Epidemiol. Infect. (2010), **138**, 595–605. © Cambridge University Press 2010
doi:10.1017/S0950268809991476

REVIEW ARTICLE
Companion animals: a reservoir for methicillin-resistant *Staphylococcus aureus* in the community?

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(*Accepted 23 November 2009; first published online 8 January 2010*)

SUMMARY

This article reviews the literature on the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) in dogs, cats and horses. Over the past 10 years, MRSA has emerged as an important pathogen in veterinary medicine, especially in countries with a high MRSA burden in human hospitals. During the same period, community-associated MRSA (CA-MRSA) infections in humans without apparent links to healthcare facilities have increased dramatically. Although animal infections occur outside human hospitals, significant epidemiological, clinical and genetic differences exist between CA-MRSA in humans and the majority of MRSA infections in the different animal species. The recognition of MRSA in animals has raised concern over their role as potential reservoirs or vectors for human MRSA infection in the community. However, available data on MRSA transmission between humans and companion animals are limited and the public health impact of such transmission needs to be the subject of more detailed epidemiological studies.

Key words: Community, companion animals, MRSA, reservoir, transmission.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be an important human and veterinary pathogen and a significant burden for healthcare systems worldwide. MRSA was first reported by two groups in the UK less than 2 years after the introduction of the synthetic penicillin, methicillin [1, 2]. Although many MRSA are not multidrug-resistant, they often display clinically relevant resistance to key compounds frequently used in prophylaxis and therapy and thus reduce treatment success.

Resistance to methicillin is conferred by an altered penicillin-binding protein (PBP)2a which has a low affinity to the whole class of penicillins and makes MRSA inherently resistant to all β-lactam antibiotics [3]. PBP2a is encoded by the *mecA* gene which is located on a mobile genetic element designated staphylococcal cassette chromosome (SCC*mec*). This large element has been introduced into the *S. aureus* genome as foreign genetic material on very few occasions and possibly originated from animal-adapted bacteria [4]. At least seven types plus subtypes of SCC*mec* have been identified and their identification can be used to epidemiologically characterize isolates and investigate their relatedness [5]. The expression of *mecA* is regulated by associated repressor and inducer genes (*mecR*, *mecI*) and by various other *S. aureus* genes (*fem*, *aux*) [6]. Laboratory confirmation of MRSA typically requires either the demonstration of PBP2a by latex agglutination tests or of *mecA* after replication by polymerase chain reaction.

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Two epidemiologically, clinically and genetically distinct entities of MRSA infection are recognized in people. First, MRSA is one of the most common causes for nosocomial infections. People who, for example, are immunocompromised, elderly, exposed to antimicrobial agents or undergo surgery are most at risk of acquiring MRSA infection. Such infections are difficult to treat as the bacteria are resistant to the most useful antimicrobial agents [7]. These risk factors are associated with hospitals and other healthcare facilities (HA-MRSA) and infections typically involve genetically distinct lineages. Second, the incidence of MRSA infection in the community seems to have increased dramatically over the past 10 years. Such community-associated MRSA infections (CA-MRSA) emerged in the late 1990s in young and healthy people without the typical hospital connections [8]. Around the same time MRSA also became recognized as an important veterinary pathogen and since then animal hosts have been implicated as reservoirs and vectors for human infections outside hospitals [9–12]. It has become clear that important genetic and epidemiological differences exist among the infecting strains of MRSA encountered in the different animal host species. While MRSA strains isolated from pets tend to be of human hospital origin, those from horses are of a more varied genetic background and their origin remains largely unknown; lineages most often associated with food-producing animals seem to have evolved only recently and independently from common human *S. aureus* clones.

This review will focus in particular on dogs, cats and horses and their role in the epidemiology of MRSA outside human hospitals. These species are typically kept for companionship, are often handled closely by humans and thus, provide ideal opportunity for exchange of zoonotic pathogens such as MRSA. Furthermore, the identification of MRSA in companion animals has raised concern over the use of antimicrobial agents in veterinary practice as this may lead to selection for resistant organisms and thus have important implications for human health. In contrast, MRSA in livestock, laboratory and working animals may differ.

First reports of MRSA in companion animals

The earliest report of a methicillin-resistant *S. aureus* in companion animals describes isolation from 2/109 healthy dogs screened for staphylococcal carriage in Nigeria in 1972 and phage-typing of the two isolates suggested a human origin for both [13]. This report preceded the description of *S. intermedius* as the main coagulase-positive *Staphylococcus* isolated from dogs and speciation of the two isolates must be interpreted with care [14]. However, both strains were resistant to methicillin and other β-lactam antibiotics including the cephalosporins. This strongly supports the view that they were indeed methicillin-resistant *S. aureus* as resistance to cephalosporins has been exceedingly rare in *S. intermedius* and *S. pseudintermedius* until recently. During the 1980s and early 1990s, sporadic case reports of MRSA isolated from animals were published, mainly in human medical journals. These referred to MRSA-contaminated or carrier pets implicated as vectors for human infection where infection control during human outbreaks proved difficult [10, 11]. In the veterinary field, MRSA received attention in the late 1990s, when infections due to methicillin-resistant staphylococci were recognized in dogs and horses in the UK, USA and in Asia [9, 15–19]. Since then, MRSA has been isolated from many other companion animal species including cats, rabbits, a guinea pig, a turtle and a chinchilla and also from birds, and has included healthy and infected individuals [20–23]. In addition, infection and carriage of MRSA in companion animals are now recognized worldwide, particularly in areas where MRSA is widespread in human hospitals, including South America, Australia, New Zealand, Canada and Germany and also in The Netherlands where HA-MRSA has remained rare [22, 24–28].

Even though the incidence of infection remains largely unknown, MRSA can still be considered an uncommon pathogen in companion animals based on the frequency of MRSA isolation from clinical submissions to veterinary diagnostic laboratories. During 2003, MRSA was isolated from 95 companion animals by one UK veterinary laboratory; all but two were from dogs and cats, and accounted for 1·5% of 6519 coagulase-positive staphylococci isolated from microbiology submissions [23, 29, 30]. Based on hospital admissions, nosocomial MRSA infections in horses were recognized in 1·8/1000 and in 4·8/1000 on admission to a Canadian and an Austrian hospital, respectively [31, 32].

More information is available on MRSA carriage in companion animals but prevalence rates vary between countries, regions and groups of animals sampled. MRSA carriage appears rare in healthy populations in the community without known contact with MRSA but may be more frequent in hospitalized

Table 1. *Origin, lineage and characteristics of MRSA typically isolated from companion animal species*

Host species	Epidemiology	Sequence type by multi-locus sequence typing	SCC*mec* type most commonly associated	Country and reference
Dogs	Hospital-associated	ST22	IV	Germany [21], New Zealand [26], USA [44], UK [28, 35, 45]
		ST239	III	Australia [27]
	Community-associated	ST80	Not determined	The Netherlands [65]
Cats	Hospital-associated	ST22	IV	Germany [21], New Zealand [26]
	Community-associated	ST8	IV	USA [64]
Horses	Unspecified, lineages uncommonly isolated from humans	ST1	IV	Austria [93]
		ST8	IV	Canada [72]
		ST22		Germany [57]
		ST254	IV	Austria [93]
		ST398		Austria [55, 93], The Netherlands [41], UK [56]
		ST398	V	Germany [55], The Netherlands [41]

animals especially those sampled during MRSA outbreaks, similar to observations in people. No MRSA was isolated from healthy companion animals including 200 dogs and 300 horses in Slovenia [33], 100 dogs and 100 horses in Denmark [34], 200 horses in The Netherlands [35], 22 dogs, 24 cats and 40 horses in the UK [36], 50 dogs in the USA [37], 581 horses in Ontario and New York state on farms without a history of previous MRSA [38] and 497 horses in Atlantic Canada [39]; all studies were published between 2005 and 2008. Others authors have reported infrequent MRSA isolation from companion animal populations, including 3/148 cats in Brazil in 1998 [24], 6/815 dogs in Hong Kong [40] and 1/193 dogs in Canada [41], both in 2008. In contrast, in animals admitted to referral hospitals, carriage rates have ranged from 9% in dogs where no MRSA cases were hospitalized concurrently [42] to 20% in a small animal [43] and 16% in an equine hospital [36] during outbreak conditions in 2005 and 2007. Most recently in 2009, a new lineage, MRSA ST398, has been recognized in horses in various countries [44] and also from a dog in Germany [45]. This lineage has been able to spread rapidly between individual animals in pig herds and as this may also be the case in other animal species, the position in dogs and horses will need to be kept under review.

Epidemiology of MRSA in companion animals

S. aureus is a highly clonal organism so that epidemiological typing studies which investigate genetic relatedness between strains allow insight into the origins and spread of MRSA. Epidemiological typing of MRSA isolates and strain comparison have revealed important differences between MRSA isolated from the individual animal species. Typing technologies originally included the use of bacteriophages. This was superseded by pulsed-field gel electrophoresis (PFGE). Now other techniques such as multilocus-sequence typing (MLST), SCC*mec* typing, *spa*-typing or rapid PCR-based analysis of lineage-specific DNA segments have become available and these have been reviewed previously in a veterinary context [46].

While MRSA infection and carriage isolates from dogs and cats have mostly been identical to the HA-MRSA lineages prevalent in each country or region, the genetic background of equine isolates is more varied (Table 1). It has been shown for many countries that typically two *S. aureus* clones are responsible for the majority of human HA-MRSA infections [47]. In the UK, successful clones are currently represented by the epidemic strains EMRSA-15 and EMRSA-16 [48], and the majority of canine and feline isolates have been of these lineages [29, 43]. In other countries too, most canine and feline isolates have been indistinguishable genetically by PFGE from the local HA lineages and display the same multidrug resistance as human HA-MRSA [36, 45, 49]. Only occasionally, unusual or ancestral *S. aureus* lineages have been recognized from dogs and cats and this mirrors the findings in people [45, 50–52].

In horses, however, older or less prevalent MRSA lineages which are different from the local hospital

https://doi.org/10.1017/S0950268809991476 Published online by Cambridge University Press

lineages have predominated in both infection and carriage isolates from most countries. This pattern was first reported from Japan in 1997 where 15 equine infection isolates with identical PFGE patterns were different from the commonly identified human lineages based on comparison of coagulase isotypes [53]. Similarly, O'Mahony and colleagues found that antibiogram-resistogram types of eight equine MRSA were distinct from the most frequently isolated human strains in Ireland [49]. More recently, additional genetic analyses have identified one predominant clonal complex (CC8) in horses represented by several different sequence types (ST), including ST1, ST254, ST247 and ST8, mostly lineages that had been associated with human HA-MRSA in the past but which have since been superseded [31, 32, 54–56]. More recently, the livestock-associated MRSA lineage, ST398, has also been isolated from healthy and diseased horses in The Netherlands, Austria, Germany and the UK [44, 57, 58]; endemic HA-MRSA lineages are only rarely reported in horses as demonstrated in a recent German analysis where only 1/19 infection isolates was of hospital origin (ST22) [59].

Although MRSA infections in animals tend to occur in the community or outside human healthcare facilities and, as such, have been described by some authors as community associated [38, 60] a differentiation from the genetically and clinically distinct CA-MRSA is warranted for better understanding [61, 62]. In humans, CA-MRSA are clonally unrelated to HA-MRSA lineages and originate from many clonal complexes (CC), even those occurring within one country [8]. They typically carry the smallest SCC*mec* types IV or V [63] and they are less drug-resistant; it is suggested that this is because resistance genes can present a burden for the bacterial metabolism in less competitive environments [64]. In addition, many carry Panton–Valentine leucocidin (PVL) toxin genes which may be responsible for severe skin and soft tissue infections in previously healthy people [65]. Such CA-MRSA lineages (Table 1) and PVL toxin gene-positive MRSA have now been isolated from 12 infected animals including dogs, cats, a rabbit and a parrot in the USA and Europe [20, 66] and from healthy pets in The Netherlands and Germany [67, 68].

Transmission of MRSA between humans and companion animals

Transmission of pathogenic staphylococci between humans and animals was first suspected for farm animals in the early 1960s combined with concerns about animals as a reservoir for such organisms [69]. Early studies investigating inter-species transmission gave contradictory results though as both similar and distinct strains were isolated from animals and their in-contact people; however, conclusions may have been hampered by limited species definition for staphylococci [70, 71]. Interest was renewed when MRSA proved difficult to control in the 1990s coinciding with the availability of improved phenotypic and genotypic analysis tools. Although there is no study published to date which has specifically investigated MRSA transmission between humans and companion animals, genetic analyses, several case reports and case series strongly indicate that such transmission can occur in both directions.

First, genetic analyses of canine and feline MRSA indicate, but do not prove, that MRSA isolated from these species has originated in human hospitals and that originally MRSA transmission must have occurred from humans to pets. Such a spillover from hospitals into the community and eventually to pets via patients or healthcare workers infected, carrying or contaminated with the organism seems plausible particularly in countries with a high burden of HA-MRSA. Healthcare links of pet-owners have not been investigated systematically to date but associations with animal infection have been reported, although inconsistently [72, 73].

Second, transmission of MRSA from animals to vulnerable people is also suspected based on indirect evidence [10–12, 26, 68]. This direction is of particular concern where susceptible humans are exposed to contaminated or infected animals, where animals visit healthcare facilities for companionship to patients and where animals may be spreading PVL toxin gene-positive *S. aureus* strains. Healthy carrier animals have been implicated as sources and vectors for recurrent human infection [10, 12, 68]. In addition, carrier animals may have been involved in promoting recurrent colonization in their owners [11, 26]. Although other causes such the effect of contaminated environments were not directly investigated in these settings, indirect evidence for the role of animal vectors was provided when human re-infections and re-colonization ceased after routine treatment and hygiene measures were combined with elimination or decontamination of the suspected animal vectors.

For horses, the origin of MRSA remains unclear; the infrequent isolation of HA-MRSA from this species despite close contact with humans indicates

that factors other than exposure to human carriers are involved in the acquisition of MRSA by horses. However, equine-to-human transmission has been suggested by several groups. MRSA with indistinguishable PFGE patterns were isolated from 3/5 in-contact veterinary staff sampled for carriage in response to a series of suspected veterinary hospital-acquired infections [17]. The zoonotic potential of MRSA from equine infections was further demonstrated by a case report on three human skin infections in people caring for an MRSA-infected and -colonized foal at a veterinary teaching hospital in Canada. All three human isolates were classified as CMRSA-5, a clone commonly isolated from infected and colonized horses in that region but relatively uncommon in humans, again supporting the concept of transfer [56, 74, 75].

MRSA within a companion animal reservoir?

How far companion animals provide a true reservoir for MRSA or whether they should only be considered as contaminated living vectors remains unclear. While the definition of a reservoir implies that the host animal can maintain the pathogen indefinitely [76], this has not been investigated for any of the companion animal species to date. On the contrary, there are suggestions that MRSA carriage is not sustained for long periods by companion animal hosts in a clean environment. MRSA carriage resolved in 16 healthy rescue dogs identified during cross-sectional screening with daily cleaning and disinfection of the kennel environment alone [77]. Similarly, during an MRSA carriage eradication programme in two Canadian equine establishments, decolonization of human carriers and strict hygiene and isolation measures alone, without antimicrobial use on carrier animals, was associated with eradication of MRSA from all horses on one farm within 6 months [78]. In contrast, MRSA carriage was maintained over several weeks in a healthy dog; however, the dog lived with owners who had previously been infected with MRSA and continued to suffer from open wounds so contamination of the environment was highly likely [12]. No information on the persistence of MRSA in cats has been reported even though *S. aureus* may colonize and infect cats more frequently than dogs and horses [79, 80]. In contrast, a true reservoir role seems likely in pigs for MRSA ST398 as it has been reported to spread rapidly between animals and occurs more frequently in pigs than in people [81, 82].

Risk factors for MRSA acquisition by companion animals

With MRSA traditionally considered a human pathogen, identification of risk factors for animals could be highly significant. They are assumed to mirror those reported for HA-MRSA in people such as own carriage, contact with carriers, hospital admission and invasive procedures, and all of these risk factors have been identified in companion animals. For dogs and cats, a UK case-control study involving 182 animals with *S. aureus* infection showed that contact with human MRSA carriers was the most important risk factor for MRSA infection followed by repeated courses of antimicrobial therapy, surgery and several days of hospitalization at veterinary clinics predispose to MRSA infection when compared with methicillin-susceptible *Staphylococcus aureus* infection (R. Soares-Magalhaes *et al.*, unpublished observations). In horses, MRSA carriage on admission to an equine hospital increased the risk for nosocomial MRSA infection in a population of 120 animals in one study (OR 38·9, 95% CI 9·49–160, $P<0·0001$) [31]. While contact with carriers has been reported inconsistently for individual animal patients, the significance of surgery and orthopaedic implants for the development of equine MRSA infection can be deduced from the large number of post-surgical infections reported in animals [17, 49, 72, 83]. Antimicrobial therapy as a predisposing factor has been implicated in equine MRSA infection where ceftiofur or aminoglycosides appeared to predispose horses to MRSA carriage during hospitalization in one study [31]. Another equine study investigated risk factors for MRSA carriage prior to admission to veterinary hospitals in 67 carrier horses and identified contact with carriers, antimicrobial therapy and previous hospital admission as significant factors [84]. More recently, acquisition of MRSA directly from human healthcare environments was suspected in healthy pet therapy dogs in the USA and in the UK [52, 85], although two other screenings of therapy dogs failed to identify MRSA carriage or contamination in the UK and Hong Kong [40, 86].

In view of the importance of contact with human MRSA carriers in the development of canine and feline MRSA infections, potential sources of contact need to be considered. In this context, the high MRSA carriage rates reported in veterinary staff are relevant. They exceed rates reported for healthy community members in many countries and affect veterinary staff

with or without known contact with infected animal cases. While most countries have only very limited information on MRSA carriage rates in healthy people, estimates tend to be below 2% even where MRSA is endemic in hospitals such as in the UK, the USA, Italy or Portugal [87–92]. Veterinary staff in two small animal referral hospitals in the UK showed carriage rates of 18% [42] and 27% [36] while cross-sectional sampling of small animal veterinary staff at veterinary conferences revealed 4·4% positive in the USA [93] and 3% positive in Denmark [94]. Carriage was also high (9%), and mainly of HA-MRSA lineages, in 388 UK first opinion practice veterinary staff [95]. This is similar to an occupational risk identified in human healthcare workers but causes are less clear in veterinary staff [96].

Similar high percentages have been identified in equine veterinary staff and handlers. The earliest indication of transmission between infected horses and their veterinary staff or handlers came from a case series of 11 post-surgical MRSA infections in the USA where 3/5 sampled staff volunteers were nasal carriers [17]. Subsequently, 9·7% of 103 veterinary staff at an equine hospital in Canada and 4·6% of 43 veterinary staff at an Austrian university hospital were MRSA carriers at times when infected horses were hospitalized [38, 97]. In all three reports, human carriage isolates were of the same lineages as the equine infection isolates but distinct from the epidemic human clones in those areas. In contrast, no human carriers were identified in 12 veterinary staff sampled at a Liverpool equine referral hospital, UK, despite clinical MRSA infections being treated in three hospitalized horses during the study period [36]. However, sampling of veterinary staff unrelated to clinical infection cases at equine conferences in the USA and the UK identified MRSA in 10% of 257 [98] and in 8% of 276 [99] delegates.

MRSA contamination of veterinary clinic or hospital environments has also been recognized. MRSA was isolated from 10% of 30 sampling sites in a UK small animal referral hospital without known MRSA patients present at the time [42] and from 9·6% of 260 sites in a Canadian equine hospital while MRSA-infected horses were hospitalized [100]. A recent report from another UK university veterinary hospital demonstrated isolation of MRSA from 1·4% of 140 sites and from 3·1% of 64 staff [101].

Although the main direction of inter-species transmission and also the relevance and causes for this occupational risk in veterinary staff are still unclear, existing evidence indicates that the epidemiology of MRSA in companion animals and people caring for them are closely related.

Clinical aspects

The first reported cases of MRSA infections in companion animals involved post-operative wound infections including implant complications and chronic skin diseases in dogs [8] and dermatitis and metritis in horses [18] but ear, respiratory, urinary, arthritic and other infections have been recorded too [22, 36, 49, 72, 83]. While these infection sites are typical for staphylococcal infections generally, some clinical features have been linked to MRSA in particular. In cats, two cases of abscess formation have been reported in association with MRSA infection both with HA-MRSA and CA-MRSA lineages [66, 102] and abscesses surrounded by eosinophilic inflammatory cells were also proposed as a feline species-specific reaction pattern associated with methicillin-resistant staphylococci [103]. In this retrospective analysis of 27 histopathological specimens from feline abscesses, 23 had Gram-positive cocci centrally and 15/17 such lesions showed immunoreactivity to PBP2a. Another MRSA-associated characteristic was proposed from a retrospective analysis of 749 staphylococcal isolates from small companion animals. The authors reported that the 39 MRSA were more frequently isolated from deep infections such as urinary tract or respiratory disease compared with methicillin-susceptible *S. aureus* (MSSA) ($n=76$) which tended to affect more the skin and ears [79]. They also reported that the rate of MRSA infection in cats was similar to that in dogs while other pathogenic staphylococci were less frequently identified in feline infection. However, disease frequencies derived from laboratory submissions need to be interpreted with care especially for multidrug resistant organisms due to submission bias and clinical disease characteristics. For example, non-MRSA canine bacterial skin infections will frequently respond to empirical antimicrobial therapy and samples may only be submitted after poor clinical response. Additional confirmation of these findings in a larger number of cases is warranted as this information could advance early recognition of MRSA infection in veterinary practice and thus minimize the spread of MRSA.

Treatment of MRSA infections has relied on restoring the skin barrier function, removal of surgical implants and topical, systemic or occasionally

intra-lesional antimicrobial treatment as indicated for the type of infection [9, 104]. Although isolates from dogs and cats typically show multidrug resistance as expected for HA lineages, most canine and feline infections can be treated successfully. Antimicrobial drugs with efficacy *in vitro* against MRSA are available for use in companion animal species in many countries and include trimethoprim-potentiated sulphonamides, tetracyclines, possibly clindamycin for HA-MRSA [9, 105] and fluoroquinolones for some CA-MRSA [66, 67]. Outcomes of MRSA infection in animals are only reported infrequently. However, the prognosis appears to be related to the severity of infection and to the prognosis of the underlying trigger [9, 83, 106]. Fatal outcomes have been reported for individual debilitated patients and a causal link with MRSA has only been confirmed in one horse with severe osteomyelitis [55, 73]. To date, there is no indication that HA-MRSA is more virulent in companion animals than other coagulase-positive staphylococci such as *S. pseudintermedius* or MSSA; this is supported by a study showing that the severity of clinical signs and the prognosis for MRSA infection in a group of 46 cats was no worse than for MSSA infection ($n=33$) [106]. As only 12 cases of CA-MRSA animal infection have been reported until now and their severity is unknown, it is not clear yet whether these strains may be associated with clinically distinct entities as in some humans infected with PVL-positive strains [20, 66].

Future opportunities and conclusions

In summary, there is good but indirect evidence that companion animals can promote the recurrence of MRSA infection and carriage in humans in home environments. However, the extent of their role in MRSA transmission cannot be quantified from the information published to date. Further investigations, including longitudinal studies, into the dynamics of MRSA carriage or contamination in companion animals are now urgently required to advance our understanding of MRSA transmission between hosts and ultimately to develop better control and prevention strategies for this zoonotic pathogen.

At present, the predominance in dogs and cats of MRSA lineages that are successful in people and the worldwide pattern in horses of varied lineages belonging to CC8 suggest a degree of species-specificity of MRSA within companion animals. However, the recent emergence of CA-MRSA in pets emphasizes that the epidemiology of MRSA in pet animals is changing as it is in humans. Therefore, awareness of companion animals as possible vectors for highly virulent PVL toxin-positive MRSA strains may be critical for the success of infection control measures and monitoring of animals is warranted. In addition, the identification of antimicrobial agents as a predisposing factor for MRSA infection in companion animals, coupled with increasing use of β-lactam and fluoroquinolones in small animal practice, has renewed the discussion over the potentially dangerous implications that veterinary use of antimicrobial agents may have for human health [107, 108].

However, the vital companionship that animals provide to people and the currently incomplete understanding of the role of animals in the spread of MRSA warrant a continued effort by human and veterinary clinicians and researchers to develop a better understanding for and new control strategies against MRSA.

DECLARATION OF INTEREST

None.

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https://doi.org/10.1017/S0950268809991476 Published online by Cambridge University Press