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The origin of human pathogens: evaluating the role of agriculture and domestic animals in the evolution of human disease

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ABSTRACT

Many significant diseases of human civilization are thought to have arisen concurrently with the advent of agriculture in human society. It has been hypothesised that the food produced by farming increased population sizes to allow the maintenance of virulent pathogens, i.e. civilization pathogens, while domestic animals provided sources of disease to humans. To determine the relationship between pathogens in humans and domestic animals, I examined phylogenetic data for several human pathogens that are commonly evolutionarily linked to domestic animals: measles, pertussis, smallpox, tuberculosis, taenid worms, and falciparal malaria. The majority are civilization pathogens, although I have included others whose evolutionary origins have traditionally been ascribed to domestic animals. The strongest evidence for a domestic-animal origin exists for measles and pertussis, although the data do not exclude a non-domestic origin. As for the other pathogens, the evidence currently available makes it difficult to determine if the domestic-origin hypothesis is supported or refuted; in fact, intriguing data for tuberculosis and taenid worms suggests that transmission may occur as easily from humans to domestic animals. These findings do not abrogate the importance of agriculture in disease transmission; rather, if anything, they suggest an alternative, more complex series of effects than previously elucidated. Rather than domestication, the broader force for human pathogen evolution could be ecological change, namely anthropogenic modification of the environment. This is supported by evidence that many current emerging infectious diseases are associated with human modification of the environment. Agriculture may have changed the transmission ecology of pre-existing human pathogens, increased the success of pre-existing pathogen vectors, resulted in novel interactions between humans and wildlife, and, through the domestication of animals, provided a stable conduit for human infection by wildlife diseases.

Key words: agriculture, domestic animals, disease evolution, disease ecology, measles, pertussis, smallpox, malaria, tuberculosis, tapeworm.

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I. INTRODUCTION

The advent of agriculture in human societies is believed to have been a significant event in the evolution of human disease. It has been proposed that many pathogens of human civilization could not have existed in humans prior to the development of agriculture (Fiennes, 1978; McNeill, 1989; Diamond, 1997, 2002). Only as a result of agriculture could population densities become large enough to permit the persistence of 'civilization pathogens', which cause our most fatal diseases and transmit rapidly from person to person, resulting in either death or immunity. Because of their virulent transmission, such diseases could not have persisted in small, pre-agricultural human populations and must therefore have originated elsewhere.

The traditional view of the relationship between farming, disease, and humans is that pathogens were derived from domestic animals. 'Most and probably all of the distinctive infectious diseases of civilization transferred to human populations from animal herds. Contacts were closest with the domesticated species, so it is not surprising to find that many of our common infectious diseases have recognisable affinities with one or another disease afflicting domesticated animals' (McNeill, 1989, p. 45). Our fatal 'civilization' diseases are believed to have arisen in this way (McNeill, 1989; Diamond, 1997, 2002; Tanabe, 2001), including (but not limited to) measles, tuberculosis, smallpox, influenza, pertussis, and falciparal malaria (see Table 11.1 in Diamond, 1997). Because many of our domestic animals tended to be social, living in herds even prior to domestication (Clutton-Brock, 1981), they may have served as hosts for pathogens adapted to exploiting and persisting in clumped populations (McNeill, 1989). Since domestication is linked to the development of agriculture, the close proximity of domesticated animals and the increased human population density supported by agriculture may have allowed herd pathogens to exploit humans successfully and eventually to evolve into uniquely human diseases (Fiennes, 1978; McNeill, 1989; Diamond, 1997). 'Thus, the evolution of these diseases depended on the two separate roles of domestication: in creating much denser human populations, and in permitting much more frequent transmission of animal diseases from our domesticates than from hunted wild animals' (Diamond, 2002, p. 703).

Although the domestic-origins hypothesis has been proposed for several decades (Cameron, 1956; McNeill, 1989; Diamond, 1997, 2002; Tanabe, 2001), tests of its veracity are limited. Past evidence for pathogen ancestry focused on morphological and antigenic similarities; for instance, pathogens taken from domestic animals and humans caused similar immune responses in experimentally infected mammalian models (Norrby, Sheshberadaran & McCollogh, 1985; Arico *et al.*, 1987). However, similar immune responses by the host do not necessarily indicate an evolutionary relationship since they could also result from convergent pathogen strategies in response to the host's immune system. Host ranges of animal pathogens are broader than those of human species, suggesting an animal origin for human pathogens if specialisation is a derived trait (Stead *et al.*, 1995). Given that morphological and antigenic similarities could conceivably arise through convergent evolution and that host specialisation is not necessarily a derived trait, it is therefore questionable whether these data provide evidence for the origin of human pathogens in domestic animals.

II. CASE STUDIES

Recent advances in molecular techniques have generated genetic evidence and new phylogenies that permit a more thorough test of hypotheses concerning the origin of human pathogens. To determine whether evidence for a domestic origin exists, I examined several human pathogens: measles, pertussis, smallpox, tuberculosis, taenid worms, and falciparal malaria. These particular pathogens were chosen because: (a) they are significant causes for human morbidity and mortality; (b) it has clearly and commonly been asserted that they have arisen from domestic animal pathogens (Cameron, 1956; McNeill, 1989; Diamond, 1997, 2002; Tanabe, 2001); and (c) quality molecular data were available to evaluate the assertations. Each of these pathogens is considered in detail below.

(1) Measles

The measles virus belongs to the genus *Morbillivirus*, which also includes rinderpest (a serious infectious agent in ruminants), canine distemper virus, peste des petits ruminants, phocid distemper, and cetacean morbillivirus (Barrett, 1999). Morbilliviruses cause acute infection in their hosts, i.e. infected individuals recover or die. Generally, morbilliviruses cause serious disease in their hosts and transmission is limited to species belonging to the same order (Barrett, 1999).

Measles, rinderpest, and canine distemper were previously grouped into a single genus because of morphological and antigenic similarities (Fiennes, 1978). Measles could thus have originated either from canine distemper in domestic dogs or from rinderpest in cattle. Canine distemper was suggested to be the more likely candidate by some authors because it infects a wider host range than the other two viruses (Fiennes, 1978; Appel & Summers, 1995). Other analyses of serological and various protein sequence

similarities suggested that rinderpest was the basal group for the genus, meaning that both measles and canine distemper were derived from it and the host breadth of canine distemper virus was secondarily acquired (Norrby *et al.*, 1985; Norrby *et al.*, 1992).

The most recent evidence obtained from a phylogeny of several entire protein gene sequences suggests rinderpest is most closely related to measles and they form a derived group relative to canine distemper and other members of the genus (Westover & Hughes, 2001) (Fig. 1). This analysis also found that a cluster containing Hendra virus, Nipah virus, and equine morbillivirus was basal within the *Morbillivirus* genus (Westover *et al.*, 2001). Hendra and Nipah are endemic in fruit bats, have been classified as emerging infectious diseases, and are transmitted to humans from horses and domesticated pigs (Murray *et al.*, 1995; Chua *et al.*, 1999).

This evidence supports a domestic origin for the human measles virus: measles is most closely related to rinderpest and both morbilliviruses are closely related to canine parvovirus. Additionally, because these three viruses share a common ancestor with the Hendra-Nipah cluster, it is probable that the ancestor to measles was transmitted to humans from a domestic animal. However, whether the ancestor of measles was mainly a pathogen of domestic animals, like rinderpest, or a pathogen maintained in a wildlife reservoir is unclear. Hendra and Nipah are transmitted to domestic animals by their endemic reservoir, the fruit bat; domesticates then secondarily transmit the pathogen amongst themselves and to humans (Chua *et al.*, 1999; MacKenzie, 1999).

(2) Pertussis

Pertussis, commonly known as whooping cough, is a human disease caused by bacteria in the genus *Bordetella*. Species in this genus colonise the respiratory tracts of a variety of vertebrate hosts. Although the most common pathogen in humans is *Bordetella pertussis*, a uniquely human pathogen, disease may also be caused by *B. parapertussis* (Porter, Connor & Donachie, 1994) and *B. bronchiseptica*. *Bordetella parapertussis* also causes disease in domestic sheep (Porter *et al.*, 1994) and *B. bronchiseptica* infects a range of species including (but not exclusively) dogs, horses, pigs, cats, rabbits, and occasionally humans (Woolfrey & Moody, 1991; Gueirard *et al.*, 1995).

The phylogenetic relationships within the genus *Bordetella* have been difficult to determine because of their high degree of relatedness (Musser *et al.*, 1986; Arico *et al.*, 1987; Khattak & Matthews, 1993). Recent work, using multilocus enzyme electrophoresis and insertion sequence DNA polymorphism patterns, found that *B. pertussis*, the uniquely human pathogen (Fig. 2A), occurs in a genetic cluster distinct from the clade formed by modern *B. bronchiseptica* and *B. parapertussis* (Fig. 2B) (van der Zee *et al.*, 1997; Cummings *et al.*, 2002). This finding corroborated earlier phylogenetic relationships derived using sequence comparisions for toxin genes and multilocus enzyme electrophoresis (Altschul, 1989). Using a non-pathogen pig strain of *B. bronchiseptica* (Musser, Rapp & Selander, 1987) as an outgroup, modern *B. bronchiseptica* and *B. parapertussis* may represent a more derived clade, having originated from *B. bronchiseptica* (Fig. 2C) (van der Zee *et al.*, 1997). Given the more basal placement of *B. pertussis* relative to the rest of the pathogens in the dendrogram, two possibilities exist: (1) the ancestor for pertussis was a human pathogen that subsequently spread to other species, or (2) the ancestral pathogen was a host generalist of humans and other mammals that first generated a specialist human lineage and then a more generalised pathogen that colonised domestic animals. Given that the *B. bronchiseptica* outgroup was found in pigs and other *B. bronchiseptica* strains are host generalists, the second possibility seems more likely. However, no further evidence is available for either scenario.

By contrast, the other pathogen responsible for disease in humans, *B. parapertussis* (Fig. 2D), groups closely with pathogens that infect domestic animals (van der Zee *et al.*, 1997) (Fig. 2B). Its closest relative primarily infects pigs, although it has also been found in a variety of domestic and wild species. Furthermore, these two pathogens are part of a clade includes the sheep virus *B. parapertussis*. The phylogenetic placement of human parapertussis in a clade wherein the two other species primarily infect domestic animals suggests that its ancestor was most likely derived from a pathogen infecting a domestic ancestor, either swine or ovine.

One potential issue with the interpretation of these relationships is the chosen outgroup. Apart from its greater genetic distance from the other included *Bordetella* species (Musser *et al.*, 1987), it is not clear what qualifies this particular pathogen as an appropriate outgroup. The choice of outgroup is important when attempting to interpret ancestral character states (Maddison, Donoghue & Maddison, 1984), especially in this case when evaluating the host affiliations of presumed common ancestors.

(3) Smallpox

Variola virus, the causative agent for smallpox, belongs to the genus *Orthopoxvirus*, which contains several species of veterinary and medical importance, including rabbitpox, buffalopox, monkeypox, swinepox, and cowpox (Esposito & Massung, 1995). Several of these species are multihost pathogens, capable of infecting both human and non-human hosts (Esposito *et al.*, 1995).

Variola is believed to have evolved from cowpox (McNeill, 1989; Diamond, 1997; Tanabe, 2001), a pathogen whose presumed association with cattle is revealed in its common name. However, cowpox is a misnomer. The pathogen is endemic to rodents and rarely infects cows (Baxby, 1977). Therefore, it is doubtful that cattle served as the ultimate source of variola. However, because cows can become infected, they may have served to transmit secondarily the rodent pathogen to humans.

Recent molecular work does not clarify the evolutionary origin of smallpox. Comparisons of gene sequences obtained from members of the *Orthopoxvirus* genus support the suggestion that a cowpox relative (Fig. 3A) was an ancestor to variola (Fig. 3B) (Gubser & Smith, 2002; Meyer, Neubauer & Pfeffer, 2002; Pulford, Meyer & Ulaeto, 2002;

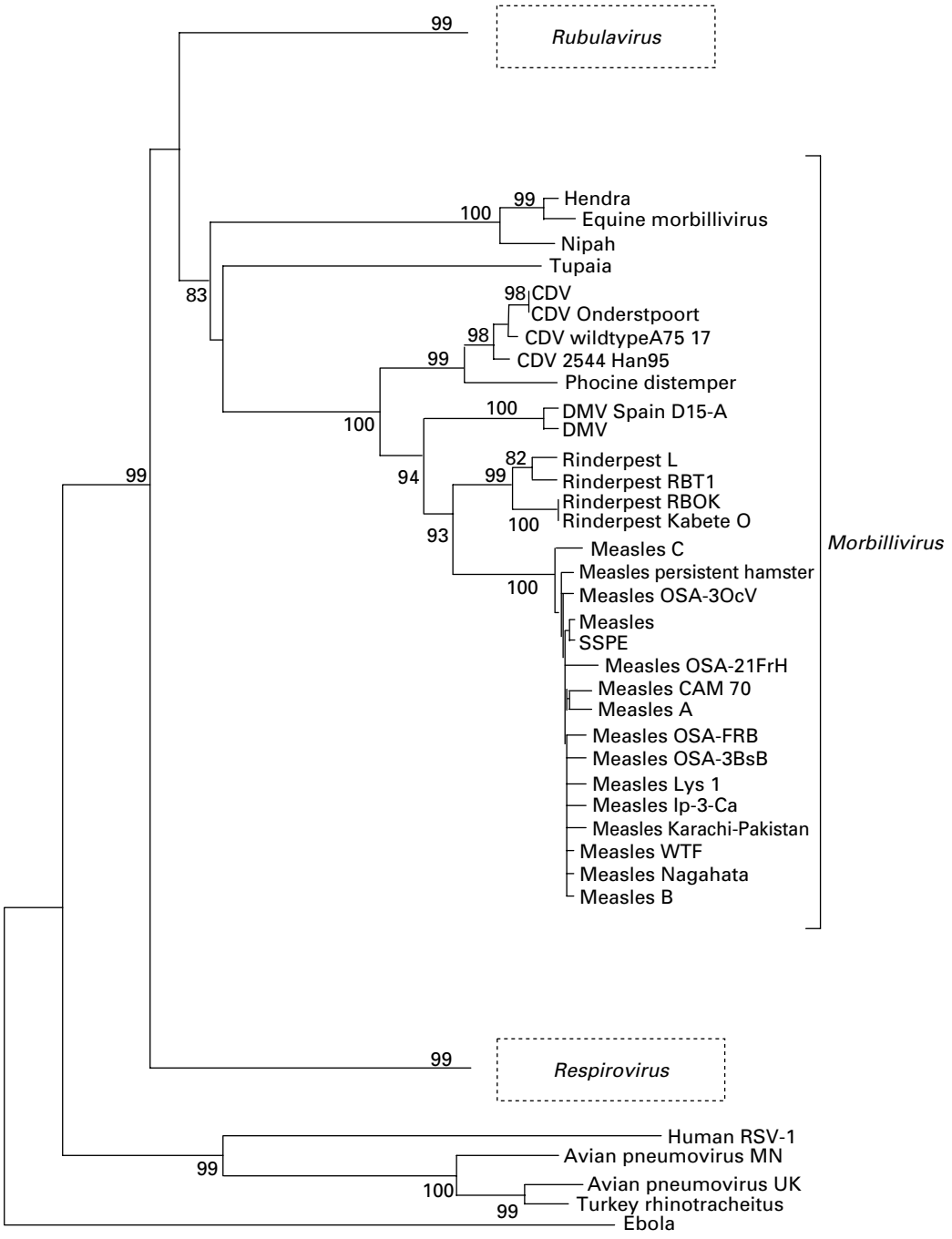


Fig. 1. Phylogeny of species belonging to *Morbillivirus* and related genera using Ebola virus as an outgroup. Species names are abbreviated as follows: CDV, canine distemper virus; DMV, dolphin morbillivirus; RSV, respiratory syncytial virus; SSPE, subacute sclerosing panencephalitus. Codes following terminal taxon labels indicate strain and protein. Measles is most closely related to rinderpest, a bovine disease, and canine distemper virus. The tree is based on differences in amino acid sequences; numbers above the branches represent bootstrap support. Modified from Westover & Hughes (2001).

Gubser *et al.*, 2004). However, the closest existing relative of smallpox is camelpox (Fig. 3C), a poorly characterised strain that causes severe disease in young camels (McGrane & Higgins, 1986; Gubser *et al.*, 2002, 2004; Pulford *et al.*, 2002), suggesting that variola might have evolved from a camel pathogen that transferred to humans at the time of camel domestication.

There are two possible evolutionary scenarios to consider: (a) smallpox evolved directly from camelpox, which itself evolved from a cowpox-like ancestor (domestication hypothesis) or (b) camelpox and smallpox emerged independently from an ancestral rodent-borne pathogen similar to cowpox (Gubser *et al.*, 2002). Camelpox and smallpox have unique unshared DNA sequences, suggesting that

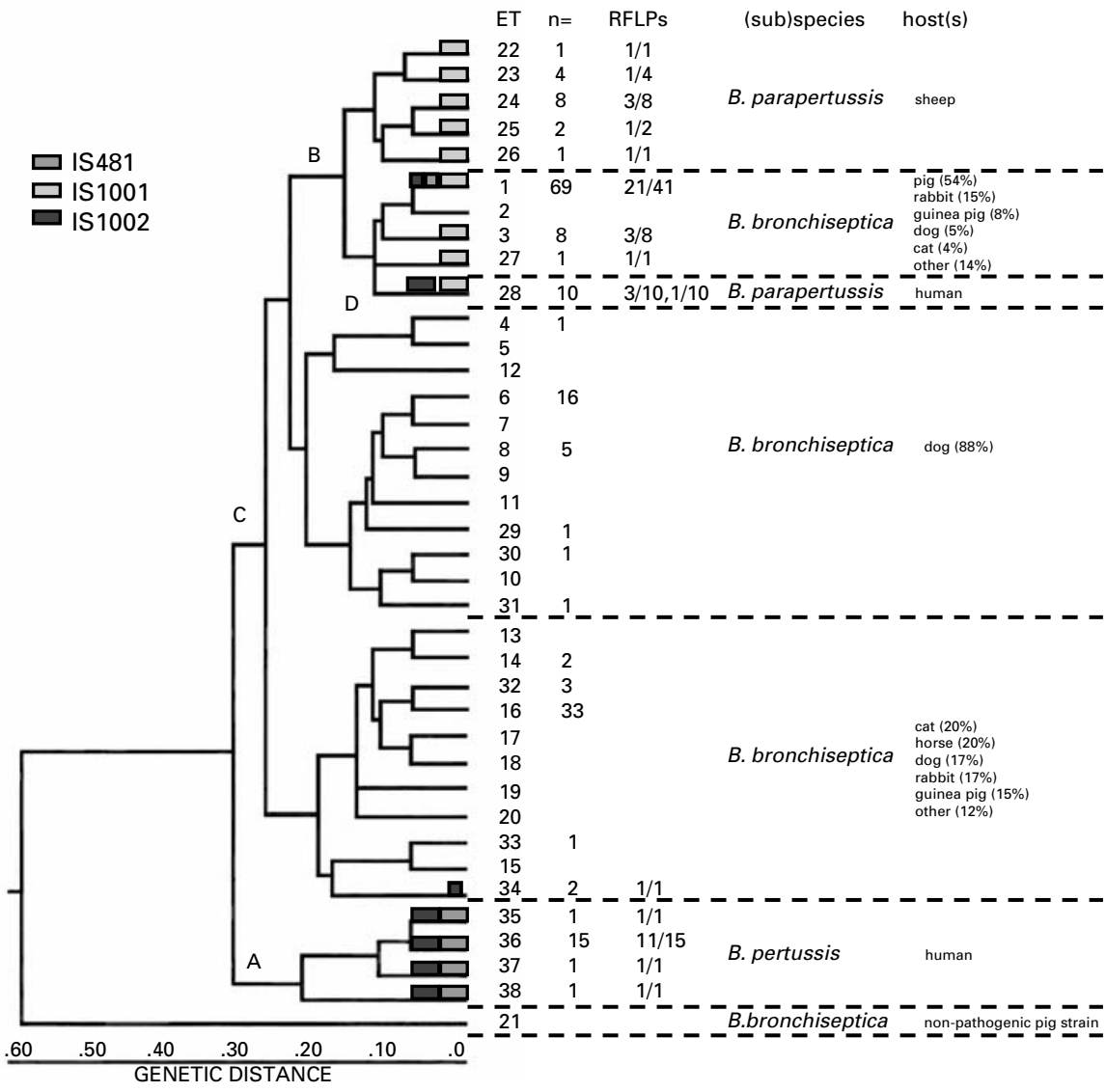


Fig. 2. Dendrogram of clusters of clones belonging to the *Bordetella* genus. The pathogen causing major human pertussis (A), *B. pertussis*, is not grouped inside a clade with *Bordetella* species that infect domestic animals (C). However, the pathogen causing minor human pertussis (D), *B. parapertussis*, is clearly associated with swine and ovine species (B). The tree is based on differences in enzyme electrophoretic types and supported by the clustering of insertion sequences. The bar below denotes relative genetic distance between clades. IS, insertion sequence; ET, electrophoretic type; RFLP, restriction fragment length polymorphism types per strain; *n*, number of strains assigned to ET (no *n* value given for historical samples no longer available). Taken from van der Zee *et al.* (1997).

independent emergence may be the best explanation (Afonso *et al.*, 2002; Gubser *et al.*, 2002). The similarity of the two species may indicate relatively recent emergence from a common ancestor rather than direct evolution of one from the other (Pulford *et al.*, 2002). Also, since the ecology of camelpox is still poorly characterised, it can therefore only be cautiously assumed that camelpox is endemic to camels (Khalafalla & Mohamed, 1996). It may be that, like cowpox, the pathogen is maintained in an unidentified rodent population and only secondarily transferred to and among camels.

(4) Tuberculosis

Human tuberculosis is largely caused by bacterium *Mycobacterium tuberculosis*. *M. tuberculosis* is part of a pathogen complex including five closely related species that cause tuberculosis in humans and animals (Baess, 1979; Nolte & Metchock, 1995; Feizabadi *et al.*, 1996; Musser, Amin & Ramaswamy, 2000). The pathogen responsible for bovine tuberculosis, *Mycobacterium bovis*, is also part of this complex (Feizabadi *et al.*, 1996). The bovine tuberculosis pathogen infects a wide range of hosts (Steele & Ranney, 1958;

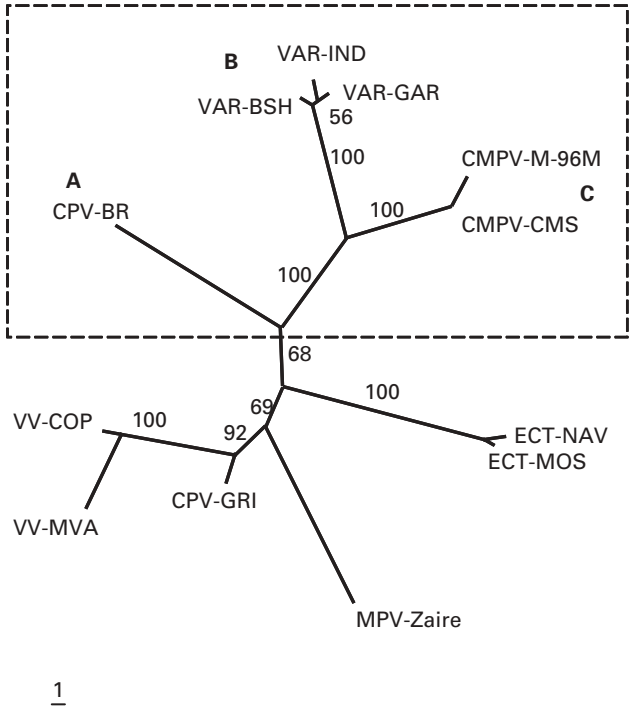


Fig. 3. Phylogenic tree of twelve *Orthopoxvirus* strains. Species names are abbreviated as follows: CMPV, camelpox virus; CPV, cowpox virus; ECT, ectromelia virus; MPV, monkeypox virus; VAR, variola virus; and VV, vaccinia. Variola virus (B), which causes smallpox, and camelpox virus (C) have a well-supported genetic relationship but any ancestral relationship is unclear. Cowpox (A) is the next closest ancestor, also a relationship with a high degree of support. The tree is based on differences in amino acid sequences and is shown in an unrooted format. The numbers above the branches indicate bootstrap support. The bar at the bottom indicates divergence scale (substitutions per site). Taken from Gubser *et al.* (2004).

Gutacker *et al.*, 2002), whereas *M. tuberculosis* is restricted to humans (Brosch *et al.*, 2002).

The wide host range of *M. bovis* has led some authors to speculate that human tuberculosis orginated from bovine species around the time of domestication (Stead *et al.*, 1995; Stead, 1997). However, recent molecular comparisons of genomic deletions and synonymous single nucleotide polymorphisms suggest that this may not be the case. Using unidirectional genomic deletions, both Mostowy *et al.* (2002) and Brosch *et al.* (2002) independently concluded that human tuberculosis is most similar to the presumed ancestor of all the tuberculosis-causing species (Behr *et al.*, 1999; Kato-Maeda *et al.*, 2001) whereas bovine tuberculosis appears to represent a highly derived lineage (Brosch *et al.*, 2002; Mostowy *et al.*, 2002). An ancestral position for human tuberculosis is further supported by the discovery of an isolate from a 17 000-year-old bison that grouped most closely with *M. tuberculosis* (Rothschild *et al.*, 2001). Independent evidence gathered through a comparison of synonymous nucleotide substitutions supports the proposal that human and bovine tuberculosis occupy distinct lineages (Gutacker *et al.*, 2002) (Fig. 4). The majority of human *M. tuberculosis* clones are located in one highly related cluster (Fig. 4 A), with the remaining, slightly more variable isolates located in one larger, well-supported clade (Fig. 4 B); the bulk of *M. bovis* clones are placed in a single cluster (Fig. 4 C), with all but one of the other *M. bovis* clones also in a distinct clade (Fig. 4 D).

These results suggest that human and bovine tuberculosis had independent evolutionary trajectories, with no clear support for the assertation that the human pathogen originated in the bovine bacterium. Instead, *M. tuberculosis* appears to be more closely related to the ancestral tubercle bacilli, having undergone far fewer DNA deletions relative to *M. bovis* (Brosch *et al.*, 2002). The two pathogens likely diverged from a common ancestor very early on, well before the development of agriculture and domestication, and the progenitor of *M. tuberculosis* may have even already been a human pathogen (Brosch *et al.*, 2002).

(5) Taenid tapeworms

Humans are the definitive hosts (used for sexual reproduction by the parasite) for three species of taenid tapeworms: *Taenia saginata*, *Taenia asiatica*, and *Taenia solium* (Schmidt & Roberts, 1989). Cattle are the obligate intermediate host for *T. saginata* and pigs serve the same role for *T. asiatica* and *T. solium* (Schmidt *et al.*, 1989).

Given the close physical association between humans and cattle and pigs since the advent of agriculture, it was postulated that human tapeworms evolved from worms that used domestic animals as definitive hosts prior to domestication (Baer, 1940; Cameron, 1956). Recently, compelling evidence has emerged to suggest that the origin of human tapeworms pre-dates domestication of cattle and pigs. The placement of human taenids within a broad phylogeny of tapeworms suggests that they became associated with the genus *Homo* prior to the evolution of modern humans (De Queiroz & Alkire, 1998; Hoberg *et al.*, 2000, 2001) (Fig. 5). Human tapeworms are most closely associated with those using felids and hyaenids as definitive hosts (Fig. 5 A), and wild bovids (but not the *Bos* spp. from which domesticated cattle are derived) as intermediate hosts (Fig. 5 B) (Hoberg *et al.*, 2001). Additionally, the sister taxa of human tapeworm species all have ties to pre-humans because of their African origins (Hoberg *et al.*, 2001).

A non-domestic origin for human tapeworms is further corroborated by molecular evidence that the divergence of the human-infecting sister species, *T. saginata* and *T. asiatica*, occurred well before the domestication of cattle and pigs between 7000 and 10 000 years ago (Clutton-Brock, 1981; Epstein & Bichard, 1984; Bradley *et al.*, 1996). The divergence of *T. saginata* and *T. asiatica* is estimated to have occurred about 160 000 years ago under the most conservative divergence calculations, but is more likely to have happened between 780 000 and 1.7 million years ago (Hoberg *et al.*, 2001).

The available evidence strongly suggests that human tapeworms arose from associations between omnivorous hominids scavenging on bovid carcasses left by felid and hyaenid predators (Sponheimer & Lee-Thorp, 1999; Hoberg *et al.*, 2001). The cycling of tapeworms between humans, cattle, and pigs appears to have occurred

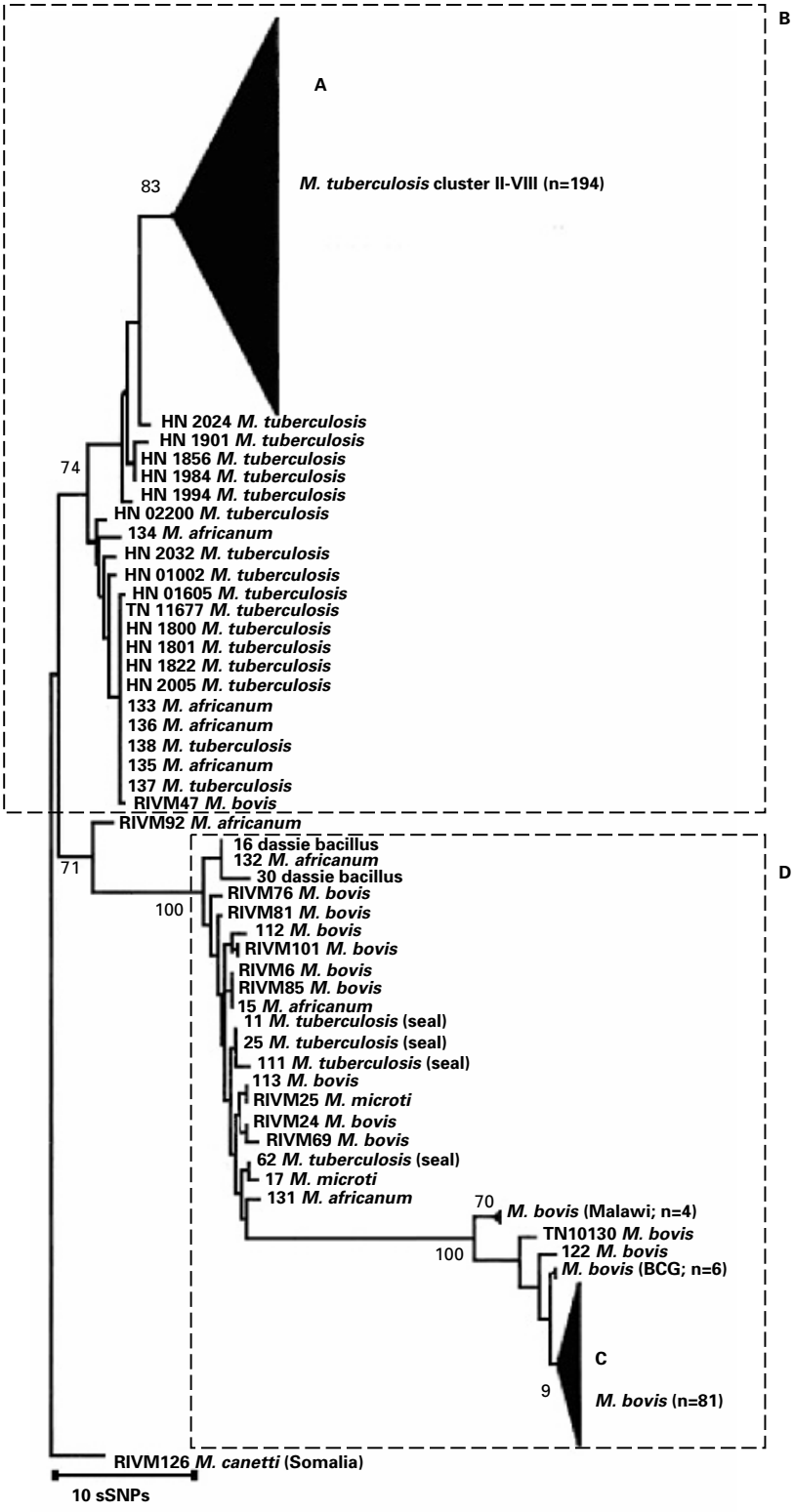


Fig. 4. Phylogeny of members of the tuberculosis complex using *Mycobacterium canettii* as an outgroup: (A) *M. tuberculosis* cluster, (B) distinct *M. tuberculosis* clade, (C) *M. bovis* cluster and (D) distinct *M. bovis* clade. The human tuberculosis pathogen, *M. tuberculosis*, and the bovine tuberculosis pathogen, *M. bovis*, occupy distinct lineages from one another. The tree is based on synonymous single nucleotide polymorphisms (sSNPs). The number of sSNPs shared is used as a relative measure of genetic distance as indicated by the bar at the bottom. Modified from Gutacker *et al.* (2002). Numbers above branches indicate bootstrap support and are only shown for major nodes.

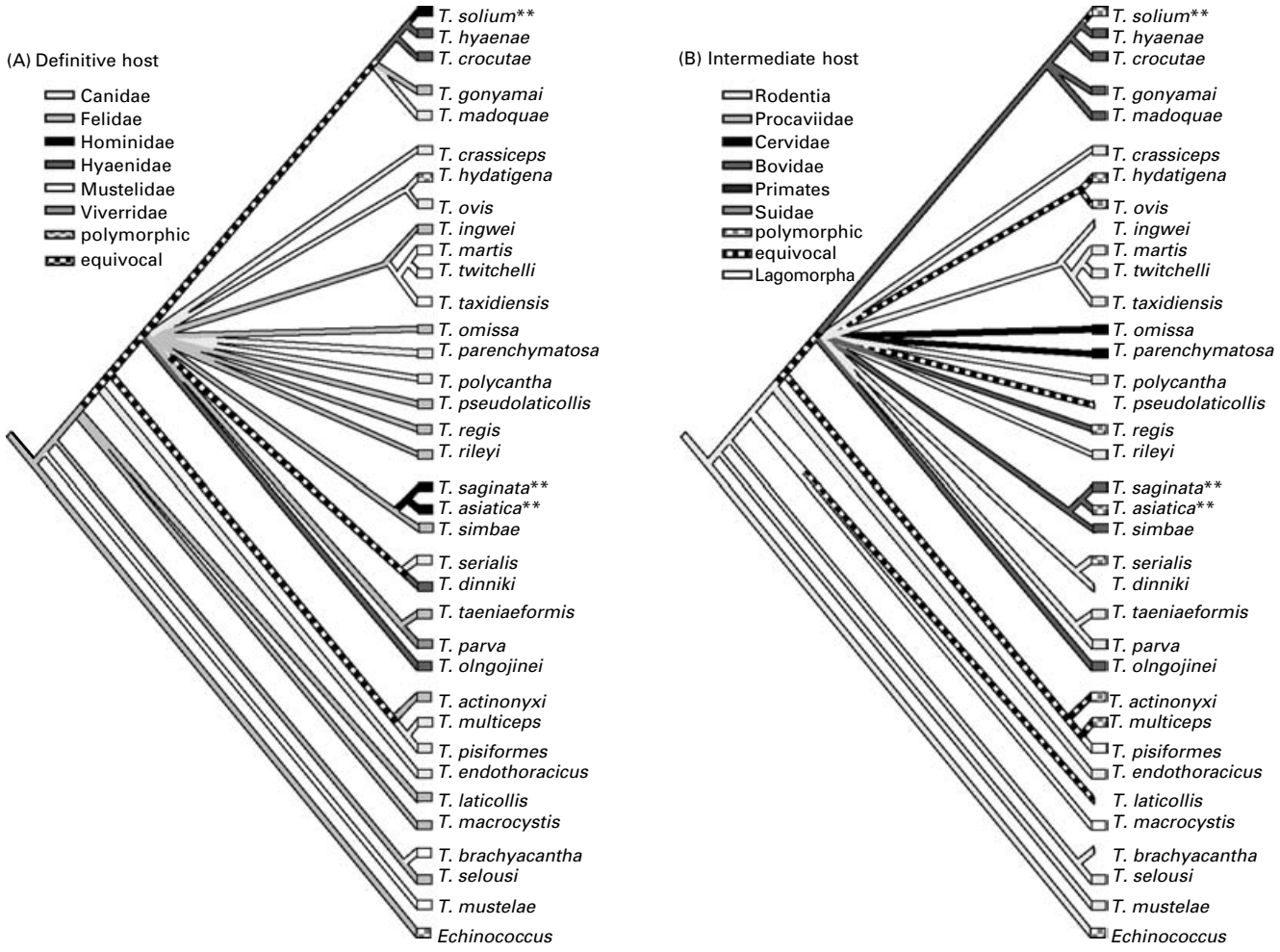


Fig. 5. Phylogenies of *Taenia* tapeworms based on comparative tapeworm morphology and using *Echinococcus* species as an outgroup. Keys to shading are located next to each tree. Asterisks indicate human tapeworm species of interest. (A) Taxonomic family of the definitive host for the tapeworm species. The definitive hosts for the closest relatives of human tapeworms are hyenas and large felids. (B) Taxonomic family of the intermediate host for the tapeworm species. Human tapeworms are found in clades for which bovids are intermediate hosts, not definitive hosts. Modified from Hoberg *et al.* (2001).

secondarily after the evolution of modern humans. While domestication did not provide the impetus for tapeworm evolution in humans, it may have provided the opportunity for human tapeworms to infect cows and pigs.

(6) Falciparal malaria

Four different pathogens, in the genus *Plasmodium*, are known to cause malaria in humans: *Plasmodium ovale*, *Plasmodium malariae*, *Plasmodium vivax*, and *Plasmodium falciparum*. All four species are transmitted to humans by *Anopheles* mosquitoes (Schmidt *et al.*, 1989). *Plasmodium falciparum* is the most virulent of the four, responsible for the majority of malaria-caused morbidity and mortality (WHO, 2000). Many other members of the *Plasmodium* genus primarily infect birds (Schmidt *et al.*, 1989) and, in early studies, *P. falciparum* was found to group most closely with avian parasites based on phylogenies constructed from SSU rRNA (Waters, Higgins & McCutchan, 1991, 1993).

It was hypothesized that a host-switching event occurred around the time of the development of agriculture, with an avian pathogen evolving into a human specialist (Waters *et al.*, 1991, 1993). This hypothesis was supported by some time estimates for the emergence of the parasite. Based on analysis of microsatellite polymorphisms in introns in *P. falciparum*, Volkman *et al.* (2001) suggested that the pathogen is of recent origin, in the range of 3200 to 7700 years (Rich *et al.*, 1998; Volkman *et al.*, 2001), which generally corresponds to the postulated time of domestication of poultry (Clutton-Brock, 1981; Volkman *et al.*, 2001).

Other molecular evidence disputes the recent avian origin of falciparal malaria (Hughes & Verra, 2001; Mu *et al.*, 2002; Joy *et al.*, 2003; Leclerc *et al.*, 2004). The closest known relative of *Plasmodium falciparum* (Fig. 6A) is actually *Plasmodium reichenowi* (Fig. 6B) (Escalante & Ayala, 1994; Escalante, Barrio & Ayala, 1995; Leclerc *et al.*, 2004), a species absent from the previous phylogenies (Waters *et al.*, 1991, 1993) and whose host is a chimpanzee. The

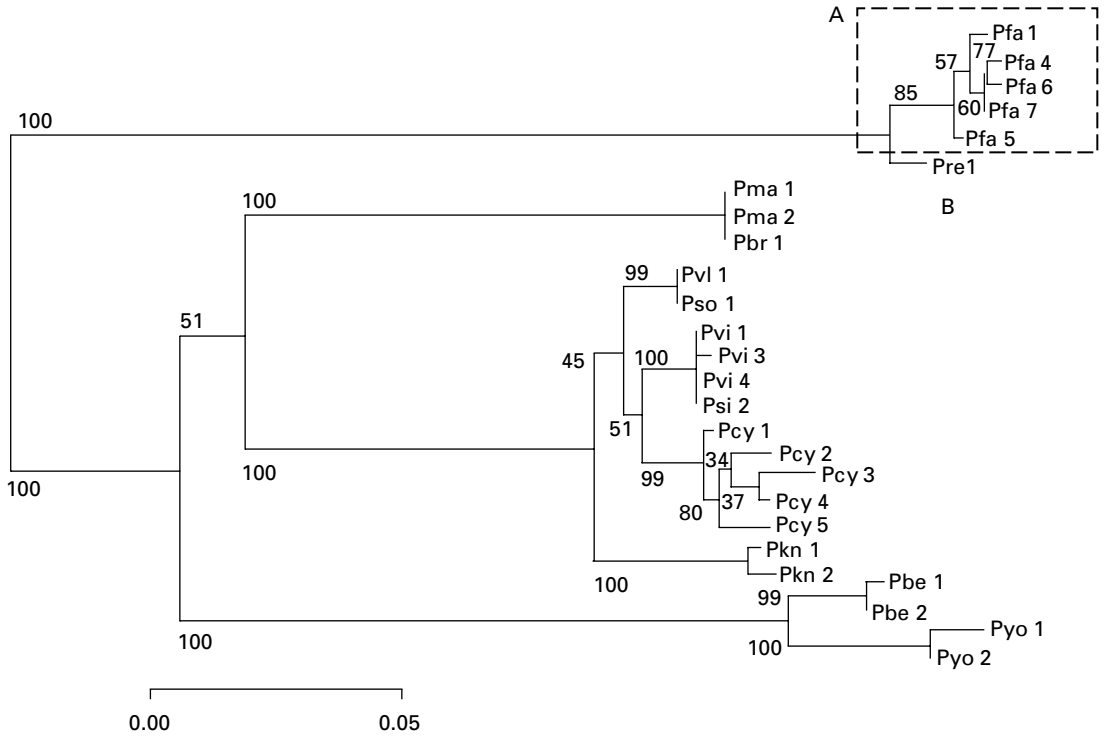


Fig. 6. Phylogeny of *Plasmodium* species that infect primates. Species names are abbreviated as follows: Pbe, *P. berghei*; Pbr, *P. brasilianum*; Pcy, *P. cynomolgi*; Pfa, *P. falciparum*; Pkn, *P. knowlesi*; Pma, *P. malariae*; Pre, *P. reichenowi*; Psi, *P. simium*; Pso, *P. simiovale*; Pvi, *P. vivax*; Pvl, *P. vivax*-like; and Pyo, *P. yoelii*. Rodent pathogens *P. berghei* and *P. yoelii* were used as outgroups. The falciparal malaria pathogen, *P. falciparum* (A), is closely related to the chimpanzee pathogen, *P. reichenowi* (B), and forms a distinct phylogenetic group distant from other clades. The tree is based on nucleotide gene sequences. Circled numbers represent bootstrap support. The scale bar indicates a measure of genetic distance (Tamura). Taken from Escalante *et al.* (1995).

P. falciparum and *P. reichenowi* cluster is only distantly related to avian species (Escalante *et al.*, 1994; Leclerc *et al.*, 2004). The divergence of the human and chimpanzee parasites is estimated to have occurred around 7 million years ago (Escalante *et al.*, 1995). Joy *et al.* (2003), in an analysis of synonymous substitutions in both coding and non-coding regions of mtDNA, put the divergence of *P. falciparum* and *P. reichenowi* at between 5 and 7 million years ago; even their most conservative estimate of divergence gave the most recent ancestor around 70 000 years ago. Given that the estimated time of human divergence from chimpanzees (Haile-Selassie, 2001; Brunet *et al.*, 2002; Wall, 2003) is in the same range as the divergence of human and chimpanzee parasites (Escalante *et al.*, 1995), *P. falciparum*'s progenitor may have existed in the human lineage long before the advent of agriculture.

How can one reconcile the widely divergent estimates of Volkman *et al.* (2001) for a recent origin and Escalante *et al.* (1995) and others for an ancient origin of the human falciparal parasite? The estimated time of emergence of 6000 years ago (Volkman *et al.*, 2001) may reflect the speciation of *P. falciparum* from a single progenitor OR the demographic sweep of one falciparal clonal type through the population (Rich *et al.*, 1998; Volkman *et al.*, 2001). It has been proposed that the development of agriculture, accompanied by warming climatic conditions, may have allowed for the speciation and spread of the anthropophilic *Anopheles* mosquitoes that vector *Plasmodium falciparum* (Coluzzi, 1994). The African populations of the pathogen appear to have undergone a sudden expansion corresponding temporally to the development of agriculture and the species emergence of *Anopheles gambiae* in Africa, as determined through analysis of haplotype networks (shape and distance statistics) (Joy *et al.*, 2003); populations of *P. falciparum* in Asia and South America did not show a corresponding trend (Joy *et al.*, 2003).

III. FUTURE WORK

This review has shown that much work remains to be done before the hypothesis that many human diseases originated in their domesticated animals can be thoroughly tested. Much of the research discussed herein was published within the last few years. Further such data and phylogenies for other human pathogens are needed to allow careful evaluation of the hypothesis of a domestic-animal origin of human pathogens.

Improvements in phylogeny composition may be necessary, in the choice of outgroups and the number and type of species included. Appropriate outgroups are crucial to

quality phylogenies (Maddison *et al.*, 1984; Smith, 1994). When studying closely related organisms such as those reviewed here, it may be necessary to use a more closely related taxon member as an outgroup than is typical in cladistic analyses. While information regarding ancestry may be lost, the use of unrooted trees may help identify genetic distance between species when rooting is problematic (Gubser *et al.*, 2004).

Since significant genetic similarity between some pathogens and other members of their disease complex makes identification of relationships difficult, the quantity of sequences compared should be increased and diversified. Molecular comparisons examining genetic sequences for surface and extracellular proteins are of limited use (Musser *et al.*, 2000); such markers code for products relating to host immune function and are undoubtedly under strong selection pressure. While comparison of synonymous nucleotide substitutions, gene deletions, and/or insertion sequence copies has revealed much about the relationships of highly related human pathogens, their use can result in the loss of important phylogenetic information in the sense that such pathogens may not be compared to evolutionarily relevant taxa that may be less highly related. In order to understand better the context for a pathogen's evolution, the best approach will be to sequence greater numbers of genes within a pathogen and genomes within a pathogen cluster, although debate is still ongoing as to the preferred option given limited time and resources (Rokas & Carroll, 2005).

Lastly, since information regarding the temporal and geographic origins of human pathogens is crucial to understanding the relationship between agriculture, domestication, and human disease, future studies should follow the approaches of Hoberg *et al.* (2001) and Joy *et al.* (2003), who utilised several complementary lines of evidence to test alternative hypotheses for the origin of the pathogen of interest.

IV. AN ALTERNATIVE ROLE FOR AGRICULTURE

Given the lack of unequivocal phylogenetic evidence, the domestic origins hypothesis is neither supported nor refuted here. Additionally, the observation that some human pathogens, such as tuberculosis, *Plasmodium falciparum*, and dysentery (Pupo, Ruiting & Reeves, 2000), occupy distinct basal lineages in the phylogeny of their pathogen complex, and may pre-date the appearance of agriculture, suggests that several 'civilization' pathogens may have a different history than previously assumed.

Agriculture may simply have had a more complex series of effects than previously thought. The broader force for human pathogen evolution may have been ecological change, namely anthropogenic modification of the environment. McNeill (1989, p. 18) hints briefly at this idea: 'Clearly any change of habitat … implies a substantial alteration in the sort of infections one is likely to encounter.' Many current emerging infectious diseases are associated with human modification of the environment (Epstein, 1995; Schrag & Wiener, 1995; Daszak, Cunningham & Hyatt, 2000).

The role of agriculture in human disease may therefore have had at least three components: (a) changing the transmission ecology of pre-existing human pathogens; (b) increasing the success of pre-existing pathogen vectors, resulting in novel interactions between humans and wildlife; (c) providing a stable conduit for human infection by wildlife diseases by means of domesticated animals.

At least two possible differences in transmission strategies could have permitted parasite persistence in humans prior to increased population sizes: a wider host range and a more benign pathogenesis in humans. Pathogens may be able to shift rapidly between generalist and specialist strategies when host conditions change (Wolinsky *et al.*, 1996). Generalist ancestors are implied in the phylogenies of pertussis and tuberculosis (van der Zee *et al.*, 1997; Rothschild *et al.*, 2001) and most emerging infectious diseases are capable of infecting multiple hosts (Taylor, Latham & Woolhouse, 2001).

Diseases currently requiring large host population sizes may have had a lower persistence threshold in the past. Pre-civilization population levels may have selected for more benign pathogens whereas large population sizes, achieved following the onset of agriculture, selected for greater virulence. Many pathogen populations are composed of a suite of clonal genotypes, which may be variable in their virulence (Arnot, 1999; Lord *et al.*, 1999; Ofosu-Okyere *et al.*, 2001; Taylor *et al.*, 2001). Several of these clones may infect a given host and compete intraspecifically (Read & Taylor, 2001). The competitive outcome may ultimately rely on the population characteristics of the host (Berchieri & Barrow, 1990; Sernicola *et al.*, 1999), leading to more- or less- benign pathogens in the host population at large.

Many human pathogens have been classified as young because of their limited genetic variability (Volkman *et al.*, 2001; Gutacker *et al.*, 2002), assuming that low variability reflects recent divergence because mutations take time to accumulate (Musser *et al.*, 2000; Volkman *et al.*, 2001). However, limited variability might also reflect a selective sweep, whereby a particular group of genetic material becomes fixed within the pathogen population, perhaps due to a selective advantage (Rich *et al.*, 1998). This would mean that limited genetic variability within human pathogens may represent the success of particular clonal types in response to a recent change in host ecology, as has been implied by the relationship between the sweep of a particular toxoplasmosis clone and the time of cat domestication (Su *et al.*, 2003).

Agriculture may also have impacted human disease by changing the ecology of pathogen vectors such as mosquitoes and rodents. Slash-and-burn agriculture in Africa, which is the geographic origin of falciparal malaria, may have expanded suitable habitat for important arthropod vectors (Coluzzi, 1994). The development of agriculture may have allowed the emergence of a competitively superior human plague (*Yersinia pseudotuberculosis*) clone from a rodent pathogen progenitor (*Yersinia pestis*), which was transmitted to humans because of increased rodent to human contact (Achtman *et al.*, 1999). Rodent-transmitted Macupo and

Junin viruses 'emerged' almost simultaneously with the development of agriculture in small South American communities (Parodi *et al.*, 1958; Johnson *et al.*, 1966).

V. DOMESTIC ANIMALS AS PATHOGEN CONDUITS

While domesticated animals may not have directly provided humans with pathogens, they could represent important secondary transmission sources of pathogens maintained in wildlife reservoirs. This role of domestic animals is supported by patterns of transmission in presently emerging diseases. Domestic animals are carriers, not sources, of emerging multihost pathogens that originate from wildlife species (Daszak *et al.*, 2000). Emerging diseases are caused primarily by pathogens that are either transmitted to humans directly from wildlife or are shared between humans, wildlife, and domesticates (Morse, 1993; Krause, 1994; Cleaveland, Laurenson & Taylor, 2001). Domestic animals may enhance the transmission of wildlife pathogens to humans because they are more likely to come into contact with wild species. The close and consistent association between domestic animals and people then makes successful pathogen transfer more likely.

Influenza provides a relevant example of pathogen connectivity between wildlife, domestic animals, and humans. Genetic and serological evidence suggest that virulent influenza strains in humans result from genetic infusion of human viruses by wild avian viruses (Subbarao *et al.*, 1998; Webster, 1999). Direct transmission of influenza between birds and humans is restricted because these viruses are specialised to their endemic hosts (Couceiro, Paulson & Baum, 1993) but pigs and poultry may host the replication of both human and avian viruses, allowing avian and human strains to mix, and subsequently transmit strains containing avian genes back to humans (Scholtissek, 1990; Kida *et al.*, 1994; Ito *et al.*, 1998; Matrosovich *et al.*, 1999; Brown, 2000; Matrosovich, Krauss & Webster, 2001). However, it is important to note that at least one strain, the 1918 influenza virus, appears to have transferred directly from birds to humans (Taubenberger *et al.*, 2005).

VI. CONCLUSIONS

(1) Examination of recent phylogenies of several human pathogens gave only equivocal support for the hypothesis that they originated from pathogens of domestic animals.

(2) Additional good-quality molecular and ecological evidence for other important pathogens is needed before the domestic origins hypothesis can be properly assessed.

(3) The available data for tuberculosis, taenid tapeworms, and malaria suggest that it is premature to assume that increased human densities following the development of agriculture resulted in the acquisition of current 'civilization' diseases from domestic animals.

(4) The development of agriculture is postulated to have a more complex effect on the emergence of human pathogens by: (a) changing the transmission ecology of pre-existing human pathogens; (b) increasing the success of pre-existing pathogen vectors, resulting in novel interactions between humans and wildlife; (c) providing a stable conduit for human infection by wildlife diseases by means of domesticated animals.

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