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Seasonality and factors associated with cryptosporidiosis among individuals with HIV infection

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SUMMARY

The seasonality and factors associated with *Cryptosporidium* infection were assessed in a cohort of HIV-infected patients in Los Angeles County to better define the epidemiology of cryptosporidiosis among individuals with HIV. Data were analysed from a cohort of 4247 patients $\geqslant 13$ years of age with HIV infection enrolled from four outpatient facilities in Los Angeles, 1990–6. Cryptosporidiosis was diagnosed in 120 (2·8%) patients. Among the 1296 individuals with complete follow-up until death, cryptosporidiosis occurred in 69 (5·3%). The seasonal rate of cryptosporidiosis showed a modest bimodal trend with the highest rates occurring in March–May and September–October. There was no difference in the rate of cryptosporidiosis for the periods of heaviest rainfall (December–March) and low rainfall (April–November). Infection rates were higher among males (1·59 per 100 person-years) than females (0·92) and lower in blacks (0·98) than other racial/ethnic groups (1·80). A significant trend of decreasing cryptosporidiosis was observed with increasing age, with the highest rate (2·34) in the 13–34 year age group. A strong association between cryptosporidiosis and CD4+ count was noted. These data suggest that cryptosporidiosis among HIV-infected individuals in Los Angeles County exhibits a modest spring and fall seasonality. This pattern of occurrence of cryptosporidiosis appears temporally unrelated to local rainfall patterns. Our findings suggest that HIV-infected men, individuals in younger age groups and those with CD4+ lymphocyte counts $< 100 \times 10^6$/l are at increased risk of cryptosporidiosis. Blacks with HIV infection appear less likely than other racial/ethnic groups to be diagnosed with *Cryptosporidium* infection. These results may provide insight into possible routes of transmission and sources of cryptosporidiosis infection in individuals with HIV.

INTRODUCTION

Cryptosporidiosis is a debilitating and untreatable opportunistic infection in individuals with severe HIV infection and contributes to reduced survival and quality of life in these patients [1]. As with other HIV-associated opportunistic infections, there is a paucity of information on the epidemiology of cryptosporidiosis among individuals infected with HIV [2]. Determining risk factors and possible sources of *Cryptosporidium* infection would be of value in

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recommending strategies for preventing exposure and infection and prolonging survival of individuals with HIV.

To help gain insight into possible environmental sources of *Cryptosporidium* we assessed the seasonal occurrence and factors associated with cryptosporidiosis in a cohort of individuals with HIV infection in Los Angeles County, USA. One potentially important source of *Cryptosporidium* is municipal drinking water, a fact that continues to cause considerable anxiety among HIV-infected individuals, their family members and contacts. Outbreaks of waterborne cryptosporidiosis have been well-documented [3–5]. Several outbreaks have been associated with contaminated municipal water supplies, and HIV-infected individuals may be significantly affected during such community-wide epidemics [6]. However, the importance of municipal water as a source of *Cryptosporidium* during non-outbreak conditions in both immunocompetent and immunocompromised populations is unclear [7]. Therefore, as part of the assessment of seasonality, we attempted to determine if cryptosporidiosis was more common during months of heavy rainfall when surface water run-off and potential contamination of open drinking water reservoirs is greatest.

METHODS

Data source and patients

Data were available from the medical records of HIV-infected patients $\geqslant 13$ years of age receiving medical care in Los Angeles County at four outpatient clinics participating in the Centers for Disease Control and Prevention Adult/Adolescent Spectrum of Disease Study [8]. The sites, which provide routine care to HIV-infected patients, are among the largest in the county and report approximately one third of all AIDS cases locally. These clinics were selected to be representative of the facilities providing HIV care in Los Angeles County and included two public clinics, a health maintenance organization and a private medical group. In each of these clinics the patient population consists either exclusively or predominantly of HIV-infected individuals. All eligible HIV-infected patients from one of the public facilities were enrolled. All HIV-infected women were enrolled from the second public clinic. Women were targeted at this site as a way of increasing the representation of women in the local and national sample. At the remaining two facilities all patients were initially targeted for enrolment. However subsequent enrolment at these two sites focused on minorities, women and injection drug users in an effort to meet the goal of increasing the proportion of these under represented groups. Trained medical records technicians reviewed medical records for basic demographic data, HIV-exposure category, AIDS-defining conditions, other infections and conditions, treatment, and laboratory data including CD4+ lymphocyte count. Any occurrence of laboratory-confirmed cryptosporidiosis was used to define cases. Only newly diagnosed (incident) cases were included in the analysis. The medical record was re-abstracted at 6-month intervals. Data were analysed for all patients enrolled in the cohort and followed during the period June 1990–May 1996.

Statistical analysis

Demographic variables, HIV risk category and CD4+ count were compared by initial bivariate analysis for patients with and without cryptosporidiosis. The denominator for calculation of rates was person-time. The amount of person-time contributed by each patient was determined from time of study entry to first occurrence of cryptosporidiosis or, for those without cryptosporidiosis, date of last contact or date of death. The Mantel–Haenszel test and Mantel–Haenszel test for linear trend were used to assess possible associations with cryptosporidiosis [9]. A Cox proportional hazards approach was employed to control for potential confounding variables. The software programme EGRET was used for all multivariate analyses. Variables entered into the Cox analyses included gender, race, age (13–34, 35–44, 45–54, > 54), HIV risk category, CD4+ lymphocyte count (< 50, 50–99, $\geqslant 100$), and clinic. Variable selection for the final Cox model was based on the change-in-estimate criterion [10]. Specifically, if addition of a covariate altered the rate ratio by $> 10\%$ it was included in the model. Adjusted rate ratios, 95% confidence limits and P values were computed. Since confounding varied by factor, a different model was constructed to assess each factor assessed. To evaluate the adequacy of the Cox model both residual and influence measures were assessed and results from the Cox analyses were compared to those obtained using stratified analysis [11]. Crude survival for patients with cryptosporidiosis was estimated by the

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Table 1. *Demographic and risk characteristics and cryptosporidiosis infection among individuals with HIV infection, Los Angeles County, 1990–6*

Factor	*n*	No. (%) with cryptosporidiosis	Person time/years	Rate/100 person years	*P* value
Gender					
Female	757	10 (1·3)	1083	0·92	0·10
Male	3490	110 (3·2)	6924	1·59	
Race/ethnicity					
White	1624	47 (2·9)	3242	1·45	ref
Black	1009	17 (1·7)	1743	0·98	0·17
Latino	1424	50 (3·5)	2636	1·90	0·18
Asian/other	190	6 (3·2)	386	1·56	0·85
HIV risk group					
Heterosexual	413	6 (1·5)	613	0·98	ref
Male–male sex	2649	80 (3·0)	5565	1·44	0·37
IDU	311	5 (1·6)	462	1·08	0·86
Male–male sex/IDU	224	8 (3·6)	415	1·93	0·22
Transfusion	105	3 (2·9)	162	1·85	0·36
None identified	545	18 (3·3)	791	2·28	0·07
Age-group*					
< 35	1517	51 (3·4)	2174	2·34	
35–44	1675	50 (3·0)	3281	1·52	
45+	1047	18 (1·7)	2532	0·71	< 0·001‡
CD4+ count†					
< 50	1683	89 (5·3)	2806	3·17	< 0·001
50–100	761	26 (3·4)	1631	1·59	< 0·001
> 100	1602	2 (0·1)	3415	0·06	ref

* 8 patients with unknown age.
† 201 patients with missing CD4+ count.
‡ Test for trend.

Kaplan–Meier Product Limit method. The cumulative occurrence of cryptosporidiosis among individuals followed to death was also calculated.

To determine possible seasonal variation in occurrence, the rate of cryptosporidiosis by month was calculated and 95% confidence intervals computed. The denominator for each month was the sum of all patients still enrolled and active to the study for each respective month over the study period. The seasonal data were aggregated for the total study period because they were too sparse to present for each individual year. In addition, data were obtained from the National Weather Service on the occurrence and level of rainfall by month for the Los Angeles area. Information on rainfall from a centralized area (Los Angeles Civic Center) was used. The average monthly rainfall over the study period was calculated and possible correlation between the rate of cryptosporidiosis and average monthly rainfall was evaluated. In addition, the rate of cryptosporidiosis for the months of heaviest rainfall (December–March) was compared to the rate of cryptosporidiosis for the months of low rainfall (April–November). Since there may be delay between run-off and possible contamination and subsequent exposure and development of disease due to distribution times within the water system and incubation period following exposure, the relationship between cryptosporidiosis and rainfall was also assessed after allowing for a possible 1 month delay.

RESULTS

A total of 4247 individuals with HIV infection were enrolled during the study period: 757 (18%) of the patients were female; whites represented 1624 (38%), blacks 1009 (24%) and Latinos 1424 (34%). The predominant HIV risk category among cohort patients was male-to-male sex (2649, 62%); 311 (7%) were injection drug users.

Cryptosporidiosis was diagnosed by detection of oocysts in faeces in 120 (2·8%) patients representing

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Table 2. *Factors independently associated with cryptosporidiosis among individuals with HIV, Los Angeles County, 1990–6*

Factor	Adjusted rate ratio	95% CI	*P* value
Gender*			
Male	2·8	(1·1, 7·2)	0·03
Female	Referent		
Race/ethnicity†			
Latino	0·98	(0·65, 1·48)	0·02
Black	0·52	(0·28, 0·93)	0·09
Asian/other	0·87	(0·37, 2·0)	0·78
White	Referent		
Age group‡			
45+	0·25	(0·19, 1·1)	0·01**
< 35–45	0·60	(0·32, 0·94)	
13–34	Referent		
CD4+ count			
< 50	36·5	(9·0, 148·3)	< 0·01
40–99	22·1	(5·2, 93·2)	0·0
100+	Referent		
Site§			
Public	0·67	(0·32, 0·89)	0·02
HMO	0·54	(0·42, 1·1)	0·09
Private	Referent		

* Age and an interaction term for gender and age included in Cox model.
† Age and CD4+ count included in the model.
‡ CD4+ count included in the model.
§ Age included in the model.
** Test for trend.

an overall crude rate of 1·5/100 person-years. Among the 1296 individuals with complete follow-up until death, cryptosporidiosis occurred in 69 (5·3%, 95% CI 4·1%, 6·5%). Rates of infection were higher among males (1·59) than females (0·92) and lower in blacks (0·98) than other racial/ethnic groups (1·8) (Table 1). A significant trend of decreasing cryptosporidiosis was observed with increasing age, with the highest rate (2·34) in the 13–34 year age group. A strong association between cryptosporidiosis and CD4+ count existed with substantially higher rates (2·59) seen in individuals with CD4+ lymphocyte counts less than 100×10^6/l. The median crude survival of patients with cryptosporidiosis was 11 months.

Multivariate analysis confirmed the findings of the bivariate analysis. After controlling for confounding variables the rate of cryptosporidiosis was nearly three times higher in men (adjusted rate ratio = 2·8, 95% CI 1·1, 7·2) than women and the rate among blacks was one-half that of whites (adjusted rate ratio = 0·52, 95% CI 0·28, 0·93, Table 2). Age (test for trend, $P = 0{\cdot}01$) and CD4+ count ($< 100 \times 10^6$/l) continued to be strongly associated with cryptosporidiosis (Table 2).

The seasonal rate of cryptosporidiosis demonstrated a modest bimodal trend with the highest rates occurring in the period of March–May (1·48/1000 person-months, 1·37 and 1·37 respectively, Fig. 1) and the months of September and October (1·45/1000 person-months and 1·68 respectively, Fig. 1). There was no difference in the rate of cryptosporidiosis for the months of heaviest rainfall (December–March, 1·1/1000 person-months) and the months of low rainfall (April–November, 1·3/1000 person-months, Table 3). These results did not change after adjusting for a possible one month lag between possible contamination and subsequent exposure and disease. Selected periods of excessively heavy rainfall did not result in increases of cryptosporidiosis in this cohort. No correlation between average monthly rainfall and monthly rate of cryptosporidiosis was noted (Fig. 2).

DISCUSSION

These data suggest that cryptosporidiosis among HIV-infected patients in Los Angeles County exhibits a modest spring and fall seasonality. This pattern appears temporally unrelated to local rainfall patterns. Our findings indicate that HIV-infected men, individuals in younger age groups and those with CD4+ lymphocyte counts $< 100 \times 10^6$/l are at increased risk of cryptosporidiosis. Blacks appear less likely than other racial/ethnic groups to be diagnosed with *Cryptosporidium* infection.

We failed to find a link between the occurrence of cryptosporidiosis among individuals with HIV in Los Angeles County and periods of heavy local rainfall and possible contamination of open drinking water reservoirs. The absence of an apparent link between rainfall and *Cryptosporidium* suggests that the existence of open reservoirs may not place HIV-infected individuals and, by extension, the general community at risk for cryptosporidiosis. This may reflect the presence of only low levels of oocyst contamination in watershed areas, and/or effective management of these areas, which prevents, or reduces, reservoir contamination. Limited data from local testing demonstrate very low levels of oocyst recovery [12] and would support this premise; however, questions

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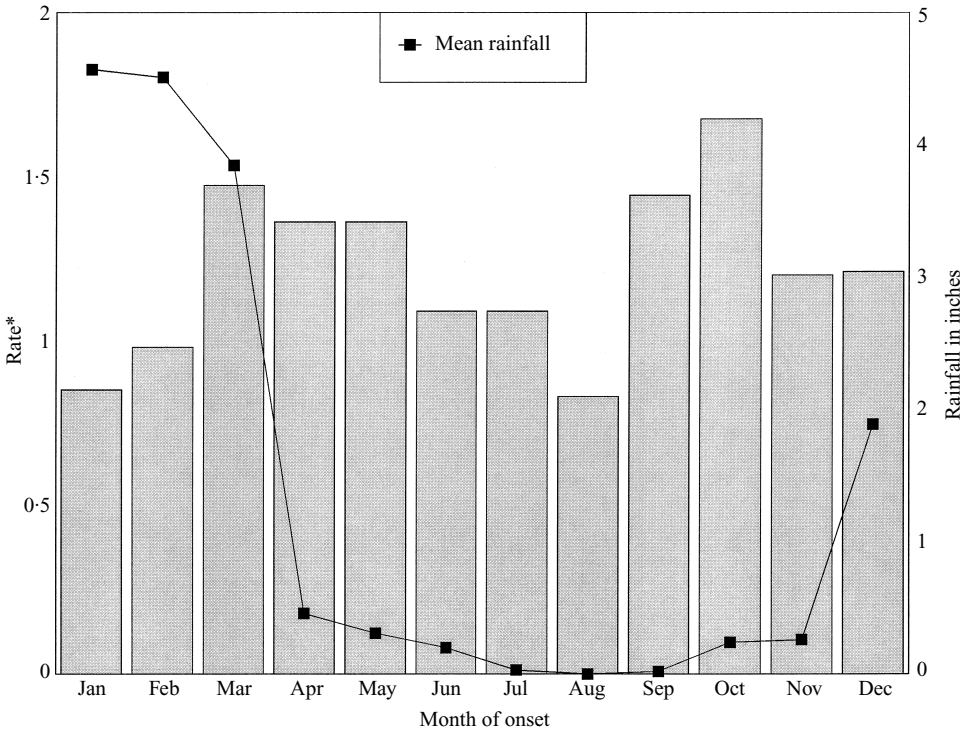

Fig. 1. Rate of cryptosporidiosis by month of onset among individuals with HIV and mean monthly rainfall in inches, Los Angeles County, 1990–6.

Table 3. *Rate of cryptosporidiosis among individuals with HIV infection during months of heavy rainfall* (*December–March*) *and months of low rainfall* (*April–November*), *Los Angles County*, *1990–6*

	Months of heavy rainfall (Dec.–Mar.)	Months of low rainfall (Apr.–Nov.)
Average rainfall in inches (range)	3·7 (1·9–4·6)	0·2 (0–0·5)
Rate of cryptosporidiosis per 1000 person-months (95% CI)	1·1 (0·8–1·5)	1·3 (1·0–1·5)

regarding the sensitivity, specificity and predictive value of current techniques for detection and identification in environmental samples argue for cautious interpretation of such data [13]. Alternatively, our findings may reflect low viability and/or infectivity of oocytes that may be present, or the absence of *Cryptosporidium* species capable of establishing infection in humans. It may well be that, given the increased inter-rainfall period temperatures, oocysts on land will succumb to the effects of raised temperatures and desiccation. Other factors that can affect the likelihood of water contamination and water-associated cryptosporidiosis include animal population diversity and density, both wild and domestic, in the catchment area.

A previous local analysis found no increase in cryptosporidiosis among AIDS patients residing in an area receiving unfiltered water [12]. However, the analysis used AIDS surveillance data which typically lack complete information on the occurrence of opportunistic infections [14]. In the current study we were able to access a more complete data source for ascertainment of cryptosporidiosis and to investigate the hypothesis that local rainfall, and possible reservoir contamination, might be associated with an increased risk of cryptosporidiosis in HIV-infected patients.

The seasonal pattern of cryptosporidiosis we observed was not dramatic and suggests that, if seasonal factors or exposure exist, they do not exert a strong effect on the occurrence of cryptosporidiosis among individuals with HIV. A number of previous studies have assessed the temporal occurrence of cryptosporidiosis among immunocompetent populations. These reports, from various localities, have found that the peak seasonal occurrence of cryptosporidiosis is typically during the spring and summer months in temperate climates [15–23]. However, some studies

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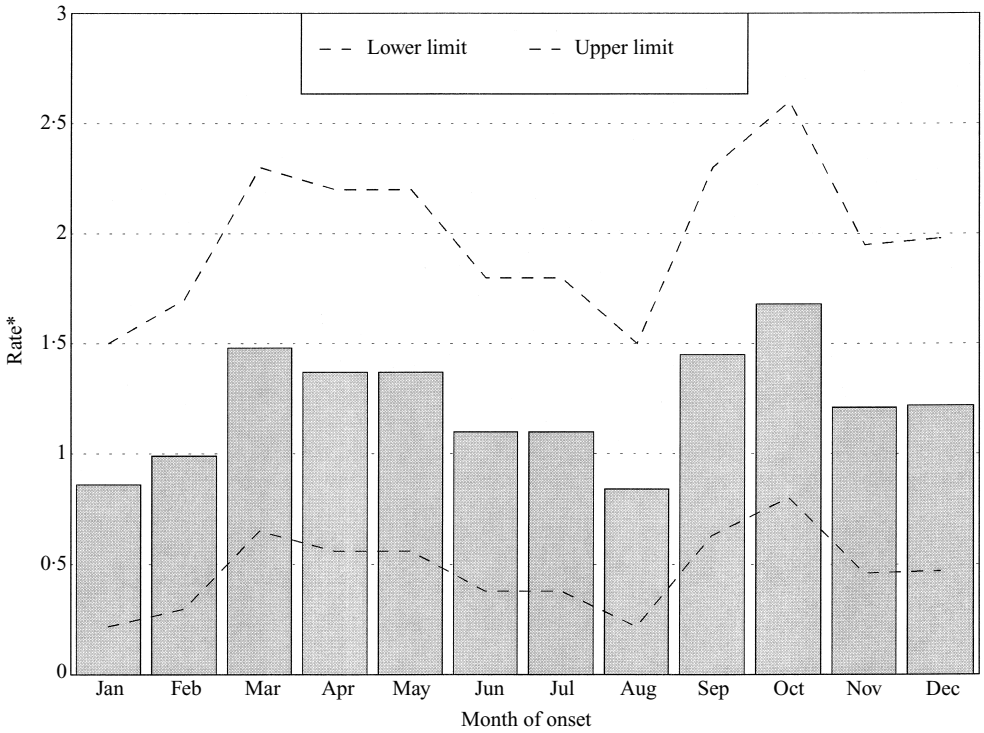

Fig. 2. Rate of cryptosporidiosis among individuals with HIV by month of onset, Los Angeles County, 1990–6. *, rate per 1000 months experience.

have identified either primary or secondary peaks in autumn and winter (24–28). In both industrialized and developing countries the temporal patterns of cryptosporidiosis often coincide with periods of heaviest rainfall which suggests possible run-off contamination and subsequent waterborne transmission [15, 29, 30]. Seasonal peaks may also reflect agricultural practices and exposures such as lambing and calving and application of faeces as fertilizer [14, 31]. Temporal patterns may also be attributed to such factors as seasonal attendance in child care centres and ensuing transmission associated with these centres [32].

The lower rate of cryptosporidiosis among blacks with HIV has been reported previously [33, 34] and may be a proxy for specific *Cryptosporidium*-related cultural, dietary or demographic exposures or be an indication of herd immunity and susceptibility. Alternatively, this result may reflect a racial/genetic-based susceptibility to *Cryptosporidium*, however no scientific evidence currently exists to support such an explanation.

Our findings also suggest that age is independently associated with cryptosporidiosis in this population. The age distribution observed, declining rates with increasing age, is consistent with sexual transmission which has been previously implicated [33]. Several aspects of the organism and disease indicate that the potential for faecal–oral contact during sexual contact would appear to be high. Patients with *Cryptosporidium* infection can excrete enormous numbers of oocysts [35], asymptomatic shedding may be prolonged [36, 37], and oocysts are directly infectious when shed. In addition, although issues of *Cryptosporidium* infectivity are still unresolved and infectious dose may differ based on both strain and recipient host species, some *Cryptosporidium* isolates appear to have a small infectious dose for humans, even in the immunocompetent host [38]. Moreover, other enteric protozoa transmitted through the faecal–oral route are recognized to be spread through sexual contact [39].

Our results must be interpreted cautiously for several reasons. Since biliary cryptosporidiosis in patients with HIV appears to occur frequently [40] it is possible that *Cryptosporidium* may sequester in the biliary tract and later reactivate to cause enteric disease when immune status deteriorates. If such a phenomenon occurs, then suspected acute disease may, in fact, represent reactivated, latent infection that has been newly recognized and would therefore complicate any analysis of seasonality. In addition, participation of only selected facilities within Los Angeles County, and selected patients at some of these sites, indicate that the study cohort may not be

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representative and that selection bias could be introduced. Moreover, because conditions of environmental contamination and exposure to *Cryptosporidium* may vary between communities, our conclusions cannot necessarily be extrapolated to other localities. It is also possible that small, but potentially important, associations with cryptosporidiosis were not detected due to insufficient sample size and power. Similarly, a possible municipal water risk might be obscured if a large proportion of individuals consumed bottled water or other alternative sources of water. Finally, any analysis of data obtained from medical records will have limited information on important exposures of interest.

Currently, sources of infection of *Cryptosporidium* among individuals with HIV remain uncertain. Our results would suggest a possible seasonal source and exposure or exposures which are more common in men, non-blacks and those in younger age groups. More definitive controlled epidemiologic studies are needed to define specific exposures that may implicate environmental sources of *Cryptosporidium* infection. Such studies should be augmented by laboratory-based efforts to determine if *Cryptosporidium* can be recovered from epidemiologically implicated source(s) and to ascertain if such isolates are genetically similar to those recovered from patients.

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