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Evolution of the human ABO polymorphism by two complementary selective pressures

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The best-known example of terminal-glycan variation is the ABO histo-blood group polymorphism in humans. We model two selective forces acting on histo-blood group antigens that may account for this polymorphism. The first is generated by the invasion of opportunistic bacterial or other pathogens that interact with the epithelial-mucosal surfaces. The bacteria adapt to the microenvironments of common host phenotypes and so create frequency-dependent selection for rarer host alleles. The second is generated by intracellular viruses, and accounts for the observed differentials between the ABO-phenotype frequencies. It is thought that viruses acquire histo-blood group structures as part of their envelope from their previous host. The presence of host antigens on the viral envelope causes differential transmission of the virus between host types owing to the asymmetric action of ABO natural antibodies. Our model simulations show that these two forces acting together can account for the major features of the ABO polymorphism in humans.

Keywords: ABO histo-blood groups; natural antibodies; bacteria; virus; evolution

1. INTRODUCTION

There is constant pressure on vertebrate hosts to generate diversity to combat rapidly evolving pathogens (Haldane 1949; Pfennig 2001). Such needs are particularly obvious at the exocrine epithelial (mucosal) surfaces, the first points of contact with invading bacteria and viruses. These surfaces are coated with a layer of highly glycosylated proteins. The terminal saccharide profile of such proteins is, in part, determined by histo-blood group glycosyltransferases encoded by several different loci, including the well-known ABO/H, Se, Lewis and Galα1,3Gal structures (Henry *et al.* 1995; Oriol *et al.* 1999; Ravn & Dabelsteen 2000; Henry 2001). These genetic systems are all polymorphic across a range of mammalian species; for example, ABO/H in humans, primates, pigs, dogs and rabbits (Zweibaum & Bouhou 1973; Zweibaum *et al.* 1974; Mourant *et al.* 1976; Balanzino *et al.* 1994; Blancher & Socha 1997). Depending on ethnicity, 1–20% of humans in a given population lack expression of the ABO on a majority of mucosal surfaces and in secretions owing to a non-functional Se locus, but will nevertheless express the respective ABO antigens, for example on erythrocytes (Henry 2001).

We examine a general pathogen-related explanation for the evolution of ABO genetic diversity. In humans, three alleles, *A, B* and *O,* specify four phenotypes, O (*OO* genotype), A (*AA* and *AO* genotypes), B (*BB* and *BO* genotypes) and AB (*AB* genotype). *A* and *B* encode dominant glycosyltransferases with specificity for different monosaccharides, whereas *O* encodes a non-functional product (Yamamoto *et al.* 1990). The lack of an ABO histo-blood group generates natural antibodies. Thus, natural antibodies against the A- and B-specific carbohydrate termini are produced prolifically in O individuals. The reverse is not the case, with A and B hosts producing natural antibodies against each other, but having no O-specific natural antibodies. This asymmetry is the result of the non-functionality of the *O* allele.

Previous attempts to explain the ABO genetic diversity have mainly focused on infectious-disease prevalence (Berger *et al.* 1989; Vogel & Motulsky 1997; Fischer *et al.* 1998; Gagneux & Varki 1999; Henry 2001; Marionneau *et al.* 2001). In an earlier modelling study, Fischer *et al.* (1998) demonstrated the possibility of an ABO polymorphism using a simple population-genetic model with two independent bacterial species, one adapted to be costly to hosts containing the *A* allele and the other to be costly to hosts containing the *B* allele. However, their choice of fitness coefficients was arbitrary, and the approach to polymorphic equilibrium exhibited rapid (damped) cycles.

We model the evolution of the ABO polymorphism through the action of two different types of pathogen. The first, a bacterial pathogen, adapts through accumulated mutations to exploit common host phenotypes and creates frequency-dependent selection in favour of rarer ABO alleles. Several precedents for bacterial-pathogen adaptation to different glycosylated host structures have been described (Karlsson 1998; Marionneau *et al.* 2001). Such pathogens generate polymorphism under a wide range of conditions but fail to explain the frequency distribution of ABO phenotypes. In particular, the O phenotype is rarely found at a frequency of less than *ca*. 30% anywhere in the world, and A and B phenotypes often have similar frequencies, which can be as high as or higher than that of

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O, but in many regions are consistently lower than that of O (Mourant *et al.* 1976; Vogel & Motulsky 1997). To explain this variable frequency distribution, we propose that a second type of pathogen is needed with differential transmission between hosts. These differences arise when viruses pick up host patterns of terminal glycosylation as part of their envelopes. Thus, a virus released from an A host carries a signature on its envelope that is recognized by the natural immune systems of O and B hosts. But a virus emanating from an O host lacks terminal glycosylation and so will not be recognized easily by the natural immune systems of A, B and AB hosts. This asymmetry can explain the relative abundance of O phenotypes in many populations. Our simulation results suggest that both types of transmission may be needed to generate and maintain the present range of *A*, *B* and *O* allele frequencies seen in human populations.

2. MODEL

(a) *Bacterial pathogens*

For simplicity, we first consider a biallelic, *A* and *O*, histo-blood group system, with three genotypes, *AA, AO* and *OO,* giving rise to two phenotypes, A and O (see Appendix A for the *n*-allele case). Consider a population of opportunistic bacteria or other pathogens. The bacteria are assumed to arise in the environment from harmless strains. We model bacterial strains by assigning an integer value u to each strain, where u is the net degree of adaptation. Higher values of u denote better adaptation to O hosts and worse adaptation to A hosts, and lower values of u denote better adaptation to A hosts and worse adaptation to O hosts, subject to the constraint of maximal adaptation, $-m \leqslant u \leqslant m$.

After the passage of a u bacterium through an A host, a fraction μ of its progeny are $u-1$, as they gain a mutation that better adapts them to A hosts. By contrast, passage through an O host generates a fraction μ of $u+1$ progeny. The conditional probability of a mutation from strain v to strain u within a host of genotype PQ is denoted by $\kappa_u^{PQ,v}$. Hence the mutation probabilities after passage through an A host are $\kappa_{v-1}^{AA,v} = \kappa_{v-1}^{AO,v} = 1$ for $v > -m$, and the mutation probability after passage through an O host is $\kappa_{v+1}^{OO,v} = 1$ for $v < m$. No further adaptation occurs once maximal adaptation has been achieved, so that $\kappa_{-m}^{AA,-m} = \kappa_{-m}^{AO,-m} = \kappa_{m}^{OO,m} = 1$. Crucially, we assume that the bacteria cannot achieve optimal adaptation to a particular host type through single mutations, so $m > 1$.

Infected individuals suffer a number of fitness costs. First, they are assumed not to reproduce (very ill people are unlikely to reproduce, though they can recover without loss of fitness). Second, they die with a probability that depends on the degree of adaptation of the infecting bacterial strain. We investigate the extreme situation where only fully adapted bacteria kill infected hosts. Designating $\delta_{PQ,u}$ as the probability of death of a host of genotype PQ infected with bacteria of strain u, the death rates caused by bacteria with maximal adaptation are $\delta_{AA,-m} = \delta_{AO,-m} = \delta_{OO,m} = \delta_m > 0$; otherwise $\delta_{PQ,u} = 0$.

(b) *Viral pathogens*

In addition, we consider a pathogenic virus that is passed from host to host via contact transmission. We assume that the population is subject to periodic viral epidemics that have their origins in some external source (e.g. immigration of infected individuals).

Again, for simplicity consider a biallelic, *A* and *O*, histo-blood group system (see Appendix A for the *n*-allele case). A virus transmitted from an A host carries A-specific terminal glycosylation on its envelope, unlike virus transmitted from an O host, and so is more likely to be neutralized when infecting an O host that carries anti-A natural antibodies. This leads to differential transmission between host phenotypes. We assume that transmission probabilities depend only on phenotype and not on genotype (i.e. *AA* and *AO* genotypes have the same transmission probabilities). Denoting by $\tau_{\mathrm{Q}}^{\mathrm{P}}$ the transmission rate from a host of phenotype P to a host of phenotype Q, differential transmission implies that $\tau_{\mathrm{A}}^{\mathrm{A}}, \tau_{\mathrm{O}}^{\mathrm{O}}, \tau_{\mathrm{A}}^{\mathrm{O}} > \tau_{\mathrm{O}}^{\mathrm{A}}$, and, in the extreme case, $\tau_{\mathrm{O}}^{\mathrm{A}} = 0$.

As before, we assume that infected individuals do not reproduce. Infected hosts die from the viral infection with a probability γ and recover with a probability ν. The parameters for the model were chosen so that invasion of an initially disease-free population by the virus results in a transient epidemic (i.e. $R_0 < 1$), which dies out over a short period. This allows us to avoid the complications that are likely to arise from an endemic process, involving coevolution between virus and host. The population is subjected to repeated epidemics owing to periodic invasion by the virus. An epidemic is initiated by infection of a proportion of the population independent of genotype. We assume that epidemics are relatively frequent (usually two per host generation).

(c) *Population dynamics*

A standard population-dynamic model is used to follow changes in population size and hence the frequency of each AO genotype. The population is assumed to be under density-dependent selection, which maintains a stable population density. In addition, the different genotypes are subject to selection arising from bacterial and viral infection as set out in §§ 2a and 2b. We track the sizes of the susceptible, bacterial-infected and virus-infected host populations for each genotype. We assume that there is a negligible probability that a host will sustain both types of pathogen simultaneously, and so ignore co-infection. We also follow the evolution of the bacterial population.

(d) *ABO system*

We also study an extended, three-allele (*A*, *B*, *O*), system based on the same principles as the two-allele model described in §§ 2a–c. Initially the bacteria are not adapted to any of the four phenotypes. As before, the passage of bacteria through an O host improves adaptation to O hosts and decreases adaptation to A, B and AB hosts. Similarly, mutually antagonistic mutations accumulate after infection of other host phenotypes.

For the three-allele system with differential transmission of the virus, we assume that there is reduced contact transmission from an infected host to a susceptible host if the susceptible host has natural antibodies against the infected host's pattern of terminal glycosylation. This implies that $\tau_{\mathrm{A}}^{\mathrm{A}}, \tau_{\mathrm{B}}^{\mathrm{B}}, \tau_{\mathrm{O}}^{\mathrm{O}}, \tau_{\mathrm{AB}}^{\mathrm{AB}}, \tau_{\mathrm{A}}^{\mathrm{O}}, \tau_{\mathrm{B}}^{\mathrm{O}}, \tau_{\mathrm{AB}}^{\mathrm{O}}, \tau_{\mathrm{AB}}^{\mathrm{B}}$ and $\tau_{\mathrm{AB}}^{\mathrm{A}}$ are greater than $\tau_{\mathrm{O}}^{\mathrm{AB}}, \tau_{\mathrm{A}}^{\mathrm{AB}}, \tau_{\mathrm{B}}^{\mathrm{AB}}, \tau_{\mathrm{B}}^{\mathrm{A}}, \tau_{\mathrm{A}}^{\mathrm{B}}, \tau_{\mathrm{O}}^{\mathrm{A}}$ and $\tau_{\mathrm{O}}^{\mathrm{B}}$.

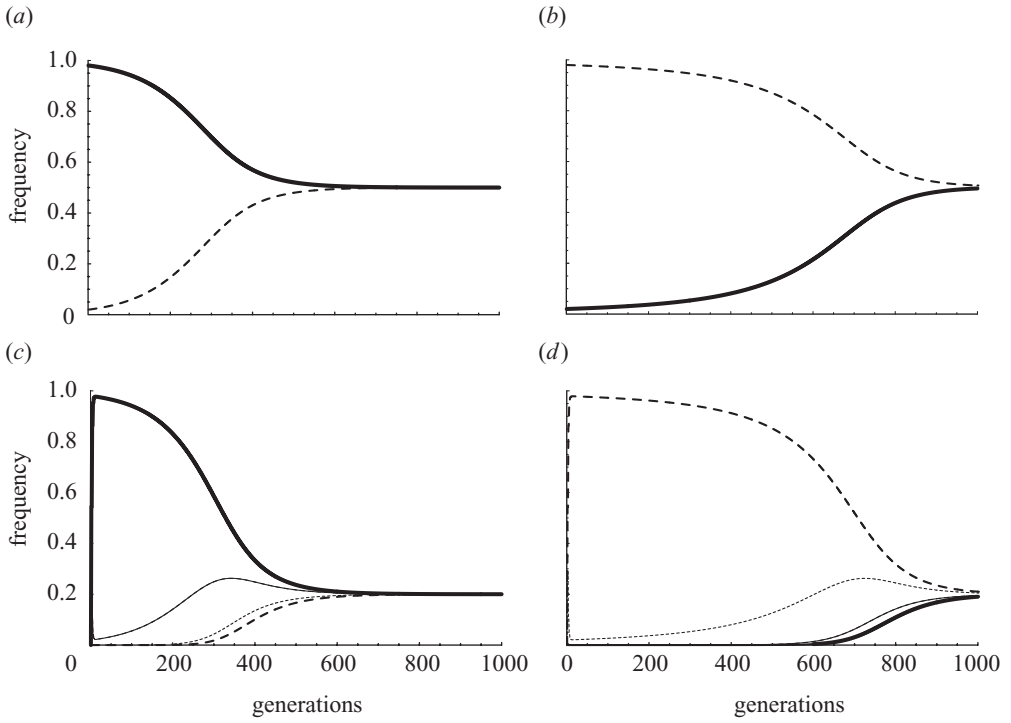

Figure 1. Selection caused by bacteria. (*a*,*b*) Evolution of the frequencies of O (solid line) and A (dashed line) phenotypes under selection from bacteria. Time is measured in 'generations' (the average lifetime of a disease-free host). (*a*) Invasion of A phenotype, and (*b*) invasion of O phenotype (initial frequency of 0.01). The number of mutations for maximum bacterial adaptation is taken to be $m = 2$, and the maximally adapted death rate is $\delta_m = 0.02$. (*c*,*d*) Corresponding frequencies of the bacterial load V_u: dashed line is $u = -2$; dotted line is $u = -1$; thin solid line is $u = 1$; thick solid line is $u = 2$; other parameter values: $K = 10\,000$, $\beta = \delta = 0.01$, $a_0 = 1$, $\delta_V = 0.95$, $\omega = 1/K$, $\mu = 0.01$ (see Appendix A for notation).

Full details of the model assumptions are given in Appendix A. The extra assumptions required for the dynamics of the full model with *A*, *B* and *O* alleles are given in Appendix B. The evolutionary behaviour of the different models was examined by simulation.

3. RESULTS

(a) *Bacterial pathogens*

Whatever the initial frequencies of the *A* and *O* alleles, at equilibrium there is a stable polymorphism (figure 1). The A and O phenotypes have equal frequency at equilibrium, with the frequency of the *A* allele being $x_A = 0.29$. The reason for polymorphism is simple. The environmental bacteria adapt more strongly to whichever phenotype is more common, so this favours the rarer host phenotype. However, this frequency-dependent selection occurs only because ancestral bacterial strains require more than one adaptive step to achieve maximum exploitation of the host. A single-step process maintains the population proportions of host phenotypes, resulting in the non-invadability of monomorphic populations.

Although this mechanism leads to the maintenance of polymorphism, it cannot explain why, in many populations, the O phenotype has a higher frequency than the A (and B) phenotype and is rarely less than 30%, whereas the A (and B) frequency often is (Mourant *et al.* 1976).

(b) *Viral pathogens*

Simulations were first run excluding the possibility of bacterial infection. For differential transmission of a virus, we assume that the transmission rates τ_A^A, τ_O^O and τ_A^O are all equal to a constant $\tau > 0$, and $\tau_O^A = 0$. As expected, differential transmission results in a decline in the frequency of A relative to O phenotypes, and, in the long run, the *A* allele is eliminated and the population becomes O monomorphic (figure 2). This result follows whatever the

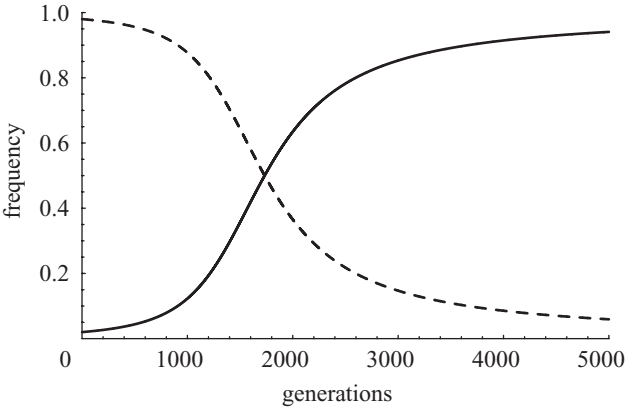

Figure 2. Selection caused by the virus. Evolution of the frequencies of O (solid line) and A (dashed line) phenotypes under selection from the virus. The contact transmission probabilities are τ_A^A, τ_O^O, $\tau_A^O = \tau$ and $\tau_O^A = 0$. The O phenotype is introduced at a frequency of 0.01 and eventually eliminates the A phenotype. Parameter values are as in figure 1 with the addition of $\nu = 0.1$, $\gamma = 0.2$, $\tau = 0.1$, $inf = 0.01$, and virus reinvasion period $T_{inv} = 1/2\delta$ (i.e. two epidemics per uninfected-host average lifetime; see Appendix A for notation). The basic reproductive rate for the viral model is $R_0 = (1 - \beta)(1 - \gamma - \nu)(1 + \tau)$, which gives $R_0 = 0.76$ with these parameter values.

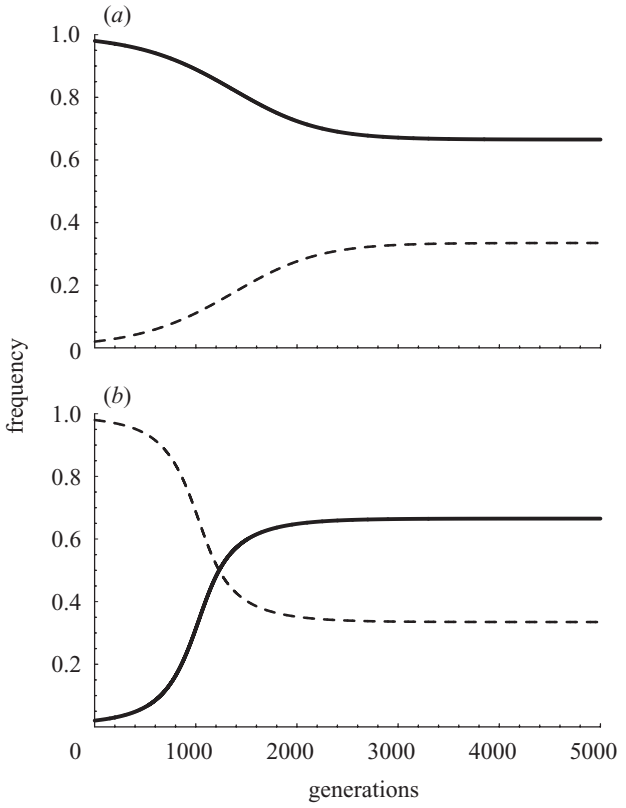

Figure 3. Integrated model. Evolution of the frequencies of O (solid line) and A (dashed line) phenotypes with opportunistic bacteria and differential transmission of the virus. (*a*) Invasion of an O monomorphic population by A, and (*b*) invasion of an A monomorphic population by O. The initial frequency of the invading allele is 0.01. Other parameter values are as in figures 1 and 2.

initial allele frequency, provided that $\tau_{\mathrm{A}}^{\mathrm{A}}, \tau_{\mathrm{O}}^{\mathrm{O}}, \tau_{\mathrm{A}}^{\mathrm{O}} > \tau_{\mathrm{O}}^{\mathrm{A}}$. The conclusion is that differential transmission of a viral agent can explain why there are fewer A than O phenotypes, but not why there are any A phenotypes at all.

(c) *Integrated model*

The integrated model was then simulated, incorporating both bacterial and viral infection. Together these generate a stable blood-group polymorphism with a lower frequency of the A phenotype (figure 3). The difference between the frequencies of A and O phenotypes increases with $\tau = \tau_{\mathrm{A}}^{\mathrm{O}} - \tau_{\mathrm{O}}^{\mathrm{A}}$, the difference between the probability of viral transmission from O to A and that from A to O (figure 4). It also increases with the strength of selection generated by the viral pathogen relative to that caused by the bacterial pathogen. This is shown in figure 4 for fixed mortality effects of the virus and variable mortality with maximum bacterial adaptation (δ_m).

The results described above are general and not dependent on specific model assumptions. We also examined a neutral model of bacterial adaptation, in which the adaptations to A and O hosts are not antagonistic but are independent. We assume that the host population is periodically invaded by opportunistic bacterial pathogens that show no initial difference in adaptation to either host type. The bacteria then adapt to both A and O hosts, with a speed of adaptation that is proportional to the frequency of each host type. As before, this generates frequency-dependent selection in favour of the rarer host type, but at equilibrium A and O phenotypes are equally common. A higher frequency of the O phenotype is seen only in combination with differential viral transmission.

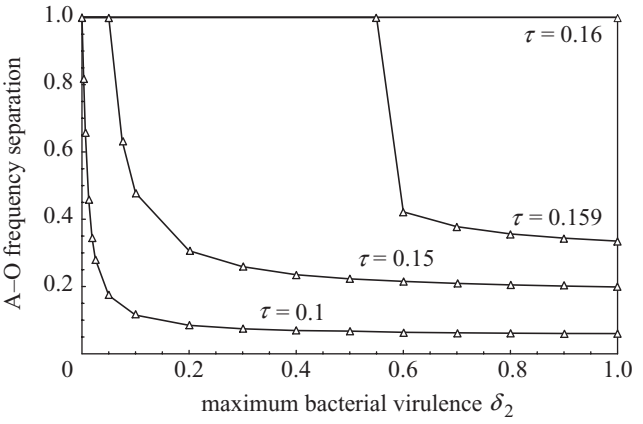

Figure 4. Difference between O and A frequencies. Separation between the stable frequencies of O and A phenotypes for various values of the maximally adapted bacterial virulence δ_m and the viral transmission rate τ. The number of mutations for maximum bacterial adaptation is $m = 2$. Other parameter values are as in figures 1 and 2.

(d) *ABO system*

Simulations of the extended three-allele *ABO* model in the absence of differentially transmitted virus show high equal frequencies of the A and B phenotypes (31%), a lower frequency of the O phenotype (25%) and an even lower frequency of the AB phenotype (13%). At equilibrium, the frequency of the *O* allele (0.5) is twice those of the *A* and *B* alleles (0.25) (figure 5*a*).

For differential transmission of the virus, we assume that transmission rates $\tau_{\mathrm{A}}^{\mathrm{A}}, \tau_{\mathrm{B}}^{\mathrm{B}}, \tau_{\mathrm{O}}^{\mathrm{O}}, \tau_{\mathrm{AB}}^{\mathrm{AB}}, \tau_{\mathrm{A}}^{\mathrm{O}}, \tau_{\mathrm{B}}^{\mathrm{O}}, \tau_{\mathrm{AB}}^{\mathrm{O}}, \tau_{\mathrm{AB}}^{\mathrm{B}}$ and $\tau_{\mathrm{AB}}^{\mathrm{A}}$ are all equal to a constant $\tau > 0$ and that $\tau_{\mathrm{O}}^{\mathrm{AB}}, \tau_{\mathrm{A}}^{\mathrm{AB}}, \tau_{\mathrm{B}}^{\mathrm{AB}}, \tau_{\mathrm{B}}^{\mathrm{A}}, \tau_{\mathrm{A}}^{\mathrm{B}}, \tau_{\mathrm{O}}^{\mathrm{A}}$ and $\tau_{\mathrm{O}}^{\mathrm{B}}$ are all zero.

Given this asymmetry, the frequency of the O phenotype increases relative to those of the other phenotypes as it contains both anti-A and anti-B natural antibodies, whereas the frequency of the AB phenotype decreases as it lacks both anti-A and anti-B natural antibodies. When the effect of the virus is strong relative to that of the bacteria, the frequency of the O phenotype rises until it exceeds those of the A and B phenotypes (figure 5*b*). This model can account for most of the features of the ABO phenotype frequency distribution.

A notable feature of this and the previous models is that there are no oscillations in allele frequency during the approach to equilibrium (cf. Fischer *et al.* 1998). As shown in figures 1, 3 and 5, the approach to equilibrium is monotonic.

4. DISCUSSION

In this study, we have developed a model to examine two potential key selective forces acting on histo-blood group antigens. The first is generated by opportunistic bacterial pathogens (and other microbes) that interact with the epithelial-mucosal surface. These pathogens face a within-host microenvironment that differs according to

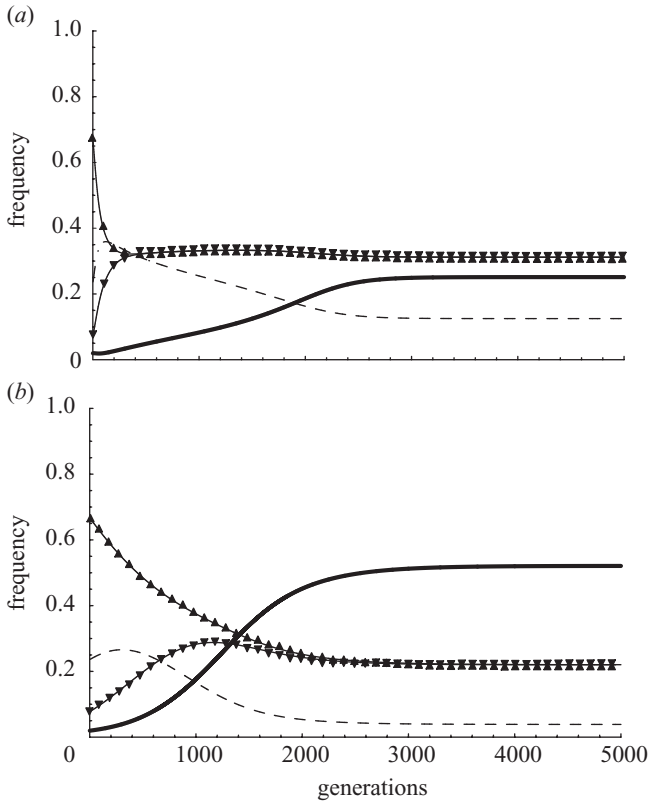

Figure 5. ABO evolution. Evolution of O (solid line), A (up-triangles), B (down-triangles) and AB (dashed line) phenotype frequencies under the influence of (*a*) bacteria alone and (*b*) bacteria and virus. The simulations use the bacterial parameters $m = 2$ and $\delta_m = 0.02$ and the viral transmission rate $\tau = 0.1$. Other parameter values are as in figures 1 and 2 (see Appendix B for details).

host histo-blood group. Host phenotype can potentially affect pathogen cell adhesion and invasion, competition with resident bacteria, host sensitivity to pathogen glycosidase activity and the host's immune function (Henry 2001). The essential idea formalized in our model is that bacteria adapt to common host phenotypes and so create frequency-dependent selection for rarer host phenotypes and hence rarer host alleles. This frequency dependence will maintain host polymorphism when several mutational changes are required for bacteria to adapt to particular host genotypes.

Evidence for these assumptions comes from the observation that the severity of disease is associated with ABO phenotype in several highly pathogenic bacteria, including *Vibrio cholerae* (Glass *et al.* 1985; Swerdlow *et al.* 1994), *Escherichia coli* O157 (Blackwell *et al.* 2002), *Campylobacter jejuni* (Ruiz-Palacios *et al.* 2003) and *Shigella* species (Sinha *et al.* 1991). Some mucosal bacteria express terminal glycan-specific glycosidases that in *Shigella* have been shown to correlate with virulence (Prizont & Reed 1991). In addition, the Lewis system has been associated with some bacterial infections; for example, the Le(b) type appears to be over-represented in patients with disease caused by *Helicobacter pylori* (Rad *et al.* 2002). These relationships are likely to reflect recent evolutionary pressure between microbes and hosts rather than fixed relationships, but this remains to be demonstrated. With respect to the speed of adaptation of bacterial strains to host histo-blood group phenotypes, it is also of interest to note that some bacteria can switch their own glycan phenotype very quickly. Such mechanisms have been described for several common 'mucosal pathogens', e.g. *Neisserias*, *Hemophilus*, *Campylobacter* and *Helicobacter* (Moran *et al.* 1996; Appelmelk *et al.* 1998; Bjorkholm *et al.* 2001). In addition, the Norwalk virus was recently shown to have evolved a similar 'bacterial-like' affinity for one of the ABO histo-blood group antigens (Hutson *et al.* 2003; Lindesmith *et al.* 2003).

The second key selective force we have modelled is generated by viruses, and probably viruses alone. This is required to account for the frequency distribution of ABO phenotypes observed in human populations. It has been suggested that viruses may carry histo-blood group structures as part of their envelope (Springer 1963; Springer & Schuster 1964; Gagneux & Varki 1999). Investigation of an experimental system has shown that the measles virus will pick up the ABO glycosylation pattern of the cell in which it was produced (Preece *et al.* 2002). Furthermore, measles virus emerging from A-specific cells, or from B-specific cells, was neutralized by subsequent exposure to O serum containing anti-A and anti-B natural antibodies (Preece *et al.* 2002). Similar findings were recorded in a study of HIV (Arendrup *et al.* 1991). Furthermore, retroviruses pick up the closely related Galα1,3Gal antigen, as do *rhabdo*, *lenti* and *spuma* viruses (Takeuchi *et al.* 1996, 1997). Thus, a virus released from an A host carries A antigens on its envelope that are recognized by the natural immune systems of O and B hosts, but not A or AB hosts. However, since O hosts lack terminal glycosylation, viruses released from these hosts will not be recognized easily. Consequently O to A, B or AB transmission is likely to be more common than the reverse. Thus, host antigens are likely to cause differential transmission of viruses between histo-blood group types.

These assumptions are strongly supported by previous laboratory and epidemiological data that have drawn connections between bacterial and viral pathogens, and natural antibodies associated with histo-blood group polymorphism (Springer & Horton 1969; Berger *et al.* 1989; Mourant 1989; Arendrup *et al.* 1991; Vogel & Motulsky 1997; Henry 2001; Preece *et al.* 2002). For example, studies have indicated the expected pattern of susceptibility during influenza outbreaks, with AB histo-blood group phenotypes being more affected than O phenotypes (Aho *et al.* 1980; Naikhin *et al.* 1989).

Our model simulations suggest that both opportunistic bacterial infection and differential viral transmission are needed to account for the observed histo-blood group frequency distribution. With only the bacteria, a stable equilibrium is reached with higher frequencies of the A and B phenotypes than of the O phenotype. Although some populations have such a pattern, it is very common to find populations where O is the predominant phenotype. With only the virus, the O phenotype alone persists as the spread of the *O* allele causes the elimination of the *A* and *B* alleles. However, once both forces are combined, a range of phenotype frequencies is possible depending on the relative strength of bacterial and viral selection. If the bacterial force is stronger, A and B phenotypes are most frequent, whereas if the viral force is stronger, the O

phenotype is most frequent. In all cases, the frequency of O never falls below 25%.

These model results capture the diversity of ABO phenotype frequencies found in human populations, as reported in Mourant *et al.* (1976; also Hill & Motulsky 1999). African populations typically display 42–58% O, 21–29% A, 16–26% B and 2–6% AB. Southeast Asians display a similar picture. Europeans and other Asians, in contrast, tend to have less O, but rarely below 30%, with A varying between 20% and 48%, B between 5% and 36%, and AB between 1% and 10%. Amerindians and many isolated island populations have high O phenotype frequencies, from 54% to 100%, with correspondingly low A, B and AB frequencies.

Our model suggests that these patterns are accounted for by varying strengths of selection generated by differential viral transmission. Populations with higher frequencies of the O phenotype are predicted to have suffered greater selection pressure from viral infection than from environmental bacterial infections. Furthermore, previously isolated populations may have been drastically affected by viral epidemics on contact with Europeans (Diamond 1999), leading to strong selection in favour of O phenotypes in these populations. One pattern our model does not explain is the slightly lower frequency of the B allele relative to the A allele. This could be explained by stronger differential transmission to B than to A.

Our findings now need to be rigorously tested at several levels. More careful population-level analyses of the association between ABO types and pathogenic agents are needed. The effect on human disease association should be carefully reassessed, alongside studies of severe epidemics in the wild in other species. Population studies should also address the important issue of whether the source of a viral pathogen can affect the type of individual to which it is transmitted. This could be done with volunteers or in animal models. More cell-culture experimental models should be established, for viruses as well as bacteria, to study in more detail how their glycosylation affects transmission to a new host. Such extended studies promise to shed more light on the evolution of terminal glycosylation in general and histo-blood group polymorphisms in particular. Such studies are also likely to lead to an increased understanding of factors important for the development of future strategies to combat bacterial and viral diseases.

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APPENDIX A

(a) *Basic model*

Consider a single autosomal locus with n alleles $A_1, A_2, \ldots, A_n$. A population of size N is composed of subpopulations of genotypes A_iA_j, of size N_{ij}, with associated genotype frequencies $X_{ij} = N_{ij}/N$ and allele frequencies $x_i = X_{ii} + \frac{1}{2}\Sigma_{j\neq i}X_{ij}$. For notational convenience, we use the population variables $R_{ij} = \frac{1}{2}N_{ij}$ for $i \neq j$ and $R_{ii} = N_{ii}$. If R'_{ij} is the population size after a given discrete time-step, then the basic model is

$$R'_{ij} = R_{ij} + \beta x_i x_j N - \delta(N)R_{ij}. \quad \text{(A 1)}$$

Here, β is the probability that a female produces an offspring in the given time-step, and $\delta(N)$ is the density-dependent probability of death from all causes unrelated to the given locus. The total population size changes to $N' = \Sigma_{i,j}R'_{ij}$, which results in the dynamic

$$N' = N + [\beta - \delta(N)]N. \quad \text{(A 2)}$$

We take $\delta(N) = \frac{1}{2}\delta(1 + N/K)$, where δ and K are fixed constants, and equation (A 2) then results in a stable population density $N^* = (2\beta/\delta - 1)K$, provided that $2\beta > \delta$. Note that $N^* = K$ when $\beta = \delta$ and in this case $1/\delta$ is the expected lifetime of an individual in a population of size K.

(b) *Bacterial pathogens*

Let S_{ij} and $I_{ij,u}$ be the subpopulations of R_{ij} consisting of susceptible hosts and those infected with bacteria of strain u, respectively. Then $R_{ij} = S_{ij} + \Sigma_u I_{ij,u}$. To calculate the number of individuals of genotype A_iA_j infected with bacteria of strain u, we need to account for mutation in the bacteria after they have infected a host. The conditional probability of a mutation from strain v to strain u within a host of genotype A_iA_j is denoted by $\kappa_u^{ij,v}$. The overall probability of a mutation is μ. After infection and mutation, we obtain the following susceptible and infected subpopulations of host genotypes

$$S^0_{ij} = (1 - c_{\text{tot}})S_{ij} \quad \text{(A 3)}$$
$$I_{ij,u} = \left((1 - \mu)c_u + \mu\sum_v \kappa_u^{ij,v}c_v\right)S_{ij},$$

where c_{tot} is the probability of infection of a susceptible host and c_u is the probability of infection by a strain of type u. These probabilities are given by

$$c_{\text{tot}} = \frac{V_{\text{tot}}}{a_0 + V_{\text{tot}}}, \quad c_u = \frac{V_u}{a_0 + V_{\text{tot}}}, \quad \text{(A 4)}$$

where the environmental load of bacteria of strain u is V_u, the total environmental bacterial load is $V_{\text{tot}} = \Sigma_u V_u$ and a_0 is a constant.

The updating time-period is taken to be the reproductive cycle of the invading bacteria:

invasion of host → reproduction within host → possible mutation → discharge of new pathogens into the environment → death or recovery of host.

Thus, an individual infected with bacteria at the beginning of the period either dies or recovers (and again becomes susceptible) by the end of the period. Thus, the full dynamics of host and bacteria are

$$S'_{ij} = \beta x_i^0 x_j^0 N + (1 - \delta(N))\left\{S^0_{ij} + \sum_u (1 - \delta_{ij,u})I_{ij,u}\right\},$$
$$V'_u = (1 - \delta_V)V_u + \omega\sum_{i,j} I_{ij,u}. \quad \text{(A 5)}$$

Here, x_i^0 and x_j^0 refer to the allele frequencies in the susceptible S^0 subpopulation, $\delta_{ij,u}$ is the probability of death of a host of genotype A_iA_j infected with bacteria of strain u, δ_V is the environmental death rate of bacteria and ω is the reproductive output of bacteria from infected individuals.

Note that, with $\beta = \delta$ and $N^* = K$, $n_V = 1/\delta$ is the number of bacterial reproductive cycles in the average lifetime of an uninfected host in a disease-free equilibrium population. In our simulations we take $n_V = 100$, and hence $\beta = \delta = 0.01$ (figure 1). This is on the small side for n_V with respect to the average lifetime of a human. However, this value was chosen to reduce the computational requirements of the simulation, and is sufficient to indicate that the average host will be exposed to a large number of potential infection opportunities during its lifetime. Also, by rescaling V if necessary, ω in equation (A 5) can be fixed arbitrarily. We set $\omega = 1/K$. Taking $\delta_V < 1$ means that a bacterium can persist outside a host for a period longer than its reproductive life cycle. This has the effect of making the bacterial invasion endemic. However, the same effect can be achieved with $\delta_V = 1$ by decreasing a_0, so our results do not depend on this feature.

(c) *Viral pathogens*

Let $\mathcal{J}_{ij}$ be the subpopulation of R_{ij} infected with the virus. We assume that there is a negligible probability that a host will sustain both types of pathogen simultaneously, and so ignore co-infection. Then $R_{ij} = S_{ij} + \Sigma_u I_{ij,u} + \mathcal{J}_{ij}$. Let $Z_{ij} = \mathcal{J}_{ij}/N$ be the infected proportion.

To calculate $\mathcal{J}_{ij}$ in the next time-period, we take into account possible differential transmission of the virus between host genotypes. Let τ_{ij}^{kl} be the probability of transmission (per time-step) from an infected host of genotype A_kA_l to a susceptible host of genotype A_iA_j. Then equation (A 3) is augmented to

$$S_{ij}^0 = \left\{1 - c_{\text{tot}} - \sum_{k,l} \tau_{ij}^{kl} Z_{kl}\right\} S_{ij},$$
$$\mathcal{J}_{ij}^0 = \mathcal{J}_{ij} + S_{ij} \sum_{k,l} \tau_{ij}^{kl} Z_{kl}. \qquad \text{(A 6)}$$

As before, we assume that infected individuals do not reproduce and that they die from the viral infection with probability γ and recover with probability ν. These extra selective forces can be incorporated into equation (A 5):

$$S'_{ij} = \beta x_i^0 x_j^0 N + (1 - \delta(N))\left\{S_{ij}^0 + \sum_u (1 - \delta_{ij,u}) I_{ij,u} + \nu \mathcal{J}_{ij}^0\right\},$$
$$\mathcal{J}'_{ij} = (1 - \delta(N))(1 - \nu - \gamma)\mathcal{J}_{ij}^0. \qquad \text{(A 7)}$$

An epidemic is initiated by the infection of a proportion of susceptibles:

$$S_{ij} \rightarrow (1 - inf)\, S_{ij},$$
$$\mathcal{J}_{ij} \rightarrow \mathcal{J}_{ij} + inf S_{ij}, \qquad \text{(A 8)}$$

where *inf* is a (small) constant proportion.

APPENDIX B

In the three-allele *ABO* model, bacteria adapt to the four host phenotypes through mutually antagonistic mutations. Bacterial strains are labelled by a pair of indices $(s,0)$ or $(0,s)$ with $-m \leqslant s \leqslant m$. Decreasing s for strains of type $(s,0)$ implies increasing adaptation to A phenotypes, and increasing s implies increasing adaptation to B phenotypes. Similarly, decreasing s for $(0,s)$ strains implies increasing adaptation to AB phenotypes, and increasing s implies increasing adaptation to O phenotypes. Maximal adaptation occurs when $s = \pm m$. Thus, bacteria of type (0,0) that acquire a mutation on passing through a host produce progeny of type (0,1) if the host phenotype is O, of type $(0, -1)$ if the host phenotype is AB, of type $(-1,0)$ if the host phenotype is A and of type (1,0) if the host phenotype is B. Bacteria of type $(s,0)$ with $-m < s < 0$ that acquire a mutation produce progeny of type $(s - 1,0)$ if the host phenotype is A and of type $(s + 1,0)$ if the host has any other phenotype. Bacteria of type $(s,0)$ with $0 < s < m$ that acquire a mutation produce progeny of type $(s + 1,0)$ if the host phenotype is B and of type $(s - 1,0)$ if the host has any other phenotype. Similar remarks apply to $(0,s)$ with respect to passage through AB or O hosts. This scheme leads to strain-dependent host death rates $\delta_{ij,u}$ with $u = (0,s)$ or $(s,0)$. Non-zero values used in the simulations are $\delta_{OO,(0,m)} = \delta_{AB,(0,-m)} = \delta_m$ and $\delta_{AA,(-m,0)} = \delta_{AO,(-m,0)} = \delta_{BO,(m,0)} = \delta_{BB,(m,0)} = \delta_m$ with $\delta_m > 0$.

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