. We searched for and retrieved all medical records of patients diagnosed with PR by dermatologists from December 1st, 2014 to July 31st, 2017. The diagnosis was made only if the patient had fulfilled at least three out of the following four clinical features: 1) herald patch, 2) peripheral collaret scales, 3) predominant truncal and proximal limb distribution of the lesions, and 4) orientation of lesions along the lines of cleavage. These diagnostic criteria were laid down and validated by us (13, 14). For each visit by every patient, we retrieved data for the monthly mean air temperature, mean total rainfall, and mean relative humidity. PR patients that had dengue fever were studied along with healthy controls. The detection of NS1 antigen was done using the Panbio Dengue Early enzyme-linked immunosorbent assay (ELISA) (Inverness Medical Innovations, Australia). The detection of IgM antibodies was done using the Dengue-IgM capture ELISA kit (National Institute of Virology, Pune). IgG anti-dengue antibodies were detected using the dengue IgG capture ELISA (PanBio Pty Ltd, Queensland, Australia).

The following steps were used for the statistical analysis:

a) 2 × 2 contingency tables were drawn to calculate the odds ratio (OR) and risk ratio (RR), as well as a chi-square test, and finally a two-tailed Fisher's exact test ($p < 0.05$ was considered statistically significant);

[1]Department of Dermatology and Venerology, H. B. T. Medical College and Dr. R. N. Cooper Municipal General Hospital, Mumbai, Maharashtra, India. [2]Department of Dermatology, Dr. Vasantrao Pawar Medical College, Nashik, India. [3]Department of Family Medicine and Primary Care, University of Hong Kong and Queen Mary Hospital, Pokfulam, Hong Kong. ✉**Corresponding author: manojpawar624@yahoo.com**

b) linear regression model.

Temporal clustering was investigated using a regression model. The monthly incidence of PR was taken as a dependent variable, with meteorological variables such as monthly average temperature, monthly average precipitation, and the occurrence of dengue fever considered as independent variables. The statistical relationship was evaluated using Pearson's correlation analysis in the statistical software package SPSS (version 20.0, SPSS Inc., Chicago, IL) and online statistics programs.

### Time-series analysis

Monthly PR and dengue incidences were cross-correlated using the cross-correlation function (CCF). In a cross-correlation in which the direction of influence between two time series is hypothesized, the influential time series is called the "input" time series and the affected time series is called the "output" time series. The application of cross-correlations in this text infers that the input time series refers to the incidence of dengue in a patient and the output time series refers to an occurrence of an auto-immune response to the dengue virus manifesting as a PR rash.

## Results

A total of 136 PR patients were found to fulfill the diagnostic criteria. The male:female ratio was 1:1.13. They were between 13 months and 59 years old with maximum incidences in the age clusters 20–29 and 30–39 (Tables 1 and 2).

For the epidemiological data analysis, the seasonality plot indicates a trend characterized by a peak in post-monsoon and winters (September–January, peak month November) and a trough in summers (peak, April), and the magnitude of the seasonal variation increases at the same rate as the yearly mean levels. Therefore, we tested this distribution pattern to determine whether it was statistically significant. The expected incidence for 12 months was calculated for a year from the total number of new PR patients and the number of hospital working days in each month during the same year. Then the mean ± standard deviation of 3 years was obtained for each month for the expected number of PR patients. Statistical tests were performed to compare actual and expected numbers of first visits during each month. Statistical significance was detected in September, November, and December ($p < 0.01$ for 2014 and 2017, but not in the 2016 seasonal cohort) and also in January and February ($p < 0.05$ for 2016 and 2017).

Regarding precipitation and temperature as independent predictive parameters for the incidence of PR, it was found that heavy rainfall is associated with decreased incidence of PR (this correlates with our hypothesis of dengue virus being one of the etiological factors in the development of PR because high rainfall is associated with decreased breeding of the dengue vector (i.e., *Aedes* mosquitoes) and, as discussed above, increased PR was observed with a drop in temperature.

**Table 2** | **Distribution of patients with pityriasis rosea by month, meteorological data, and Ns1Ag and/or IgM/IgG antibody positivity.**

| Month | Patients | Average temperature (°C) | Average precipitation (mm) | Cases with Ns1Ag and/or IgG/IgM antibody positivity (only documented cases) |
|---|---|---|---|---|
| January | 14 | 17.5 | 12 | 3 |
| February | 7 | 19.5 | 16 | 0 |
| March | 1 | 23.3 | 60 | 0 |
| April | 0 | 26.0 | 141 | 0 |
| May | 5 | 26.8 | 278 | 1 |
| June | 3 | 28.1 | 315 | 0 |
| July | 2 | 28.9 | 313 | 2 |
| August | 1 | 29.0 | 261 | 0 |
| September | 25 | 28.6 | 181 | 8 |
| October | 17 | 26.2 | 100 | 9 |
| November | 36 | 22.5 | 15 | 11 |
| December | 28 | 18.7 | 6 | 4 |
| Total | 136 | – | – | 38 |

### Temperature and pityriasis rosea (PR) incidence

The regression equation for $Y$ (where $Y$ = PR incidence and $X$ = temperature in Celsius) was $\hat{y} = -0.61521X + 58.50307$ (Fig. 1a). Our interpretation is that the negative value showed an inverse relationship; that is, the incidence of PR increased with decreased temperatures.

### Rainfall and PR incidence

The regression equation for $Y$ (where $Y$ = PR incidence and $X$ = rainfall in mm) was $\hat{y} = -0.05421X + 19.25344$ (Fig. 1b). Our interpretation is that increased rainfall was associated with decreased PR incidence.

The results from linear regression plots were further analyzed for Pearson's coefficient, and we found that the monthly incidence of PR is significantly associated with months with less rainfall ($R = -0.55$, $p = 0.0001$). Such an incidence is also associated with the colder months, although the association is insignificant ($R = -0.38$; $p = 0.23$).

### PR and dengue incidence

The regression equation for $Y$ (where $X$ = incidence of Ns1Ag-positive dengue cases per month and $Y$ = incidence of PR per month) is $\hat{y} = 2.68596X + 3.0778$.

The correlation coefficient (PMMC) $r$ was found to be 0.8714 ($p = 0.0002$; highly significant), which shows a positive correla-

**Table 1** | **Epidemiological data and its comparison with other studies.**

| Study | Location | PR patients | Male:female | Seasonal variation |
|---|---|---|---|---|
| Harman et al. (1998) | Eastern Anatolia, Turkey | 399 | 1:1.21 | Peak during spring, autumn, and winter |
| Nanda et al. (1999) | Kuwait | 117 | 1:1.38 | Not reported |
| Tay et al. (1999) | Singapore | 368 | 1.19:1 | No variation |
| Traore et al. (2001) | Burkina Faso | 36 | Not reported | Not reported |
| Chuh et al. (2003) | Hong Kong | 41 | 1:1.05 | February, July, April |
| Chuh et al. (2005) | Minnesota, United States, Kuwait, and Diyarbakır, Turkey | 1,379 | Not reported | Clusters found but did not mention the seasons |
| Sharma et al. (2010) | Uttar Pradesh, India | 200 | 2:1 | September to December |
| Ayanlowo et al. (2010) | Lagos, Nigeria | 427 | 1:1.55 | October, August, March |
| Ganguly et al. (2013) | Southern India | 73 | Male preponderance | No variation |
| This study (2018) | Northeast India | 136 | Female preponderance | September to January |

PR = pityriasis rosea.

tion between the incidence of Ns1Ag or antibody positivity and PR (Fig. 1c).

I. Cross correlation Function-SARIMA model results – PR:
   a) Autocorrelation (ACF) and partial autocorrelation function (PACF) for PR incidence (Figs. 2a–2c):
   ACF and PACF plots were deployed to identify patterns in the above data, which are stationary on both mean and variance, to identify the presence of AR (autoregressive) and MA (moving average) components in the residuals. The ACF function shows a perfect sinusoidal pattern with a spike at lag 1; on extrapolating the data to the PAC function, the same correlation is seen at lag 1 ($p$ = 0.037).

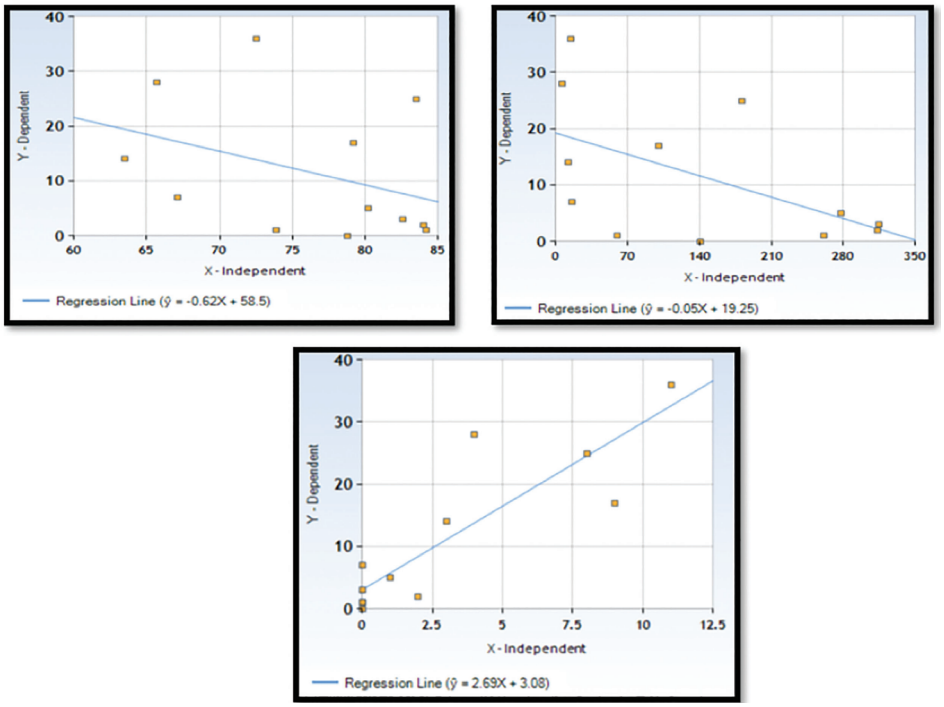


Figure 1 (clockwise) | 1a: Temperature and pityriasis rosea (PR) incidence, 1b: rainfall and PR incidence, 1c: PR and dengue incidence.

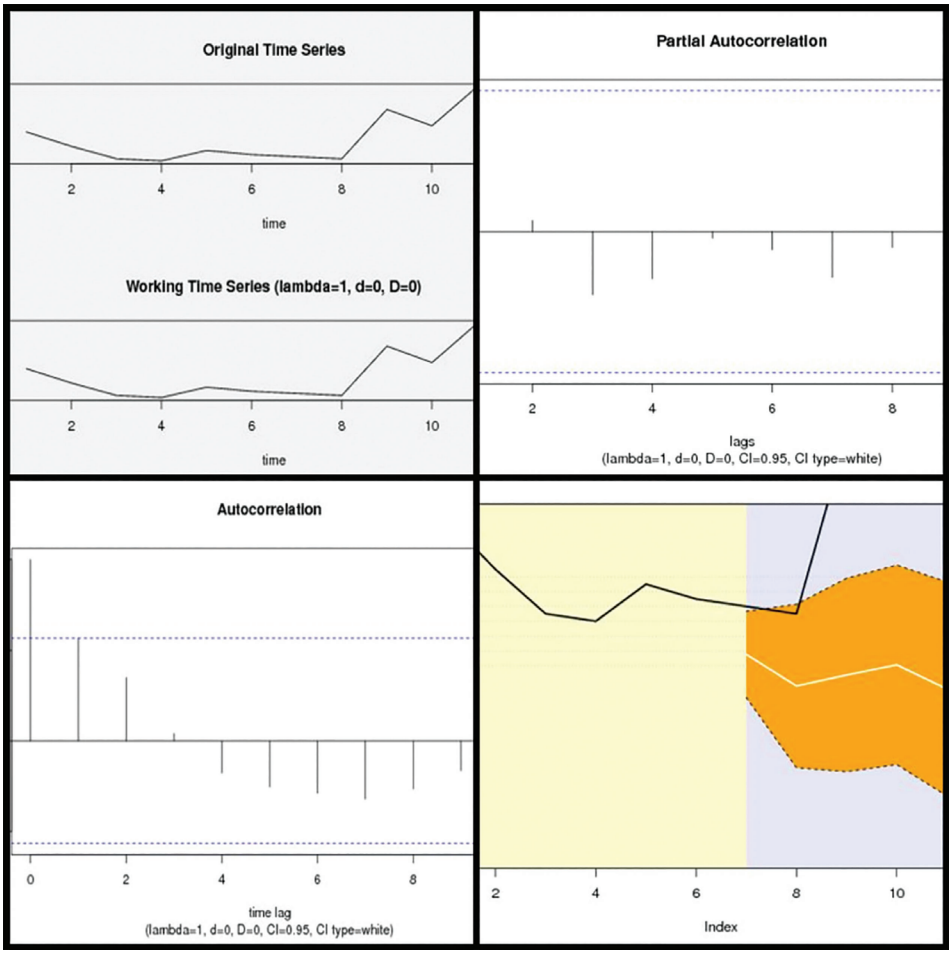


Figure 2a, b, c, d (clockwise) | Original, partial autocorrelation function, and autocorrelation function plots for pityriasis rosea (PR) incidence derived from original time series after prewhitening and SARIMA extrapolation forecast for PR incidence.

b) SARIMA forecast for PR incidence:
For prewhitening, the model SARIMA ($p$ = 1, $d$ = 0, $q$ = 0, $P$ = 2, $D$ = 1, $Q$ = 2 $p$ = 1, $d$ = 0, $q$ = 0, $P$ = 2, $D$ = 1, $Q$ = 2) was selected. Strong negative correlation coefficients were found at lags of the 7th and 8th months. Weak negative associations were found at lags of 7 to 9 months (Fig. 2d).

II. Cross correlation Function-SARIMA model results – PR with preceding history of Ns1Ag or antibody positivity (Figs. 3a–3c): Both the ACF and PACF functions showed a significant positive correlation at 0 and 1 lag ($p$ = 0.028).

c) SARIMA forecast for PR cases with Ns1Ag positivity or antibody incidence (Fig. 3d):
A significant positive correlation was found at lag 12 months ($p$ = 0.04). Of the 136 PR patients, 38 were seropositive for either/both IgG and IgM or Ns1Ag (27.94%) in contrast to 19 (13.97%) Ns1Ag or IgM and IgG antibody seropositive cases in 136 matched controls. Seropositivity for Ns1Ag or antibody in PR patients was significantly higher than those found in controls (OR = 2.3878, 95% confidence interval (CI) = 1.294 to 4.4061; RR = 2, 95% CI = 1.217 to 3.2868; Yates $x^2$ = 7.19 $p$ = 0.0073; two-tailed Fisher's exact probability test $p$ = 0.00698), indicating a higher risk of developing PR with a preceding history of dengue viral infection. Furthermore, the bivariate Granger causality for PR incidence and NsAg1 and/or antibody positivity revealed that the incidence of seropositivity to dengue virus infection can be used to forecast the development of PR rash as a significantly positive correlation at lag 2 months ($F$ = 10.3, $p$ = 0.0237).

## Discussion

This retrospective study found temporal clusters of PR in the dry winter months of September to January, with the correlation being statistically significant for the months of September, November, and December ($p$ < 0.01 for 2014 and 2017 but not in the 2016 seasonal cohort) and also in January and February ($p$ < 0.05 for 2016 and 2017); however, the overall correlation was weak. The association between the infectious etiology, especially human herpesvirus 6 and 7, with PR is controversial; reasonable evidence suggests that PR is not associated with cytomegalovirus, Epstein–Barr virus, parvovirus B19, picornavirus, influenza and parainfluenza viruses, *Legionella* spp., *Mycoplasma* spp., and *Chlamydia* spp. (15, 16). Interestingly, in this study, the retrospective histories of dengue fever emerged as a significant correlate against a matched cohort of 136 patients visiting the dermatology outpatient department for other ailments. The average duration between the onset of PR and dengue was 78.34 days. The most interesting example of PR with dengue was that of a pair of twins, both of whom presented with typical PR lesions with a history of dengue fever 5 weeks earlier. The outbreaks of dengue occurred from August to October, indicating increased vector transmission in the monsoon and post-monsoon periods. However, we admit that the monthly rate of den-

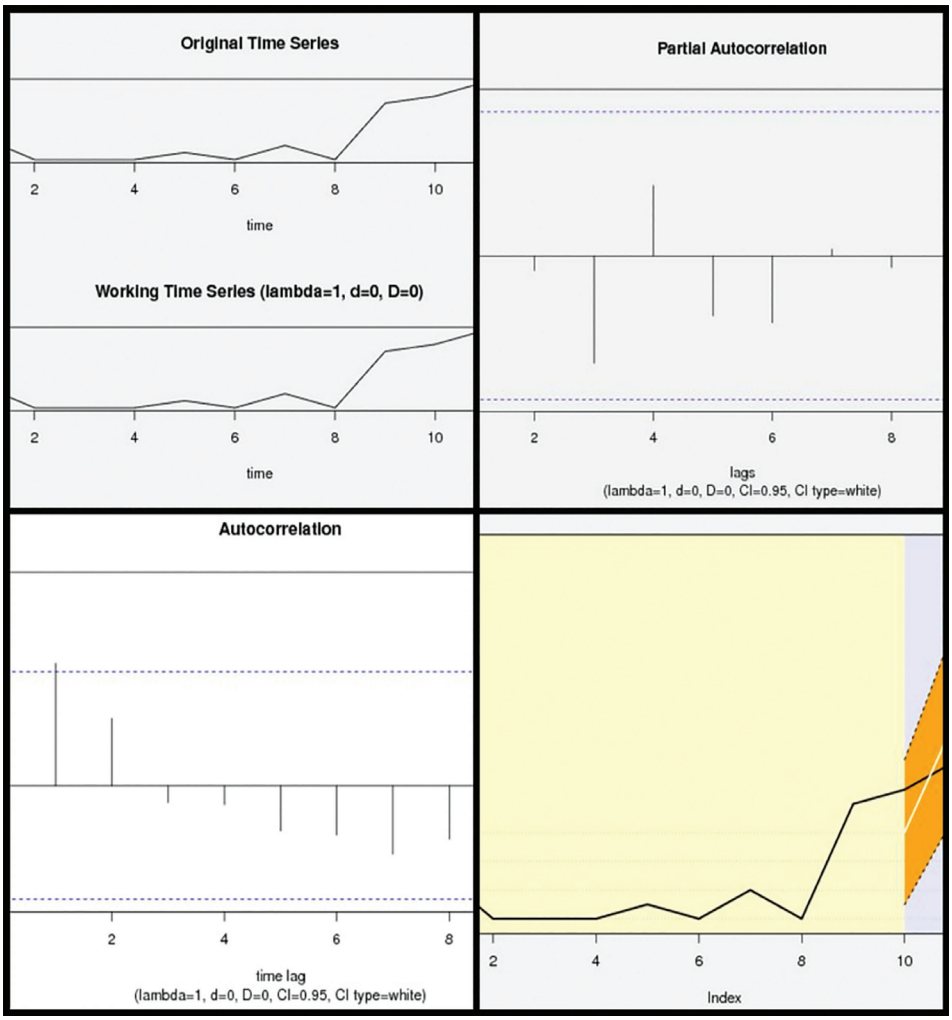


Figure 3a, b, c, d (clockwise) | Original, partial autocorrelation function, and autocorrelation function plots for preceding history of NsAg1 and/or IgG or IgM positivity and SARIMA extrapolation forecast for pityriasis rosea cases with preceding dengue history.

gue fever may only be a confounding variable. The significance of this should be investigated further in future studies.

The age and sex distribution in our study is in line with other epidemiological studies on PR (3–7). Some of these studies reported a higher incidence of PR during winter (10, 11), whereas one reported a higher incidence in the early rainy season (8) and some reported no seasonal variation (6, 12) (Table 1).

Our study has certain limitations. The most important limitation of this study is that the data were collected at one clinic in one geographical location only. Having adequate resources, we previously performed epidemiological studies in multiple geographical locations (9). However, we lack a similar scale of material support in this study. Confounding variables could thus negate the generalization of our results to other geographical locations and other clinical settings. We also failed to elucidate the underlying mechanisms for our results being similar to or different from those of other investigators (3–11) to an acceptable level of evidence. Although our study followed the morphological features delineated by Chuh et al., there is another proposed classification of PR by Drago et al., in which PR variants, including atypical forms, are classified on the basis of differences in pathogenesis, clinical features, and the course of the disease (19). This classification included pregnant patients, who were not part of our study population.

The temporal clustering documented in this study might suggest a role of dengue virus as an autoimmune trigger, modulated by environmental factors that cause the syndrome in previously unexposed, genetically susceptible individuals, with asymptomatic infection leading to protective immunity in the majority of the population. The fact that PR is self-limited strongly suggests a definitive immune response that terminates the inflammatory process.

## Conclusions

We found temporal clusters of PR in the dry winter months of September to January, with the correlation being statistically significant for the amount of rainfall. Interestingly, retrospective histories of dengue fever emerged as a significant correlate. Thus, temporal clustering and dengue infection as significant correlates may imply the infectious etiology of PR. However, the significance of this warrants further multicentric investigations, preferably at different geographic locations.

## References


1. Drago F, Ranieri E, Malaguti F, Losi E, Rebora A. Human herpesvirus 7 in pityriasis rosea. Lancet. 1997;349:1367–8.
2. Chuh A, Zawar V, Sciallis GF, Lee A. The diagnostic criteria of pityriasis rosea and Gianotti–Crosti syndrome—a protocol to establish diagnostic criteria of skin diseases. J R Coll Physicians Edinb. 2015;45:218–25.
3. Messenger AG, Knox EG, Summerly R, Muston HL, Ilderton E. Case clustering in pityriasis rosea: support for role of an infective agent. Br Med J (Clin Res Ed). 1982;284:371–3.
4. Harman M, Aytekin S, Akdeniz S, Inaloz HS. An epidemiological study of pityriasis rosea in the eastern Anatolia. Eur J Epidemiol. 1998;14:495–7.
5. Nanda A, Al-Hasawi F, Alsaleh QA. A prospective survey of pediatric dermatology clinic patients in Kuwait: an analysis of 10,000 cases. Pediatr Dermatol. 1999; 16:6–11.
6. Tay YK, Goh CL. One-year review of pityriasis rosea at the National Skin Centre, Singapore. Ann Acad Med Singapore. 1999;28:829–31.
7. Traore A, Korsaga-Some N, Niamba P, Barro F, Sanou I, Drabo YJ. Pityriasis rosea in secondary schools in Ouagadougou, Burkina Faso. Ann Dermatol Venereol. 2001;128:605–9. [French]
8. Chuh AA, Lee A, Molinari N. Case clustering in pityriasis rosea: a multicenter epidemiologic study in primary care settings in Hong Kong. Arch Dermatol. 2003; 139:489–93.
9. Chuh AA, Molinari N, Sciallis G, Harman M, Akdeniz S, Nanda A. Temporal case clustering in pityriasis rosea: a regression analysis on 1379 patients in Minnesota, Kuwait, and Diyarbakır, Turkey. Arch Dermatol. 2005;141:767–71.
10. Sharma L, Srivastava K. Clinicoepidemiological study of pityriasis rosea. Indian J Dermatol Venereol Leprol. 2008;74:647–9.
11. Ayanlowo O, Akinkugbe A, Olumide Y. The pityriasis rosea calendar: a 7 year review of seasonal variation, age and sex distribution. Nig Q J Hosp Med. 2010;20: 29–31.
12. Ganguly S. A clinicoepidemiological study of pityriasis rosea in south India. Skinmed. 2013;11:141–6.
13. Chuh AAT. Diagnostic criteria for pityriasis rosea – a prospective case control study for assessment of validity. J Eur Acad Dermatol Venereol. 2003;17:101–3.
14. Zawar V, Chuh A. Applicability of proposed diagnostic criteria of pityriasis rosea: results of a prospective case-control study in India. Indian J Dermatol. 2013;58: 439–42.
15. Chuh AA, Chan HH. Prospective case-control study of chlamydia, legionella and mycoplasma infections in patients with pityriasis rosea. Eur J Dermatol. 2002; 12:170–3.
16. Chuh A, Chan H, Zawar V. Pityriasis rosea—evidence for and against an infectious aetiology. Epidemiol Infect. 2004;132:381–90.
17. Mubki TF, Bin Dayel SA, Kadry R. A case of pityriasis rosea concurrent with the novel influenza A (H1N1) infection. Pediatr Dermatol. 2011;28:341–2.
18. Kwon NH, Kim JE, Cho BK, Park HJ. A novel influenza a (H1N1) virus as a possible cause of pityriasis rosea? J Eur Acad Dermatol Venereol. 2011;25:368–9.
19. Drago F, Ciccarese G, Rebora A, Broccolo F, Parodi A. Pityriasis rosea: a comprehensive classification. Dermatology. 2016;232:431–7.

## Supplementary data and figures

### Statistical methods used

For the cross-correlation function, the correlation coefficient, or Pearson product-moment correlation coefficient (PMCC), was calculated using the formula:

$$r = \frac{n\sum_{i=1}^{n} x_i y_i - \sum_{i=1}^{n} x_i \sum_{i=1}^{n} y_i}{\sqrt{(n\sum_{i=1}^{n} x_i^2 - (\sum_{i=1}^{n} x_i)^2)(n\sum_{i=1}^{n} y_i^2 - (\sum_{i=1}^{n} y_i)^2)}}$$

where n is the total number of samples, $x_i$ ($x_1$, $x_2$, . . . , $x_n$) are the $x$ values, $y_i$ is the $y$ values, and $r$ (PMCC) is a numerical value between −1 and 1 that expresses the strength of the linear relationship between two variables. When $r$ is closer to 1 it indicates a stronger positive relationship.

### The cross-correlation calculation for univariate time series was calculated as follows:

The cross-correlation of time series requires the time series to be stationary and prewhitened. Stationarity is defined by a constant mean and equal variance at all times, and it can be achieved by detrending or differencing. Prewhitening removes spurious correlations based on temporal dependencies between adjacent values of the input time series and it removes these influences from the output time series. The parameters lambda, $d$, $D$, and seasonality were used to apply a Box–Cox transformation and (non-)seasonal differencing in order to induce stationarity of the time series. The confidence interval was computed assuming a white noise time series (CI type = white noise).

### SARIMA modeling

Multiplicative seasonal auto-regressive integrated moving average (SARIMA) models with all possible combinations of parameters $p$, $q$, $P$, $Q \in \{0, 1, 2\}$ and with $d$, $D \in \{0, 1\}$ were evaluated using Akaike's information criterion (AIC) on untransformed and logarithmically transformed monthly meteorological data from 2014 to 2017. The selected SARIMA model was then used to prewhiten meteorological data series, PR, and Ns1Ag positivity and PR incidence time series.

For the formulas used, the seasonal ARIMA model incorporates both non-seasonal and seasonal factors in a multiplicative model. One shorthand notation for the model is ARIMA$(p, d, q) \times (P, D, Q)S$, with $p$ = non-seasonal AR order, $d$ = non-seasonal differencing, $q$ = non-seasonal MA order, $P$ = seasonal AR order, $D$ = seasonal differencing, $Q$ = seasonal MA order, and $S$ = time span of repeating seasonal pattern.

The model could be written more formally as:

(1) $\Phi(B^S)\varphi(B)(x_t - \mu) = \Theta(B^S)\theta(B)w_t$

The non-seasonal components are:

AR: $\varphi(B) = 1 - \varphi_1 B - \ldots - \varphi_p B^p$

MA: $\theta(B) = 1 + \theta_1 B + \ldots + \theta_q B^q$

The seasonal components are:

Seasonal AR: $\Phi(B^S) = 1 - \Phi_1 B^s - \ldots - \Phi_P B^{PS}$

Seasonal MA: $\Theta(B^S) = 1 + \Theta_1 B^s + \ldots + \Theta_Q B^{QS}$

Analysis was carried out using Wessa online: Wessa P., (2017), (Partial) Autocorrelation Function (v1.0.15) in Free Statistics Software (v1.2.1), Office for Research Development and Education, URL http://www.wessa.net/rwasp_autocorrelation.wasp.

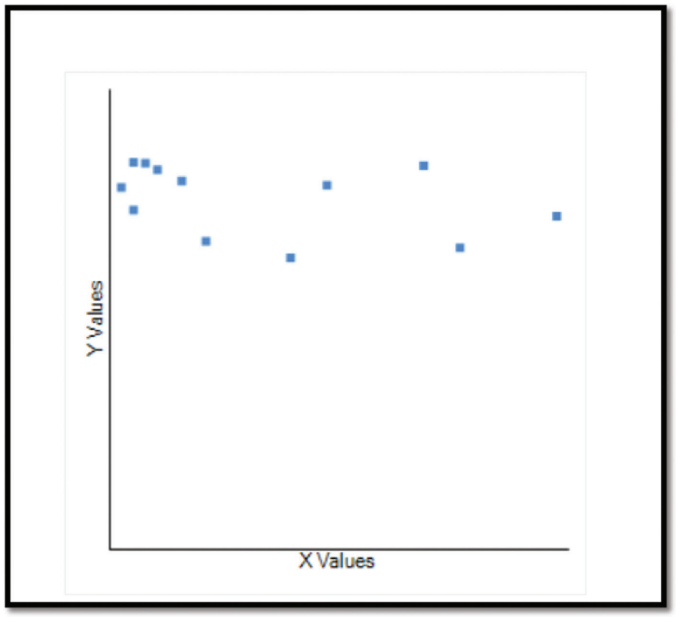


Figure 1s | Pearson correlation between average monthly temperature in Celsius and pityriasis rosea cases: $R = -0.3762$. (The $p$-value is 0.22837. The result is not significant at $p < 0.05$.).

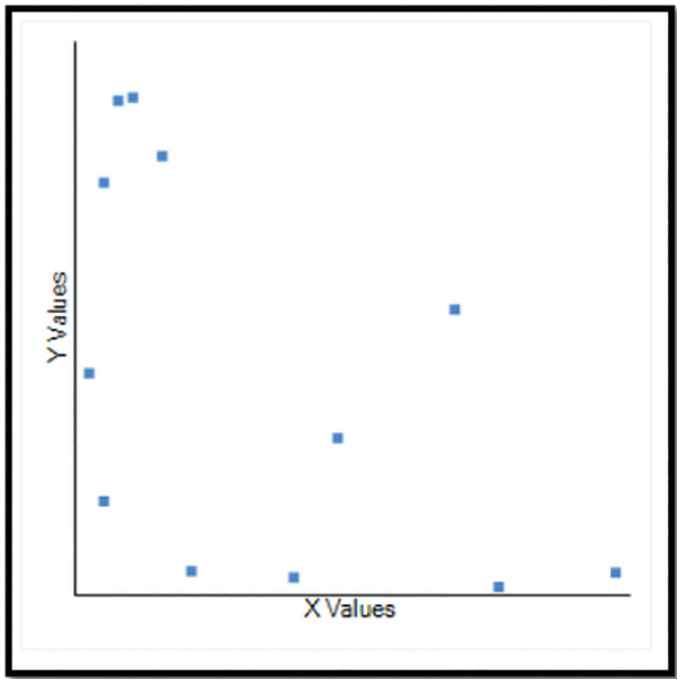


Figure 2s | Pearson correlation between average monthly precipitation and incidence of pityriasis rosea ($R = -0.5458$). This is a moderate negative correlation, which means there is a tendency for increased incidence ($p = 0.0001$). The value of $R^2$, the coefficient of determination, is 0.2979.

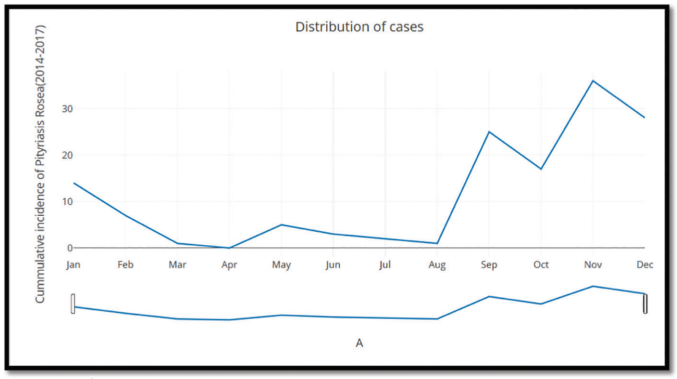


Figure 3s | Plot between average monthly precipitation and incidence of pityriasis rosea.