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# REVIEW ARTICLE
# Pityriasis rosea – evidence for and against an infectious aetiology

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## SUMMARY

Pityriasis rosea, first named as such in 1860, probably holds the longest record for an exanthem suspected to be associated with an infection but for which an exact cause has not been found. The distinctly *programmed* clinical course, the lack of recurrence for most patients, and the presence of temporal case clustering provide the strongest evidence to support an infectious aetiology. Further support comes from seasonal variation and the association with respiratory tract infections, the unfavourable social and economic background of cases, and a history in some cases of contact with patients with pityriasis rosea. The apparent therapeutic efficacy of several treatment modalities does not provide strong evidence for or against an infectious aetiology. The roles of human herpesvirus 7 and to a lesser extent human herpesvirus 6 remain controversial. There exists reasonable evidence that pityriasis rosea is not associated with cytomegalovirus, Epstein–Barr virus, parvovirus B19, picornavirus, influenza and parainfluenza viruses, *Legionella* spp., *Mycoplasma* spp. and *Chlamydia* spp. infections. Evidence is also unsubstantiated as yet for alternative aetiological hypotheses such as autoimmunity, atopy, and genetic predisposition.

## BACKGROUND

The term pityriasis rosea (PR) was first coined by the French dermatologist Camille Melchior Gibert in 1860 [1]. Compared to several other exanthems, PR probably holds the longest record for an exanthem believed to be associated with an infectious aetiology but for which a specific causal organism has not yet been identified.

It is important to establish whether the existing data on PR does support an infectious aetiology, as it determines whether continuing the search for the infectious agent is worthwhile. The identification of an infectious cause paves the way for active intervention to modify the course of the disease.

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## EVIDENCE FOR AN INFECTIOUS AETIOLOGY

### General evidence

Perhaps the strongest evidence to support an infectious aetiology for PR is its distinct clinical course. A herald patch is followed by a secondary eruption, with complete remission mostly within 8 weeks, and almost all within 12 weeks. This *programmed* course of events is similar to that of many viral infections associated with rashes.

Moreover, most sufferers do not have a second attack, a phenomenon also exhibited by many viral

diseases. In a series of 826 patients [2], the rate of a second attack was 2·8%. In a population study with 939 patients [3], only 17 (1·8%) had recurrent PR after an average of 4·5 years of follow-up. The average interval between eruptions was 3·8 years, ranging from 0·3 to 10 years.

There are early reports of attempts to transmit PR or to treat PR with convalescent plasma. These studies are probably unrepeatable on human participants owing to modern ethical standards. One investigator cultured the blister contents of primary and secondary lesions in PR for bacteria, with negative results [4]. He then injected the contents percutaneously into the skin of volunteers. An aberrant form of PR was seen, characterized by the appearance of many disseminated papules in the characteristic distribution, with a shorter clinical course. Early reports of patients who received pooled immunoglobulin (Ig) [5] or convalescent sera [6] were reported to have a shorter rash duration.

An electron microscopy study on lesional biopsy of the herald patch [7] reported virus-like spherical particles of 70 nm size in the intercellular spaces and the cytoplasm of Langerhans cells. Another study also reported virus-like particles in the dyskeratotic keratinocytes [8].

A PR-like disease occurs in one other animal apart from humans, namely the pig [9]. Also known as porcine juvenile pustular psoriasiform dermatitis, PR in pigs is a sporadic disease usually affecting piglets 8–12 weeks old. Erythematous annular plaques with distinct borders and bran-like scales are seen. Spontaneous resolution in 6–8 weeks is the rule. Several piglets in the same litter may be affected concurrently, suggesting an infectious, probably viral, aetiology [10].

## Seasonal variation

Seasonal variation offers only indirect evidence to support an infectious aetiology, as many confounding variables are present. Seasonal variation is seen in diseases clearly known not to be infectious, such as hay fever, seasonal affective disorder, or even stroke [11].

Camille Melchior Gibert himself stated that PR *occurred in young people in the hot season* [12]. Epidemiological studies have reported contradictory results. Studies in England [13], Rochester in Minnesota [3] and Sudan [14] reported higher incidence of PR in the colder months. A study in Lagos [15] reported higher incidence in the early part of the rainy season. A study in Brazil [16] and one in Singapore [17] reported a bimodal distribution, with a higher incidence in June, October/November in Brazil, and a higher incidence in March/April and November in Singapore. Studies in Uganda [18], Nigeria [19], and Turkey [20], and another study in Singapore [21] reported no seasonal variation.

A weakness of these studies is that virtually all data were collected in specialist settings, and did not accurately reflect the picture in primary-care settings. Another weakness is that climate data were discussed but not quantitatively analysed. In essence, data on seasonal variation in PR has been conflicting, and offers limited support for an infectious aetiology in PR.

## Concurrent cases

A community outbreak or epidemic of PR has never been reported. However, there have been many reports of two or more patients with PR in the same family or close environment [22]. PR occurred in two sisters separated by a period of 6 weeks [23]. Another report described two sisters with successive onset of PR 61 days apart [24]. A 60-year-old farmer was reported to have PR, followed by his 30-year-old daughter 3 months later [25].

Four cases of PR occurred within 1 month in a whaling ship on a trip to the Antarctic [26]. The author argued that as the whaling ship was a closed community of approximately 300 men, this was suggestive of an infectious aetiology. A 39-year-old woman had recurrent PR annually for 5 years [27]. Her husband had a severe attack of PR 6 years before her first attack.

Twelve cases of concurrent PR in the same household were reported in a series of 1045 patients [28]. Five such incidents were described in another series of 108 patients [2]. In a population-based study [3], 29 episodes involving 58 patients were identified in which PR had occurred in one other person in the same household or in another presumed close contact, out of a total of 939 patients. These data offer some support for an infectious aetiology.

## Associations with other diseases or conditions

Epidemiological studies reported associations of PR with history of respiratory tract infections

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[29], unfavourable social and economic background [30], and contact with patients with PR [31]. In one study [29], every third patient of a series of 747 patients with PR diagnosed in the Mayo Clinic, Rochester was selected as a study subject. The control subjects were specifically selected healthy individuals matched for sex and age. Out of 249 patients and 249 controls, 12% of patients and 6% of controls had an infection within 3 months before PR ($P=0{\cdot}014$). Eight per cent of patients and 2% of controls had respiratory tract infections ($P=0{\cdot}004$). The authors concluded that respiratory tract infections may be a predisposing factor for PR.

A cross-sectional study based on 1-day surveys in secondary schools in Burkina-Faso reported 36 cases of PR out of 6000 pupils examined [30]. The prevalence of PR was higher in the middle socioeconomic (0·9/100 pupils examined) and underprivileged (0·8/100 pupils examined) classes than in the privileged class (0·3/100 pupils examined). This gradient along the social classes was statistically significant ($P=0{\cdot}048$).

An interesting study compared the incidence of PR in dermatologists with that in otolaryngologists [31]. The investigators sent a questionnaire to 343 dermatologists and 279 otolaryngologists. The response rates were 69% and 63% respectively. Post-specialization dermatologists were adopted as the study group. Pre-specialization dermatologists and otolaryngologists were adopted as two control groups to eliminate recall bias.

The investigators found that the incidence of PR was similar in the otolaryngologists and pre-specialization dermatologists. From this they concluded that recall bias was minimal. They discovered that the incidence of PR for post-specialization dermatologists was 3–4 times higher than in either the otolaryngologists or pre-specialization dermatologists. They concluded that frequent exposure to PR by post-specialization dermatologists led to increased risk. However, since primary-care physicians [32], and presumably other non-dermatological specialists, are known to underdiagnose PR, a source of systematic bias is possible.

Associations with respiratory tract infections, contact history, and unfavourable social and economic background are characteristics of many infectious diseases spread by the respiratory route. Therefore, these associations offer some support for an infectious aetiology.

### Case clustering

Of particular epidemiological interest is the phenomenon of case clustering in PR. This approach has been applied in diseases including childhood leukaemia [33] and Kawasaki disease [34]. Case clustering only offers indirect evidence for an infectious aetiology, as other factors may also lead to clustering.

In one primary-care study, significant spatial-temporal clustering was reported, but for female patients only [13]. The investigators also adopted a *moving window* test, and detected a temporal cluster of 16 cases within a 28-day period. This study was, however, criticized in that the degree of clustering discovered was insufficient to substantiate an infectious hypothesis [35]. No controls were included to demonstrate the validity of the methodology. The statistics depended on an arbitrary temporal scanning size, and different results would have been obtained by varying the scanning size.

A recent study [36] on 41 patients with PR adopted a novel regression analysis which does not depend on the window size, and reported three statistically significant clusters ($P=0{\cdot}031$), which occurred in the second coldest month in the year, the second hottest month, and a temperate month. The authors concluded that significant temporal clustering independent of seasonal variation occurred in their series of patients with PR. The strength of this study lays in its having been conducted in primary-care settings, and in that climate data was analysed quantitatively. However, because it was retrospective, some cases have been missed, and the reliability of diagnoses made by primary-care physicians may have been low.

## EVIDENCE FOR SPECIFIC INFECTIOUS AETIOLOGY

### Human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7)

Drago and colleagues [37, 38] reported the detection of HHV-7 DNA by nested polymerase chain reaction (PCR) in the skin, peripheral blood mononuclear cells (PBMC) and plasma of all 12 patients with PR. HHV-7 DNA was undetectable in the plasma and skin of 11 control specimens. They subsequently detected human herpes virus particles *in various stages of morphogenesis* in 15 (71%) out of 21 patients with PR [39].

Watanabe and colleagues [40] detected HHV-7 DNA in 16 (44%) out of 36 patients with PR in either

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or both of acute and convalescent plasma samples, and in none out of 31 plasma samples of age- and sex-matched controls. In another study with 14 other patients with PR, Watanabe et al. [41] detected HHV-7 DNA in 13 (93%) out of 14 lesional skin specimens, 12 (86%) out of 14 non-lesional skin specimens, 10 (100%) out of 10 saliva specimens, 10 (83%) out of 12 PBMC specimens, and 8 (100%) out of 8 sera specimens. HHV-6 DNA was detected in 12 (86%) out of 14 lesional skin, 11 (79%) out of 14 non-lesional skin, 8 (80%) out of 10 saliva, 10 (83%) out of 12 PBMC, and 7 (88%) out of 8 serum samples of patients with PR. Control samples demonstrated rare positivity for either HHV-6 or HHV-7 DNA in skin or sera. Infiltrating mononuclear cells expressing HHV-7 and HHV-6 mRNA were detected in perivascular and periappendageal areas in 8 (100%) and 6 (75%) out of 8 PR skin lesions respectively, compared to mRNA positivity in 1 (13%) out of 8 normal skin and psoriasis skin controls. Watanabe et al. [41] concluded that PR is associated with systemic active infection of both HHV-6 and HHV-7.

More recently, Vag et al. [42] reported evidence of primary HHV-7 infection in patients with PR by nested PCR, antibody avidity, electron microscopy and monoclonal antibodies.

However, these positive results were not confirmed by most other investigators [43–51]. Kempf et al. [43] detected HHV-7 DNA and expression of HHV-7-specific immunodominant pp85 antigen in only 1 (8%) out of 13 lesional biopsy specimens of PR and in 2 (14%) out of 14 biopsy specimens of control subjects. Yoshida [44] detected approximately equal HHV-7 DNA signal intensity in whole-blood samples of four patients with PR and three healthy controls. Yasukawa et al. [45] detected HHV-7 DNA in 1 (7%) out of 14 patients with PR and none out of 15 controls. Kosuge et al. [46] detected HHV-7 DNA in 13 (43%) out of 30 PBMC samples of patients with PR and 14 (56%) out of 25 PBMC samples of controls. Offidani et al. [47] investigated for HHV-7 DNA by PCR in urine, saliva, PBMC and skin scales of 12 patients with PR and 20 control subjects. All urine, PBMC and scale samples were negative for HHV-7 DNA, but five (42%) saliva samples from patients and 14 (70%) saliva samples from controls had detectable HHV-7 DNA.

More recently, Wong et al. [48] reported negative PCR and viral culture results for HHV-6 and HHV-7 on lesional biopsy specimens of all 24 patients with PR. Karabulut et al. [49] detected HHV-7 DNA in lesional biopsy specimens in 6 (28·6%) out of 21 patients with PR and in none out of 6 healthy volunteers as controls ($P=0{\cdot}28$). The investigators concluded that their results did not substantiate a role for HHV-7 infection in the pathogenesis of PR.

Chuh et al. [50] reported a case-control study of 15 patients with PR and 15 age and sex pair-matched control subjects. Acute and convalescent blood specimens were available for all patients. HHV-6 and HHV-7 DNA were tested for in both plasma and PBMC, and serological studies against both viruses were also performed. They reported no evidence of active infection with these viruses in any patient or control.

No definite conclusion can be drawn from these conflicting results. We believe that at present the association between PR and HHV-7 infection is best considered controversial. A definite answer may have to wait on enhancements in the sensitivities and specificities of investigative techniques in differentiating active primary infection, endogenous reactivation, and latent infection of these viruses, which are lifelong infections. Moreover, even if evidence of endogenous reactivation of these viruses is confirmed in patients with PR, whether such reactivation is the underlying cause of PR or whether it is coincidental secondary to immuno-dysfunction in the pathogenesis of PR remains to be elucidated.

### Cytomegalovirus (CMV)

One study reported that CMV DNA was undetectable by PCR in the plasma and PBMC of 12 patients with PR [38]. In a case-control study, IgM and IgG against CMV were investigated for 13 patients with PR and 13 age and sex pair-matched control subjects [51]. No evidence of active infection by CMV was present for any patient or control. It is, therefore, highly unlikely that CMV infection is associated with PR.

### Epstein–Barr virus (EBV)

Bonafé et al. [52] reported that a higher percentage (42%) of patients with PR had antibodies against EBV early antigen (EA) than control subjects (15%). Drago et al. [38] studied EBV DNA in the plasma and PBMC of 12 patients with PR. No positive result was found. Chuh [51] investigated whole blood in 13 patients with PR and 13 age and sex

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pair-matched control subjects for EBV viral capsid antigen (VCA) IgM, EBV VCA IgG, EBV EA IgG, EBV nuclear antigen IgG, and PCR EBV DNA. No evidence of EBV primary infection or endogenous reactivation was found in patients and controls. EBV infection is, therefore, highly unlikely to be associated with PR.

### Parvovirus B19

One study reported the detection of IgG but not IgM against parvovirus B19 in 5 (38%) out of 13 patients with PR [53]. This seroprevalence is close to that of 40–60% reported for this virus in the general population. A weakness of this study is that viral DNA was not investigated. Moreover, paired acute and convalescent sera of the patients and sera from control subjects were not tested.

In a case-control study, IgM and IgG against parvovirus B19, and PCR for parvovirus B19 DNA were investigated in whole blood in 13 patients with PR and 13 age and sex pair-matched control subjects [51]. Acute and convalescent blood samples were available for all patients. No evidence of active parvovirus B19 infection was noted in any patient or control. We, therefore, believe that parvovirus B19 infection is unlikely to be a cause of PR.

### Picornaviruses

Raskin [54] observed a cytopathic effect of scales and lesional biopsies from the herald patch and secondary lesions in PR on African green monkey kidney cells. He also found intranuclear and cytoplasmic vesicular bodies when the specimens were inoculated in primate kidney cells. Neutralizing antibodies in patients' sera could not be demonstrated. Raskin stated that he had probably demonstrated a dermatropic virus of the picorna series. Metz [55] subsequently claimed that picornavirus-like particles can be observed in keratinocytes and lymphoid cells in patients with PR. Other investigators [56] also reported the detection of picornavirus antibodies in 73% of patients with PR, but only 6% of controls.

More recently, Aractingi et al. [57] employed reverse transcriptase (RT)–PCR and *in situ* hybridization to investigate for evidence of picornavirus infection in lesional and normal skin biopsy specimens of patients with PR. They failed to discover any positive finding. It is, therefore, highly unlikely that PR is associated with picornavirus infection.

### Influenza and parainfluenza viruses

One study reported that out of 11 patients with PR, 6 (55%) gave a history of antecedent upper respiratory illness [58]. No significant rise in antibodies against influenza A or B, or parainfluenza types 1, 2 or 3 viruses was detected in acute and convalescent sera of these 11 patients. The investigators concluded that PR is unlikely to be related to these viral infections.

### *Legionella* spp.

In a prospective case-control study, 36 patients with PR and two groups of controls were investigated, the first group being 19 patients with other skin diseases and the second 200 volunteers whose blood samples were available [59]. No significant result was observed for *L. pneumophila*. Antibodies against *L. micdadei* were detected in 12 (33·3%) patients with PR, one (5·3%, $P<0{\cdot}05$) of the first group of controls, and 16 (8·0%, $P<0{\cdot}001$) of the second group of controls. The authors concluded that PR is likely to be associated with *L. micdadei* infection.

However, of the 12 patients who had *L. micdadei* antibodies detected, only 6 had a convalescent blood sample available. Of these 6 patients, 4 had antibody titres unchanged in acute and convalescent specimens, 1 had an antibody rise (from undetectable to 1:256) and 1 had an antibody fall (from 1:256 to 1:64). Thus, out of 36 patients diagnosed as having PR, only 1 had a significant rise in *L. micdadei* antibodies. Moreover, IgM against *L. micdadei* was not tested. A higher seroprevalence does not imply a causal relationship.

In a prospective case-control study, IgM and IgG against *L. longbeachae*, *L. micdadei*, and *L. pneumophila* serotypes 1–14 were investigated for 13 patients with PR and 13 control subjects [60]. The strength of this study is that acute and convalescent sera were available for all patients. Moreover, all control subjects were age and sex pair-matched. No evidence of active infection by these bacteria was noted for all patients and all controls. We therefore believe that PR is not associated with these *Legionella* infections.

### *Mycoplasma* spp.

Hudson et al. [58] tested for *Mycoplasma* spp. antibodies in their prospective study of 23 patients with PR. No control subject was recruited. Eleven patients returned to take a convalescent blood sample.

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Of these 11 patients, all had insignificant titres of antibodies against *Mycoplasma* spp. detected in acute and convalescent specimens. Absence of evidence of *M. pneumoniae* infection was subsequently reported in another series of patients with PR [52].

Out of 30 patients with PR, Ishibashi et al. [61] reported six patients for whom '*M. pneumoniae* infection was strongly suspected serologically'. They concluded that their results suggested that PR may possibly be caused by *M. pneumoniae* infection, although not all cases were serologically positive. However, of these 6 patients, 2 had static antibody titres in the acute and convalescent blood specimens, 1 had a significant antibody rise (from 1:32 to 1:256), while in 3 the antibody titres fell. IgM tests were not performed. Thus in this uncontrolled study, only 1 of 30 patients had a significant antibody rise against *M. pneumoniae*.

More recently, Sharma et al. [62] suspected that mycoplasma may be one of the possible reasons to explain the efficacy of erythromycin on their patients with PR.

In a case-control study, IgM, IgG and IgA against *M. pneumoniae* were studied in 13 patients with PR and 13 age and sex pair-matched control subjects [60]. Acute and convalescent sera were available for all patients. No evidence of active infection was noted in any patient or control. This provides adequate evidence that PR is not associated with *M. pneumoniae* infection.

### *Chlamydia* spp.

In a case-control study, IgM and IgG against *C. pneumoniae* and *C. trachomatis* groups B (serovars B, E, D), C (serovars C, J, H, I), and I (serovars G, F, K) were investigated for 13 patients with PR and 13 age and sex pair-matched control subjects [60]. No evidence of active infection by these organisms was found for any patient or control.

## EVIDENCE AGAINST AN INFECTIOUS AETIOLOGY

Perhaps the strongest evidence against an infectious aetiology for PR is that the pathogen has not been identified even after laborious searches by generations of investigators. Repeated attempts [52, 63–65] to isolate a virus by inoculating lesional biopsy specimens, blood, pharyngeal and rectal swabs with various cell lines failed to confirm a cytopathic effect and failed to demonstrate viral antigens by immunofluorescence assays [66]. Two studies by electron microscopy [52, 67] also reported absence of viral particles from lesional biopsy specimens of patients with PR.

Morgan-Capner et al. [68] obtained acute lesional biopsy specimens from 10 patients with PR, and collected convalescent sera 4–6 weeks later. If an infectious agent was present, the antigen would have been present in the former specimen and the specific antibody in the latter. They incubated cryostat sections of the lesional biopsy specimens with 1:10 dilution of convalescent sera, and added fluorescein-labelled anti-human Ig. They reported negative results when the patients' own sera or other patients' sera were used.

Another evidence against an infectious aetiology for PR is that real epidemics have not been reported. Although spatial-temporal clustering has been seen in female patients [13], it has not been reported for male patients. The reason for such a sex difference is unknown.

## RESPONSE TO TREATMENT – EVIDENCE FOR OR AGAINST AN INFECTIOUS AETIOLOGY?

Apart from topical symptomatic management, several treatments – namely UV radiation, systemic corticosteroids, and oral erythromycin – have been suspected as having a role in shortening or modifying the disease course of PR. Such response to treatment might provide indirect evidence for or against an infectious aetiology.

A potential benefit of UV radiation in PR was first reported by Hazen in 1928 [69], and a bilateral comparison study without placebo treatment and by subjective rash assessment [70] provided some evidence for its efficacy. It seems that such a response might argue against an infectious aetiology, as infectious eruptions are generally not expected to improve on UV radiation, while non-infectious rashes such as psoriasis do. However, another bilateral comparison study with placebo treatment on the untreated side and by objective rash assessment reported no sustained benefit on rash resolution or for relief of pruritus [71]. The apparent response of some patients with PR to UV radiation therefore does not argue for or against an infectious aetiology.

With systemic corticosteroids, there have been reports of clinical improvement [21] as well as rash

exacerbation [72]. No randomized controlled study has been reported.

Erythromycin was reported to be of benefit to patients with PR as early as 1954 [73]. A randomized (*pseudo-randomization* with alternate patient assignment to treatment and placebo groups) controlled study reported benefit of patients with PR on oral erythromycin [62]. We believe that this does not necessarily reflect that PR has an infectious aetiology, or that the infectious agent is an organism sensitive to erythromycin, as erythromycin exhibits immunomodulating effects [74] apart from its antimicrobial potencies. That minocycline has clinical efficacy in bullous pemphigoid [75], for instance, does not imply that bullous pemphigoid has an infectious aetiology, or that the aetiological agent of bullous pemphigoid is a bacterium sensitive to minocycline.

We, therefore, conclude that with the present state of knowledge, the apparent therapeutic benefits of several treatments in PR do not provide strong evidence for or against an infectious aetiology.

## NON-INFECTIOUS AETIOLOGIES

### Autoimmunity and genetic predisposition

An autoimmune element in the pathogenesis of PR has been suspected by some investigators [76]. They proposed that PR is an auto-aggressive disease affecting genetically susceptible individuals. It has been reported that 28% of patients with PR have T lymphocytotoxic antibodies [77], an autoantibody present in 82% of patients with systemic lupus erythematosus. PR has been reported to occur in a patient with Behçet's disease [78]. Whether the eruption is related to the disease process, the interferon treatment or is coincidental is unknown. A case-control study investigated the association of PR with autoimmune markers on 18 patients with PR and 18 controls [79]. Five patients (27·8%) and none of the control subjects were found to be positive for antinuclear antibodies at significant titres ($P = 0{\cdot}045$). A significant weakness of this study is the small number of patients investigated.

At present, the role of autoimmunity in the immunopathogenesis of PR is largely unknown. One possible cause for the association of PR with autoimmune markers may be that patients with PR share the same HLA–DR haplotypes as patients with a high incidence of autoantibodies and autoimmune diseases. If this is true, there would be a genetic predisposition for some individuals to develop PR when triggered by an active viral infection or viral reactivation, while other individuals would not. A study on the HLA–DR of patients with PR would be the next logical step to confirm or refute such a hypothesis.

### Atopy

In a case-control study, relatives of patients with PR were reported to have a higher incidence of asthma and eczema [2]. A population-based study reported that 16% of 939 patients with PR had a personal history of asthma, hay fever or atopic dermatitis [3]. The researchers [29] subsequently selected every third patient from 747 of these 939 patients for whom clinical records were available, and identified 249 cases. Comparing them with 249 paired controls, they found that 14% of patients with PR and 12% of controls had atopy of any type, and that 7% of patients with PR and 4% of controls had asthma ($P = 0{\cdot}29$). They concluded that PR is not associated with atopy.

## CONCLUSIONS

The epidemiology of PR in general supports an infectious aetiology. That most patients are between 10 and 35 years of age and that most patients do not have a relapse are typical of a disease with a viral aetiology. The age distribution is similar to the age for primary infection of viruses like EBV, probably implying that intimacy during teenage and early adulthood years might be related to spread of the agent. We would expect exceptions as many individuals, for various reasons, may contract the virus much sooner or much later. Indeed the epidemiology also exhibits this expected phenomenon, as a very small number of PR sufferers are infants [80]. The youngest reported patient was 3 months old [81] and the oldest 83 years old [82].

Data on seasonal variation in PR is conflicting. Despite the absence of true epidemics, clusters of cases have been reported throughout the last century. While such individual reports may be dismissed as coincidental, significant case clustering in PR is well documented. An infectious cause might be one option to account for such clustering. The reported associations of PR with history of respiratory tract infections, unfavourable social and economic background, and contact with patients with PR also lend support for an infectious aetiology. Although an

animal model for PR may exist, virological studies on a similar eruption to human PR in pigs have not been reported. Whether such an eruption represents the genuine porcine equivalence of human PR or whether it just bears a resemblance to the human eruption remains to be seen.

Despite the variety of evidence for and against an infectious aetiology, and the repeatedly negative attempts in identifying a definite aetiological agent, we believe that the most convincing evidence for an infectious aetiology still lies in its clinical course. The *programmed* course of events with a herald patch presumably at the inoculation site, a subsequent generalized eruption, followed by spontaneous resolution in weeks with little risk of recurrence strongly supports an infectious aetiology. We remain convinced that PR does have an infectious aetiology, and believe that further investigations to elucidate its cause are warranted.

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