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Meningitis seasonal pattern in Africa and detection of epidemics: a retrospective study in Niger, 1990–98

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Abstract

Control of epidemic meningitis is still an unresolved problem in Africa. WHO has promoted the use of surveillance and response following alerts based on weekly threshold levels. In order to avoid any waste of resources related to false-positive alerts, it was decided not to choose too sensitive thresholds. This policy, however, leads to delayed response. The seasonal pattern of epidemics provides a solution to this dilemma. We carried out a retrospective survey of district-level surveillance data in Niger from June 1990 to June 1998. We identified an early and late meningitis season. Following this pattern, we studied the performance of the WHO-recommended threshold as compared to alternative thresholds for identifying early, late and non-epidemic district-years (DYs). (A DY was defined as a 52-week period starting in the last week of June, at the district level.) We studied 296 DYs, comprising 50 early epidemic, 38 late epidemic, and 208 non-epidemic DYs. Early epidemics were more often large and accounted for almost 75% of total cases. When applied no later than the first week of March, a highly sensitive alternative threshold resulted in initiation of an alert, with a median of 3 weeks earlier than the standard threshold, with no false-positive alerts, i.e., a specificity of 1.

Keywords: meningitis, *Neisseria meningitidis*, epidemics, surveillance, threshold, prediction, evaluation, Niger

Introduction

In the 'meningitis belt' of sub-Saharan Africa, massive epidemics of meningococcal disease occur with a periodicity of 5–12 years during the dry season from December to May, against a background of hyperendemic disease (LAPEYSSONIE, 1963; REIDO *et al.*, 1995; GREENWOOD, 1999). The World Health Organization (WHO) reported a total of over 700 000 cases in African countries in the 1988–97 10-year period. Even with appropriate treatment, 5–10% of patients die (KAPLAN & FEIGIN, 1985), and 10–15% of survivors suffer neurological sequelae (SMITH *et al.*, 1988).

Development of new combined vaccines raises hope for the future, but, in the meanwhile, response efforts continue with the currently available means (PELTOLA, 1998). Based on a study in Burkina Faso, WHO promoted the development of weekly surveillance systems with the use of a threshold level (MOORE *et al.*, 1992; WHO, 1995). Nevertheless, the success of interventions is generally modest (BOSMANS *et al.*, 1980; PINNER *et al.*, 1992; SPIEGEL *et al.*, 1993; VARAINE *et al.*, 1997; VEEKEN *et al.*, 1998) because many factors combine to delay response, causing a striking decrease in the number of prevented cases (WOODS *et al.*, 2000). Thus, gaining time is of major importance. Better logistics can help and are the concern of the International Coordination Group, an initiative of WHO and non-governmental organizations (OMS, 1997; CHIPPAUX *et al.*, 1998). Threshold refinement to allow earlier recognition of a developing epidemic should also be explored, as has been advocated (LEWIS *et al.*, 2000). Unfortunately, this solution implies the use of more-sensitive thresholds, which risks the initiation of a response when in fact no epidemic is developing, i.e., a false-positive (FP) alert. Two arguments led us to identify the timing of epidemics as a potential solution to the monitoring of specificity, sensitivity, predictive values and timeliness of weekly threshold levels. First, the intuitive assumption that the extent of an epidemic is linked to the potential duration of its expansion throughout the dry season—i.e., early epidemics could be large ones. Second, the risk of FP alerts decreases when epidemics are large.

Our objectives included: to be able to describe epidemics at the district level, to give a model for meningitis seasonal patterns, and to validate a threshold based on events early in the season.

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Methods

Study location, population and time

Niger, located within the African meningitis belt, has a population of 10 million. Population estimates were calculated by increasing the 1988 census figures by an average of 3·3%, the estimated annual growth rate. The study involved 37 of the 38 health districts, with populations ranging from 30 000 to 600 000. We describe the meningitis surveillance features in these districts from June 1990 to June 1998.

Study type and definitions

The study was a retrospective review of surveillance data reported to the *Direction du Système National d'Information Sanitaire*. Meningitis surveillance is part of an active weekly surveillance system, with almost 100% coverage, and a 4-week delay in reporting to the national level. Data are reviewed and computerized at regional and national levels. Reporting is based on the clinical case definition promoted by the WHO, as laboratory diagnosis is not routinely performed. For the purposes of this study, we assumed that all reported cases were genuine meningitis cases. A district-year (DY) was a 52-week period of surveillance at the district level. A DY started on the last week of June, i.e., the 26th week of a calendar year (CY), and ended on the 25th week of the following year. This surveillance period was chosen to accommodate the meningitis season, i.e., to avoid artificial disruption in epidemic dynamic follow-up between December and January. A DY was considered non-epidemic if cumulative meningitis incidence was <100 cases reported per 100 000 inhabitants, whereas an epidemic DY had an incidence of ⩾100 cases per 100 000. For pragmatic purposes, to be able to study early and late meningitis seasons, and the related properties of threshold values, we established a week's break about half-way through the meningitis season, that would be easy to remember and meaningful in terms of numbers of relevant epidemics. Accordingly, we described early epidemics as those starting before the 10th week of the CY, late epidemics as those starting from the 10th week or later in the CY, and non-epidemic years. We defined the annual incidence median weekly increase for each of these profiles, and plotted the corresponding graphs. It should be noted that the respective number of both early

TRAGO *et al.*, 1981; GÓMEZ *et al.*, 1984). The finding of a persistently good clinical condition in patients suffering from haemoptysis should lead the clinician to suspect the presence of paragonimiasis, as a differential diagnosis from lung tuberculosis. However, the clinician should keep in mind that the confirmation of one of these diseases does not eliminate a possible concomitant infection with the other. Cases of a simultaneous presence of paragonimiasis and tuberculosis are found in the literature (AMUNARRIZ, 1984).

Radiological studies show multiple lesions; however, none of the images can be considered as pathognomonic of paragonimiasis and in some cases the radiological images are completely normal, as was reported in 11 of the 19 patients studied in Ecuador (AMUNARRIZ, 1984). A diagnosis based on the observation of operculated eggs in sputum and faeces is a simple procedure that could be performed in any clinic. This diagnostic procedure should be practised for every person that has haemoptysis and a negative bacilloscopy (tuberculin negative), as well as in patients with respiratory symptoms and a history of eating raw crab. Two drugs have been shown to be effective in treating paragonimiasis: bithionol sulphoxide and praziquantel. Patients included in the study had a very good response to treatment with praziquantel at doses of 75 mg/kg daily for 3 days. None of them reported side-effects and 100% were negative at post-treatment follow-up. Thus, we recommend the use of praziquantel as a first choice.

Marsupials, canines, felines, pigs and several rodents that in other countries have been reported to be reservoirs of *Paragonimus* sp. (LAMOTHE ARGUEMEDO, 1985) are also found in the Colombian focus. Although in certain regions humans are only accidental hosts that play no important role in the transmission cycle, among the Embera Indian communities the custom of defaecating in the water makes them excellent reservoirs, since they release parasite eggs in the appropriate environment, where they develop and continue their cycle within intermediate hosts. Therefore, an active search and treatment of cases will have a greater impact on disease control than in other communities.

The first species of *Paragonimus* to be reported in Colombia, *P. caliensis*, was described in 1968 by LITTLE. He incriminated *Strengeria* sp. crabs as the second intermediate hosts, and *Didelphis marsupialis*, *D. asarae*, *Philander opossum* and wild felines (*Felis weidii*, *F. pardalis* and *F. yagouaroundi*) as the final hosts. In 1971, MALEK & LITTLE pointed out that *Aroapyrgus colombiensis* was the first intermediate host of this species, but no human case was detected. In the foci of the Pacific Coast, we found *Aroapyrgus* sp. as a first intermediate host, which is morphologically different from *A. colombiensis*, and the crab *Hypolobocera emberarum* as a second intermediate host. As opposed to what was established in the case of *P. caliensis*, the metacercariae present in the crabs were not encysted. This suggests that the species that was found among the Emberas might be different from *P. caliensis*. An average of 8 metacercariae per crab was found, a number lower than in Peru, where an average of 26 metacercariae per crab was found (TANTALEAN *et al.*, 1974). Infestation of snails by *Paragonimus* sp. was more common (1·6%) than has been reported for other species of molluscs infested by *Paragonimus* sp. in America: *Pomatiopsis lapidaria* (0·54% by *P. kellicotti*), *A. costaricensis* (0·2% by *P. mexicanus*) (MALEK, 1985), and *A. colombiensis* (0·043% by *P. ecuadoriensis*) (AMUNARRIZ, 1991).

The Embera Indians are in permanent contact with the rivulets and creeks. Following their ancestral culture, the Emberas defaecate in the water and take several baths a day; there they wash their clothes and take water for food preparation. Creeks are places in which children play and eat raw crabs (considered to be delicacies), and where women and children fish. Additionally, the Embera culture considers that through the consumption of raw animals it is possible for men to acquire certain features of animals. In the specific case of eating crabs, it is believed that men become better hunters and also more skilled fighters. This behaviour explains the high prevalence of paragonimiasis among children, and indicates the importance of a multidisciplinary approach with social scientists to the design and implementation of control programmes.

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and late epidemics and their starting week depended on the thresholds' sensitivities: the more sensitive the threshold, the more numerous the early epidemics, and the earlier their starting point.

The thresholds under review were: (i) 15 cases per 100 000 inhabitants averaged over 2 weeks—i.e., the WHO recommended threshold; (ii) 5 cases per 100 000 inhabitants over 3 consecutive weeks—an alternative threshold that we previously selected in a regional study in Maradi, Niger (DE CHABALIER *et al.*, 2000). For easier comprehension, we also give the results of the sensitivity study of 2 other candidate thresholds: (iii) 5 cases per 100 000 over 2 weeks; and (iv) 10 cases per 100 000 over 1 week.

Assessment of threshold accuracy

As described in the regional study, we calculated overall true- and false-positive (TP, FP), true- and false-negative (TN, FN), and the subsequent sensitivity, specificity and predictive values of each threshold. We also calculated the parameters restricted to the early season, before the 10th week of the CY. This gives what could be called the early potential of the various thresholds. We then referred to the early epidemics as being the 50 detected by the threshold offering the best compromise, that was 5 cases per 100 000 over 3 weeks.

Time-saving capacity

Restricted to early DYs, we calculated the weeks at which alternative and recommended thresholds were crossed, and the difference, as an estimate of the advantage of launching an alert from the alternative threshold compared to the recommended one. For each threshold, FN epidemics were considered detected on the last week of season surveillance, i.e., the 25th week of the CY.

Early cases

These were defined as those that occurred no later than 2 weeks after a threshold was crossed. We considered that they represented the non-preventable part of the epidemic. Restricting ourselves to early DYs, we calculated the difference in early cases between the 2 thresholds, considering each of the 50 early epidemic DYs as being independent from the others.

Statistical analysis

Calculations were made with Excel (Microsoft), and proportions were compared using the Mantel Haenszel χ^2 test.

Results

Description of surveillance data

Reports for 12 926 (84%) out of 15 392 weeks of surveillance were identified (including weeks when zero cases were reported from a district). Of the 296 DYs under study, 88 (29·7%) crossed the annual threshold of 100 cases per 100 000 inhabitants, and were thus considered epidemic; 82 504 (81·6%) cases were reported during the 88 epidemic DYs out of a total of 101 148 cases reported in the study. The median incidence of cases reported during epidemic DYs and non-epidemic DYs was 238 (100·4–1177) and 27 cases (0–98) per 100 000 inhabitants, respectively. The median number of cases reported in an epidemic DY was 1140 (78–4188).

Nine districts (24·3%) out of 37 accounted for 47·7% of district epidemics, and 50·6% of epidemic cases. Together, the 1994/95 and 1995/96 DYs accounted for 60% of district epidemics, and 69% of all epidemic cases. The number of DY epidemics and reported cases, the level of the average incidence of DY epidemics, and the proportion of all cases occurring during epidemics, showed a cyclical evolution over the years (Table 1).

Stratification by annual incidence showed that DYs with a large annual incidence accounted for the majority of epidemics at district level (60·2%), and even more of the cases reported—almost 85% (Table 2).

The seasonal pattern of epidemics

Results based on the 50 early epidemics detected through the use of the alternative threshold showed that early epidemics were more often major ones, with annual incidence of over 200 cases per 100 000, as compared to late epidemics ($P = 0{\cdot}001$) (Table 3). Early epidemics accounted for 74% of the total cases reported, although accounting for <57% of all epidemics ($P < 0{\cdot}001$).

Early and late epidemics had different patterns. Early epidemics were characterized by steeper slopes and higher peaks, in addition to beginning their upswings earlier in the calendar. Figure 1 shows the median weekly increase in incidence of early and late district epidemics, as compared to the pattern of epidemic-free districts.

Threshold performance assessment

Threshold performances are shown in Table 4. As a whole and restricted to the early season, sensitive thres-

Table 2. Stratification of 88 epidemic district years (EDYs) by annual incidence and number of reported meningitis cases (Niger, 1990–98)

Annual incidence (/100 000)	Number of EDYs (%)	Number of reported cases (%)
100–150	17 (19·3)	5 031 (6·1)
150–200	18 (20·5)	7 530 (9·1)
>200	53 (60·2)	69 943 (84·8)
Total	88 (100)	82 504 (100)

Table 1. Number of districts with meningitis epidemics in the given year, mean incidence of district epidemics, and distribution of cases reported in epidemic and non-epidemic districts (Niger, 1990–98, 37 districts)

Year	Number of district epidemics	Mean incidence of district epidemics (/100 000)	Reported cases in epidemic districts	% of cases in epidemic districts/ total reported cases
1990/91	4	282	2 330	55·0
1991/92	11	206	5 463	78·8
1992/93	6	431	5 735	57·1
1993/94	9	457	10 186	82·6
1994/95	29	518	41 925	98·8
1995/96	24	243	15 135	87·0
1996/97	5	121	1 730	32·8
1997/98	0		0	0·0
Total	88	362	82 504	81·6

Table 3. Stratification of district meningitis epidemics by date of detection of the epidemic ($n = 88$)

Annual incidence (cases/100 000)	Threshold crossed before the 10th week of the calendar	Threshold crossed from the 10th week of the calendar	Total
100–150	5	14	19
150–200	4	12	16
>200	41 (77·4%)	12 (22·6%)	53 (100%)
Total	50	38	88

The analysis is based on epidemics detected with the threshold of 5 cases per 100 000 inhabitants over 3 weeks.

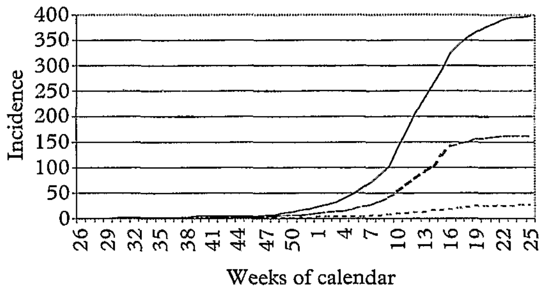

Fig. 1. Median of weekly increase of incidence over a year of surveillance at the district level, Niger, 1990–98, 296 district-years. Based on detection of epidemics with a threshold of 5 cases per 100 000 inhabitants over 3 weeks. Solid line, median of early epidemic district-years ($n = 50$); broken line, median of late epidemic district-years ($n = 38$); dotted line, median of non-epidemic district-years ($n = 208$).

holds detected significantly more TPs than the WHO threshold ($P < 0{\cdot}001$). Restricted to the early season, the numbers of FPs detected by sensitive thresholds are drastically reduced. The WHO threshold and the threshold of 5 cases per 100 000 over 3 weeks detected no FP throughout the early season, the difference being significant between thresholds ($P = 0{\cdot}001$). This is because the median week in which the FPs detected by those 2 thresholds occurred was the 15th week (i.e., mid-April), and ranged from the 10th to the 24th week. Thus, restricted to the early season, the alternative threshold of 5 cases per 100 000 over 3 weeks exhibited a maximum specificity of 1, the same as the recommended threshold.

Timeliness of alerts and unavoidable cases

The alternative threshold enabled identification of the 50 early epidemics a median of 3 weeks earlier than the WHO-recommended threshold (range: 29 weeks earlier to 1 week later). Regarding unavoidable cases, following the WHO-recommended threshold, 17 092 cases, or 28% of the 60 800 total cases declared during early epidemics, would have occurred before this 2-week delay after the threshold was crossed. Following the alternative threshold, the comparable figure was 12 234 cases (4858 fewer cases)—20% of the total ($P < 0{\cdot}001$). The use of the alternative threshold accounted for a median of 152 fewer unavoidable cases per early epidemic DY.

Discussion

In Niger, the surveillance system is almost exhaustive, and its reliability has been checked in Niamey (CAMPAGNE *et al.*, 1999). Nevertheless, use of the recommended threshold has not resulted in control of the major

Table 4. Capacity of weekly meningitis threshold levels to truly diagnose district-years under study as epidemic or not, overall, and restricted to early season, with subsequent sensitivity, specificity and predictive values (Niger, 1990–98)

(a) Overall

		Threshold criterion[a]							
		15 cases over 2 weeks		5 cases over 3 weeks		5 cases over 2 weeks		10 cases in 1 week	
TP	FP	69	6	86	24	87	47	82	30
FN	TN	19	202	2	184	1	161	6	178
Sensitivity		0·78		0·98		0·99		0·93	
Specificity		0·97		0·88		0·77		0·86	
PPV		0·92		0·78		0·65		0·73	
NPV		0·91		0·99		0·99		0·97	

(b) Early season, before the 10th week of calendar-year

		15 cases over 2 weeks		5 cases over 3 weeks		5 cases over 2 weeks		10 cases in 1 week	
TP	FP	34	0	50	0	70	8	53	3
FN	TN	54	208	38	208	18	200	35	205
Sensitivity		0·39		0·57		0·80		0·60	
Specificity		1·00		1·00		0·96		0·99	
PPV		1·00		1·00		0·90		0·94	
NPV		0·79		0·84		0·92		0·85	

TP, true positive; FP, false positive; FN, false negative; TN, true negative; PPV, positive predictive value; NPV, negative predictive value.
[a]Cases/100 000 population.

epidemics in previous years, so they could be considered as having spontaneously evolved (CHIPPAUX *et al.*, 1996). A recent study in Ghana highlighted a gap between theoretical capacities and real achievements of meningitis surveillance, with a real 23% avoided cases versus a theoretical 68% avoided cases during a meningococcal mass vaccination campaign (WOODS *et al.*, 2000). The difference was due to delayed response, and this is a strong argument for giving priority to time-saving in surveillance systems. Two approaches should then be combined: improvement of logistics and refinement of thresholds (OMS, 1997; CHIPPAUX *et al.*, 1998). Thus, our study aimed at increasing the timeliness of surveillance systems in identifying an alert. This calls for the selection of more-sensitive thresholds. Some attempts have already been made to select such thresholds (KANINDA *et al.*, in press). However, threshold choice is controversial because spurious alerts due to sensitive threshold levels would waste scarce resources (MOORE *et al.*, 1992). Our study supports the concept that the risk of spurious alerts wasting resources can be controlled. The acceptable limit of a threshold's sensitivity is that which keeps spurious alert occurrence sufficiently late in the meningitis season. In our study, restricting the use of sensitive thresholds to the early season drastically reduced the number of FPs. The alternative threshold of 5 cases per 100 000 inhabitants over 3 weeks raised no early FP. In addition, although this threshold detected 3 early epidemics fewer than the threshold of 10 cases per 100 000 over 1 week, the former had the decisive advantage of offering time to observe emerging potential epidemics before decision-making. This ensures greater reliability, and allows gradual reaction. There is a double compromise in looking for a good balance between the threshold and the early season definition. In our study, the 10th week appeared a good limit, as our analysis highlights that the main epidemic problems were over at this time of the year. Indeed, by the 10th week, 57% of epidemics, responsible for three-quarters of the cases, may have been detected, and they included four-fifths of the major epidemics (>200 cases/100 000 inhabitants). Those epidemics had the most threatening potential, and accounted for almost 85% of reported cases. Moreover, early response to such epidemics was most likely to cut down the number of unavoidable cases, to 10% of cases reported throughout an epidemic (Fig. 2). Our findings provide strong arguments for: (i) insisting on priority detection of early epidemic DYs, control of which is a determining factor for the general features of the epidemic season, at national level, and (ii) acknowledgement that for such purposes, it is possible to use a very sensitive threshold, when the spurious alerts it may cause tend to occur sufficiently late to preserve a maximum specificity early in the season.

We have shown that this strategy of splitting the meningitis season led to substantial benefits. These benefits can be measured through the earlier outset of alerts, and this was the major objective of our study. Thus, the alert could be launched a median 3 weeks earlier in each early DY. Considering the overall 50 early epidemic DYs under review, this represented 4858 unavoidable cases fewer than the actual strategy, considering the epidemic season as homogeneous. In each early epidemic DY, the alternative strategy led to a median of 152 unavoidable cases fewer per district.

In conclusion, during the early season, surveillance should be reinforced and the use of more-sensitive thresholds encouraged, in order to speed up response to emerging epidemics. In Niger, the use of the alternative threshold rate of 5 cases/100 000 over 3 weeks appears relevant up to the beginning of March, with a pre-alert by the 2nd week, in order to identify the responsible strain. Similar studies should be implemented in other meningitis belt countries in order to evaluate whether threshold levels can be adjusted according to the seasonal pattern of epidemic meningitis.

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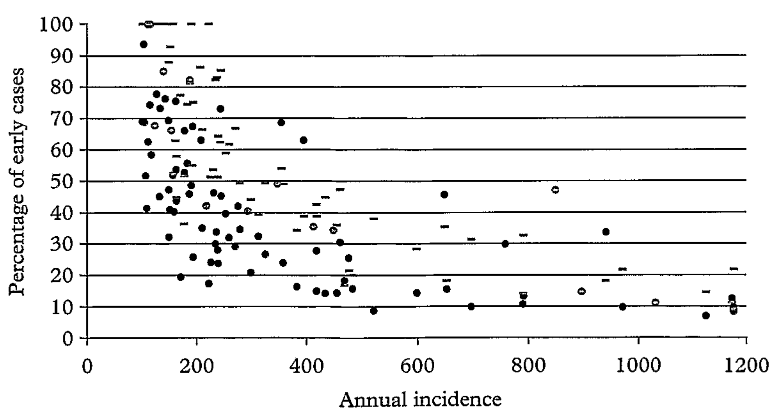

Fig. 2. Percentage of annual reported meningitis cases that occurred before the end of the 2nd week after threshold was crossed, as a function of annual incidence (per 100 000) of the epidemic (n = 88 district epidemics, 1990–98, Niger). Dashes, threshold of 15 cases per 100 000 inhabitants averaged over 2 weeks; circles, threshold of 5 cases per 100 000 inhabitants over 3 weeks.

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Book Review

Amebiasis. Tropical Medicine: Science and Practice, volume 2. J. I. Ravdin (editor). London: Imperial College Press, 2000. x+186pp. Price £40.00. ISBN 1-86094-133-8.

In 1988 Jonathan Ravdin, one of the most distinguished of the new generation of amoebiasis researchers, edited a truly impressive monograph on *Entamoeba histolytica* and the disease it causes (*Amebiasis: Human Infection by* Entamoeba histolytica, New York: John Wiley). Running to over 800 pages this multi-author work covered every aspect of the parasite and the disease and has proved invaluable to anyone wishing to enter the field. Much has happened since 1988, however, and many of us hoped that Dr Ravdin was at work on a new edition; now this much slimmer volume has appeared.

Our current knowledge is covered in 7 chapters and about 160 pages; 2 final chapters deal with current controversies and unresolved questions still awaiting further research.

The first 4 chapters concentrate on the more basic topics—organism biology, the epidemiology of amoebiasis, mechanisms of host resistance, pathogenesis, and molecular biology. The authors are well chosen and expert in their field and the chapters are up to date, most including at least some references from 1999. In the first and longest chapter, Graham Clark, Martha Espinoisa Cantellano and Alok Bhattacharya provide a detailed overview of the biology of *E. histolytica*, including many useful comparisons with the closely related but non-pathogenic *E. dispar*; this overview provides the necessary biological background for what follows. In Chapter 2 Terry Jackson first describes the data that led, after 50 years of controversy, to the separation of *E. dispar* from *E. histolytica* and then turns to our knowledge of the epidemiology of the latter organism. He quotes Elsdon-Dew's despairing comment from an earlier review—'the only value of this report is to show that it has none'—before concluding that, 30 years later, we have few more-unequivocal data than he did. In Chapter 3 Campbell and Chadee present a detailed and optimistic account of host resistance to *E. histolytica*; perhaps surprisingly, the most recent evidence seems to suggest that any human immunity to reinfection is at best partial. In the final chapter in this section Ramakrishnan and Petri discuss the various methods that *E. histolytica* uses to adhere to, kill and digest mammalian cells; the potency and variety of these virulence factors are matched only by our inability to understand what evolutionary benefit, if any, *E. histolytica* obtains from all this carnage.

The 2 following chapters, on the clinical manifestations, diagnosis and treatment of human amoebiasis, are outside my area of competence but they are written by acknowledged experts and should provide the practising physician with all the information he or she needs. Treatment of invasive amoebiasis with 5-nitroimidazoles is still highly efficacious and drug resistance is not a significant problem despite many years of use. However, the importance of following-up with a lumenal amoebicide is emphasized; without this, recurrence is a very real possibility.

Chapter 7, by Sam Stanley, discusses the possibilities of prevention, largely in the context of vaccine developments. The exciting results reported here make it highly likely that an effective vaccine will ultimately be developed; sadly it is equally likely that it will be too costly for widespread use in disease-endemic areas.

The last 2 chapters, on current controversies and unresolved questions, are inevitably more personal and not everyone will agree with the authors on what is important or even on what is unresolved. However, these chapters provide a stimulating end to an excellent introduction to a fascinating, baffling and still medically extremely signficant parasite.

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