**SUPPLEMENTARY TABLES**

**Table** **A:** Studies in which non-overlapping associations between serotype and markers of metabolic type (ST = Multi Locus Sequence Type (1); ET = Multi Locus Enzyme Electrophoresis type (2)) were observed among *Streptococcus pneumoniae.*

|  |  |  |  |
| --- | --- | --- | --- |
| Metabolic type | Country/countries included in study | No. isolates | Reference |
|  |  |  |  |
| ST | USA | 616 | (3) |
| ST | Scotland | 217 | (4) |
| ST | Australia, Canada, Denmark, Finland, the Netherlands, Sweden, Great Britain and Uruguay | 274 | (5) |
|  |  |  |  |
| ST | UK | 30 | (6) |
|  |  |  |  |
| ST | UK | 501 | (7) |
|  |  |  |  |
| ST | UK | 310 | (8) |
| ST | USA | 1168 | (9) |
|  |  |  |  |
| ST | Finland | 224 | (10) |
| ST | Finland | 437 | (11) |
|  |  |  |  |
| ST | Columbia | 629 | (12) |
| ST  ST  ST  ET | UK  Japan  Taiwan  Spain, Hungary, USA | 1030  66  68  342 | (13)  (14)  (15)  (49) |
|  |  |  |  |

**Table** **B:** Associations among antigenic and metabolic genes for 17 pathogenic and non-pathogenic bacterial species. ST refers to sequence type; ET refers to electrophoretic type. Clonal complex refers to a group of highly similar STs which share identical MLST alleles at several loci.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Pathogen | Antigenic Type | Metabolic Type | No. isolates | Reference |
| *Neisseria meningitidis* | PorA (outer membrane protein) | Clonal complex | 977 | (17) |
|  | PorA, FetA (outer membrane proteins) | Clonal complex | 3460 | (18) |
|  | fHbp (factor H binding protein) | Clonal complex | 107 | (19) |
|  | Opa (opacity related protein) | Clonal complex | 77 | (20) |
| *Staphylococcus aureus* | Spa types (Staphylococcal Protein A), ClfA & ClfB (clumping factor A & B) | Clonal complex | 224 | (21) |
|  | Spa types | ST | 182 | (22) |
| *Streptococcus pyogenes* | Emm types (M protein) | ST | 495 | (23) |
|  | Emm types (M protein) | ST | 212 | (24) |
| *Salmonella enterica* | Serovar (O and H antigens) | eBGs (eBurstGroups) | 4257 | (25) |
| *Haemophilus*  *influenzae* | Serotype | ET | 2209 | (26) |
|  | Serotype | Clonal complex | 131 | (27) |
| *Helicobacter pylori* | CagA | ST | 129 | (28) |
| *Eschericha coli* | O antigen (lipopolysaccharide) | ET | 187 | (29) |
|  |  |  |  |  |
| *Clostridium difficile* | Surface-Associated Protein A (slpA) | ST | 42 | (30) |
| *Listeria monocytogenes* | Serotype (somatic (O) antigen and flagellar (H) antigen) | ET | 175 | (31) |
| *Neisseria gonorrhoeae* | 11 Opa genes (opacity related protein) | ST | 14 | (32) |
|  |  |  |  |  |
| *Klebsiella pneumoniae* | Serotype (C pattern) | ST | 63 | (33) |
| *Campylobacter jejuni* | porA (outer membrane protein) | Clonal complex | 584 | (34) |
| *Neisseria lactamica* | FetA | ST | 275 | (35) |
|  |  |  |  |  |
| *Enterococcus faecium* | ace, salA, lsa (collagen/laminin adhesin; a cell wall-associated antigen; putative ABC transporter) | ST | 50 | (36) |
| *Streptococcus dysgalactiae subsp. Equisimilis* | Emm types (M protein) | ST | 334 | (37) |
| *Pasteurella trehalosi* | Serotype, outer membrane protein, LPS | ET | 60 | (38) |
| *Capnocytophaga species* | igA protease | ET | 50 | (39) |

**Table** **C:** Alleles of 21 virulence-associated loci that have increased in frequency (%) among non-vaccine strains, potentially through VIMS. T refers to alleles which have been truncated; X refers to alleles not present in the genomic assembly.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Vaccine strain | Non-vaccine strains | | Vaccine strain | Non-vaccine strains | | |
| Locus | Genome position | 19F ST320 | 19A ST320 | 19A ST199 | 9V ST156 | 19A ST1925 | 15/AB ST162 or 3275 | 15A/B ST199 |
| nanA | SPN23F12210 | 1189320 | 29 (0.9) | 29 (100) | 3 (0.91) | 8 (100) | 8 (100) | 2 (100) | 2 (0.81) |
| bgaA | SPN23F05830 | 571752 | 21 (100) | 21 (100) | 2 (0.91) | 9 (100) | 9 (100) | 9 (100) | 2 (0.65) |
| strH | SPN23F00730 | 69102 | 45 (0.9) | 45 (100) | 1 (0.8) | 23 (0.6) | 23 (100) | 23 (0.75) | 1 (0.83) |
| SPN23F02890 | 274732 | 19 (100) | 81 (100) | 1 (0.77) | 1 (0.8) | 1 (100) | 42 (100) | 2 (0.6) |
| fbpS | pavA | SPN23F08910 | 864927 | 17 (100) | 17 (100) | 2 (100) | 4 (100) | 4 (100) | 4 (100) | 2 (0.81) |
| eno | SPN23F10490 | 1012087 | 13 (100) | 13 (100) | 1 (100) | 8 (100) | 8 (100) | 8 (100) | 1 (100) |
| ply | SPN23F19470 | 1889503 | 12 (100) | 12 (100) | 2 (100) | 8 (0.8) | 8 (100) | 8 (100) | 2 (0.96) |
| lytA | SPN23F19600 | 1898038 | 1 (100) | 1 (100) | 3 (0.86) | 9 (100) | 3 (100) | 9 (50) | 3 (0.75) |
| nanB | SPN23F16870 | 1626581 | 37 (100) | 37 (100) | 3 (0.91) | 10 (100) | 10 (100) | 10 (100) | 3 (0.65) |
| SPN23F06940 | 681761 | 12 (100) | 12 (100) | 1 (100) | 8 (100) | 8 (100) | 8 (100) | 1 (0.92) |
| lytB | SPN23F08900 | 862890 | 59 (100) | 59 (100) | 1 (100) | 11 (100) | 11 (100) | 11 (100) | 1 (0.63) |
| cbpE | SPN23F08530 | 834686 | 30 (100) | 30 (100) | 1 (0.94) | 9 (100) | 9 (100) | 9 (100) | 1 (100) |
| phtE | SPN23F09300 | 898830 | 52 (100) | 23 (100) | 2 (0.94) | 3 (100) | 3 (100) | 3 (100) | 2 (0.94) |
| gapN | SPN23F10400 | 1002438 | 17 (100) | 17 (100) | 1 (0.94) | 9 (100) | 9 (100) | 9 (75) | 1 (0.98) |
| SPN23F04520 | 435720 | 23 (100) | 23 (100) | 26 (0.91) | 12 (100) | 47 (100) | 52 (100) | 2 (0.6) |
| ccpA | SPN23F20200 | 1959921 | 4 (100) | 4 (100) | 1 (100) | 1 (100) | 1 (100) | 1 (100) | 1 (0.98) |
| pcpA | SPN23F21690 | 2108466 | 23 (0.22) | 15 (50) | 28 (0.14) | T (0.8) | T (50) | 62 (50) | 3 (0.1) |
| cbpD | SPN23F22340 | 2181850 | X (100) | 29 (100) | 1 (0.97) | 8 (0.8) | 8 (0.75) | 8 (100) | 1 (0.71) |
| htrA | SPN23F22720 | 2219291 | 4 (100) | 4 (100) | 2 (100) | 8 (100) | 8 (100) | 8 (75) | 2 (100) |
| cbpJ | SPN23F03490 | 340640 | 33 (0.67) | 33(100) | 7 (0.91) | 1 (100) | 7 (100) | 20 (100) | 2 (0.21) |
| cbpG | SPN23F03640 | 352443 | 39 (0.67) | 39(100) | 21 (0.97) | 10 (100) | 21 (100) | 10 (100) | 2 (0.94) |

**Table D:** Outputs of the two-tailed Sign Tests comparing the average proportion of metabolic/transport alleles which are identical at a given locus (MPI), between isolates of the same serotype and randomly-selected isolates. The tests were performed for the most common serotypes in the dataset published by Croucher *et al.*(1). The sample estimate refers to the point estimate of the median difference between the two lists of modal percentage identities.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Test | No. positive differences | No. negative differences | Ties | Test statistic | Standardised test statistic | Sample estimate | Upper achieved confidence interval (0.9509) | P-value (2-sided) |
| 3 - Random | 770 | 10 | 2 | 770 | 27.17 | 0.71 | 0.71 - 0.80 | < 2.2e-16 |
| 14 - Random | 777 | 3 | 2 | 777 | 27.68 | 0.70 | 0.70 - 0.78 | < 2.2e-16 |
| 35F - Random | 780 | 0 | 2 | 780 | 27.89 | 0.74 | 0.70 - 0.74 | < 2.2e-16 |
| 9V - Random | 764 | 15 | 3 | 764 | 26.8 | 0.70 | 0.70 - 0.70 | < 2.2e-16 |
| 22F - Random | 778 | 2 | 2 | 778 | 27.75 | 0.70 | 0.70 - 0.70 | < 2.2e-16 |
| 11A - Random | 778 | 1 | 3 | 778 | 27.8 | 0.66 | 0.66 - 0.68 | < 2.2e-16 |
| 35B - Random | 780 | 0 | 2 | 780 | 27.89 | 0.70 | 0.69 - 0.70 | < 2.2e-16 |
| 15A - Random | 775 | 2 | 5 | 775 | 27.7 | 0.66 | 0.66 - 0.70 | < 2.2e-16 |
| 15B/C - Random | 769 | 10 | 3 | 769 | 27.16 | 0.53 | 0.52 - 0.53 | < 2.2e-16 |
| 23F - Random | 756 | 18 | 8 | 756 | 26.49 | 0.38 | 0.35 - 0.40 | < 2.2e-16 |
| 19A - Random | 770 | 11 | 1 | 770 | 27.12 | 0.41 | 0.40 - 0.42 | < 2.2e-16 |
| 19F - Random | 772 | 58 | 2 | 772 | 23.74 | 0.25 | 0.23 - 0.25 | < 2.2e-16 |
| 10A - Random | 748 | 20 | 14 | 748 | 26.23 | 0.36 | 0.31 - 0.36 | < 2.2e-16 |
| 6B - Random | 726 | 55 | 1 | 726 | 23.97 | 0.22 | 0.22 - 0.22 | < 2.2e-16 |
| 6C - Random | 741 | 39 | 2 | 741 | 25.1 | 0.25 | 0.25 - 0.25 | < 2.2e-16 |
| 6A - Random | 687 | 93 | 2 | 687 | 21.23 | 0.18 | 0.18 - 0.18 | < 2.2e-16 |

**Table E:** The percentage of metabolic/uptake alleles shared between pairs of serotypes. Loci in which alleles were truncated or absent were excluded from the analysis, providing a total of 756 loci. Serotypes comprising more than one metabolic type were excluded, as the modal metabolic profile is not a legitimate representation of the metabolic traits for these serotypes. The percentage of identical metabolic/uptake alleles shared across serotypes was relatively low (with any two serotypes sharing 10.1% of their metabolic/uptake alleles on average), and significantly less than 1 (Wilcoxon Mann Whitney test, V = 1540, p-value < 1.129e-10).

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **3** | **14** | **11A** | **15A** | **15B/C** | **19A** | **22F** | **23F** | **35F** | **9V** | **35B** |
| **3** | 1 | 0.077 | 0.085 | 0.057 | 0.070 | 0.077 | 0.070 | 0.085 | 0.089 | 0.028 | 0.078 |
| **14** | 0.077 | 1 | 0.120 | 0.104 | 0.097 | 0.131 | 0.083 | 0.086 | 0.079 | 0.074 | 0.093 |
| **11A** | 0.085 | 0.120 | 1 | 0.192 | 0.112 | 0.110 | 0.091 | 0.083 | 0.122 | 0.078 | 0.097 |
| **15A** | 0.057 | 0.104 | 0.192 | 1 | 0.091 | 0.102 | 0.079 | 0.085 | 0.094 | 0.077 | 0.093 |
| **15B/C** | 0.070 | 0.097 | 0.112 | 0.091 | 1 | 0.806 | 0.106 | 0.142 | 0.086 | 0.103 | 0.104 |
| **19A** | 0.077 | 0.131 | 0.110 | 0.102 | 0.806 | 1 | 0.107 | 0.143 | 0.077 | 0.120 | 0.106 |
| **22F** | 0.070 | 0.083 | 0.091 | 0.079 | 0.106 | 0.107 | 1 | 0.110 | 0.094 | 0.075 | 0.146 |
| **23F** | 0.085 | 0.086 | 0.083 | 0.085 | 0.142 | 0.143 | 0.110 | 1 | 0.085 | 0.090 | 0.091 |
| **35F** | 0.089 | 0.079 | 0.122 | 0.094 | 0.086 | 0.077 | 0.094 | 0.085 | 1 | 0.086 | 0.097 |
| **9V** | 0.074 | 0.074 | 0.078 | 0.077 | 0.103 | 0.120 | 0.075 | 0.090 | 0.086 | 1 | 0.078 |
| **35B** | 0.078 | 0.093 | 0.097 | 0.093 | 0.104 | 0.106 | 0.146 | 0.091 | 0.097 | 0.078 | 1 |

**Table F:** Outputs of the two-tailed Sign Tests comparing the average proportion of metabolic/transport alleles which are identical at a given locus (MPI), between isolates of the same ST and randomly-selected isolates. The tests were performed for the most common STs in the dataset published by Croucher *et al.*(3). The sample estimate refers to the point estimate of the median difference between the two lists of modal percentage identities.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Test | No. positive differences | No. negative differences | Ties | Test statistic | Standardised test statistic | Sample estimate | Upper achieved confidence interval (0.9566) | P-value (2-sided) |
| ST36 - Random | 758 | 2 | 9 | 758 | 27.39 | 0.70 | 0.70 - 0.70 | < 2.2e-16 |
| ST62 - Random | 762 | 3 | 4 | 762 | 27.41 | 0.68 | 0.66 - 0.68 | < 2.2e-16 |
| ST63 - Random | 762 | 2 | 5 | 762 | 27.46 | 0.70 | 0.70 - 0.70 | < 2.2e-16 |
| ST180- Random | 763 | 0 | 6 | 763 | 27.59 | 0.70 | 0.70 - 0.70 | < 2.2e-16 |
| ST199 - Random | 754 | 13 | 2 | 754 | 26.72 | 0.62 | 0.60 - 0.64 | < 2.2e-16 |
| ST433 - Random | 757 | 6 | 6 | 757 | 27.15 | 0.68 | 0.64 - 0.70 | < 2.2e-16 |
| ST558 - Random | 763 | 2 | 4 | 763 | 27.48 | 0.70 | 0.70 - 0.71 | < 2.2e-16 |
| ST498 - Random | 763 | 0 | 6 | 763 | 27.58 | 0.70 | 0.70 - 0.70 | < 2.2e-16 |
| ST460 - Random | 763 | 6 | 0 | 763 | 27.26 | 0.64 | 0.64 - 0.64 | < 2.2e-16 |
| ST320 - Random | 760 | 3 | 6 | 760 | 27.37 | 0.70 | 0.70 - 0.70 | < 2.2e-16 |
| ST338 - Random | 758 | 6 | 5 | 758 | 27.17 | 0.62 | 0.62 - 0.70 | < 2.2e-16 |
| ST393 - Random | 763 | 1 | 5 | 763 | 27.53 | 0.70 | 0.70 - 0.70 | < 2.2e-16 |
| ST439 - Random | 760 | 5 | 5 | 760 | 27.26 | 0.62 | 0.60 - 0.65 | < 2.2e-16 |
| ST695 - Random | 763 | 0 | 6 | 763 | 27.59 | 0.70 | 0.70 - 0.78 | < 2.2e-16 |

**Epidemiological Model**

The following diagram shows an SIR based representation of a system with two antigenic alleles (e.g. capsular serotypes), *a* and *b*, and two metabolic alleles, 1 and 2, thus yielding a total of four possible strains (*a1, a2, b1* and *b2*). The host population is divided into a susceptible class (S), ten infected classes (Ya1, Ya2, Yb1, Yb2, Ya1b2, Ya2b1; Va1, Va2, Vb1, Vb2), and three immune classes (Za, Zb; Zab). For clarity, the host birth and death processes are not shown. The shaded area contains all individuals who have been infected with and are subsequently no longer susceptible to serotype *a*.



Susceptible hosts (S) become infected with strain *a1*, for example, at the rate λa1= βa1 (Ya1+ Ya1b2 +Va1) where Y and V refer to primary and secondary infections with designated strains/strain combinations and βa1 is a transmission coefficient. Recovery occurs at a rate σ and leads to serotype-specific immunity, such that individuals in Za can no longer be infected by a strain of serotype *a*, and individuals in Zab are immune to both *a* and *b*.

Additionally, individuals who are currently infected by a particular metabolic type cannot be co-infected by a strain with the same metabolic type due to direct resource competition. Thus it is possible to move from Ya1 to Ya1b2 but not to Ya1b1. As an example, a susceptible individual (S) who becomes infected with strain *a1* (Ya1) can either: (i) become co-infected with strain *b2* (Ya1b2) and move directly to Zab, or (ii) clear the infection and gain immunity to a (Za), before later becoming infected with *b1* (Vb1) or *b2* (Vb2). Through either route, the individual can ultimately gain immunity to both *a* and *b* (Zab).

SIR formulations do not lend themselves to extension to multiple strains and many different srategies have been developed to overcome this problem (40). Here, we use an overlapping compartmental framework developed by Gupta et al (41) to recast these equations in the following manner:

Let *za* contain all individuals who have been infected with antigenic type *a*, as shown by the shaded area in the flow diagram,and *ya1* contain all individuals currently infected with *a1*:

Since *ya1= Ya1 + Ya1b2 + Va1,*we obtain:

by adding:

Since S + Y*b2*+ Z**b** = 1- *za* - Yb1 = 1-*za* - *yb1*(1-*za* - *ya1*) we can write:

|  |  |
| --- | --- |
|  | (S3) |
|  | (S4) |

Equations for other strains follow a similar form with λij= βijyij and the basic reproduction number R0 = βij/σij with βij= *f*(βi, βj) and σij = *g*(σi, σj) where *i* indicates it is a property associated with AT, and *j* with MT. These may be simplified further under the approximation: *yb1*(1-*za* - *ya1*) ≈ *yb1*(1-*za*), yielding eqns (1-2) in the main text .

This model may be extended to relax the strength of immunological and direct resource competition by introducing the parameters  and γ, respectively specifying the degree of resistance against co-infection by the same metabolic type and the level of strain-specific immunity.

|  |  |
| --- | --- |
|  | (S5) |
|  | (S6) |

Once again these may be further simplified using the approximation: *yb1*(1-*za* - *ya1*) ≈ *yb1*(1-*za*).

For the case  = γ = 1, we were able to validate the results using the SIR framework, and these were also in agreement with those obtained from a stochastic model containing the same assumptions published by Buckee *et al*. (17). In the latter, the antigenic type was characterised by multiple loci, which allowed transitions between different non-overlapping states to occur. This dynamical behavior may explain some of the natural historical variation in pneumococcal populations (41), but for the purposes of elucidating the effects of vaccination we stick to a single antigenic locus in our analysis.

This framework may be extended to accommodate additional alleles or to accomodate non-capsular virulence factors in the following manner:

|  |  |
| --- | --- |
|  | (S7) |
|  |  |
|  | (S8) |
|  |  |

We assume that infection by a particular strain (e.g. *a1+*) can only occur among individuals who are not immune or infected with the same serotype (i.e. 1-za), thus *j* represents the serotype of strain *i*. We also assume that infection cannot occur among individuals currently infected by other strains with either the same metabolic type or virulence factor (denoted in the equations above by *k*) and encompassing, for example *b1+, b2+, b1-, c1+, c1-, etc* for strain *a1+*.

**Supporting References**

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