Supplementary Material

Table S2: Hypotheses to explain classic epidemiological patterns: 1) host-directed acquired immunity, 2) differential exposure of hosts, 3) differential mortality, 4) progressive pathology, 5) concomitant immunity and reproductive senescence. For each observed epidemiological pattern (columns), an X indicates whether a hypothesis can plausibly explain it, and a (?) indicates a potential to explain it under some but not all circumstances. The number of patterns explained is a measure of parsimony. The final two columns list evidence supporting and refuting each hypothesis: modeling studies, human epidemiological studies, *in vitro* studies, animal model studies, and meta-analyses. Among the hypotheses examined, the most parsimonious are those involving immunity (host-directed or concomitant): (1a) host-directed anti-worm immunity, (1b) host-directed anti-fecundity immunity, and (5) concomitant immunity plus reproductive senescence (the hypothesis presented in this paper). However, no single hypothesis is unequivocally supported by the evidence.

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| Hypothesis category | Hypothesis description | Host role | Worm role |  |  | Can it explain? | | |  | |  | |  | |  |  | |  | |  | Evidence for | | Evidence against | |
|  |  |  |  | Peak egg output at school age | Peak shift | Overshoot | Peak worm burden at school age | Decline in worm burden among older adults >30-40yrs | | Decline in (fecal/ urinary) egg output among older adults  >30-40yrs | | Decline in apparent worm fecundity in adults | | Pre-treatment intensity is predictive of post-treatment intensity in individuals | | | Observed lower reinfection in older individuals | | Observed fast rebound in human population after PZQ (“hotspots”) | | |  | |  | |
| (1) host-directed acquired immunity | (a) delayed, host-driven "classical" acquired immunity to dead/dying worms | active | passive | X | X | (?)\* | X |  | |  | |  | | X | | | X | |  | | | Modeling:[1-3](#_ENREF_1)  Epidemiology:[3-13](#_ENREF_3)  Lab animal:  In vitro: [14](#_ENREF_14)  Meta-analysis: | | Modeling: [15](#_ENREF_15), [16](#_ENREF_16)  Epidemiology:[17-21](#_ENREF_17)  Lab animal: [9](#_ENREF_9), [22](#_ENREF_22)  In vitro:  Meta-analysis: [23](#_ENREF_23) | |
|  | (b) delayed, host-driven, "anti-fecundity" acquired immunity driven by either: epitopes revealed as worms die, OR epitopes on eggs (or both?) | active | passive | X | X | (?)\* | X |  | |  | | X | | X | | | X | |  | | | Modeling: [3](#_ENREF_3), [24](#_ENREF_24), [25](#_ENREF_25)  Epidemiology: [7](#_ENREF_7), [8](#_ENREF_8), [26](#_ENREF_26), [27](#_ENREF_27)  Lab animal:[28-30](#_ENREF_28)  In vitro:  Meta-analysis: | | Modeling:  Epidemiology:[31](#_ENREF_31)  Lab animal:[32](#_ENREF_32)  In vitro:  Meta-analysis: | |
|  | (c) innate susceptibility changes due to puberty hormones in people | passive | passive | X |  |  | X |  | |  | |  | | X | | | X | |  | | | Modeling:  Epidemiology:[33](#_ENREF_33)  Lab animal:  In vitro:  Meta-analysis: | | Modeling:  Epidemiology:[7](#_ENREF_7)  Lab animal:  In vitro:  Meta-analysis: | |
|  | (d) cross reactivity of invading cercariae to adult worm antigens; depending on the length of time those antibodies circulate, it could be concomitant or acquired. | passive | passive | X | X |  | X |  | |  | |  | | (?) | | | (?) | | (?) | | | Modeling:  Epidemiology: [34](#_ENREF_34)  Lab animal:  In vitro:  Meta-analysis: | | Modeling:  Epidemiology:  Lab animal:  In vitro:  Meta-analysis: | |
|  | (e) cross reactivity of invading cercariae to egg antigens decrease recruitment success; depending on the length of time those antibodies circulate, it could be concomitant or acquired. | passive | passive | X | X |  | X |  | |  | |  | | (?) | | | (?) | | (?) | | | Modeling:  Epidemiology:  Lab animal:  In vitro: [35](#_ENREF_35)  Meta-analysis: | | Modeling:  Epidemiology:  Lab animal:  In vitro:  Meta-analysis: | |
| (2) differential exposure | differential exposure - water contact patterns | active | passive | X |  |  | X | X | | X | |  | | X | | | X | | X | | | Modeling: [36](#_ENREF_36), [37](#_ENREF_37)  Epidemiology: [38](#_ENREF_38)  Lab animal:  In vitro:  Meta-analysis: | | Modeling: [39](#_ENREF_39)  Epidemiology:[11](#_ENREF_11)  Lab animal:  In vitro:  Meta-analysis: | |
| (3) differential mortality of hosts | differential mortality of hosts means that those alive at any one time is biased: older adults are observed if they are less infected because highly infected people already died | passive | passive | X | X |  | X | X | | X | |  | | (?) | | | (?) | | (?) | | | Modeling:  Epidemiology:  Lab animal:  In vitro:  Meta-analysis: | | Modeling:  Epidemiology:  Lab animal:  In vitro:  Meta-analysis: | |
| (4) progressive pathology | progressive pathology that impacts egg passage | passive | passive | X | X |  |  |  | | X | |  | | (?) | | | (?) | | (?) | | | Modeling:  Epidemiology: [26](#_ENREF_26)  Lab animal:  In vitro:  Meta-analysis: | | Modeling:  Epidemiology:[40](#_ENREF_40)  Lab animal:  In vitro:  Meta-analysis: | |
| (5) concomitant immunity + reproductive senescence of worms – this paper’s hypothesis | host-parasite immune interaction/worm life history whereby live adult worms interact with host immune system to prevent superinfection; worms experience reproductive senescence over time | active | active | X | X | X | X |  | |  | | X | | (?) | | | (?) | | X | | | Modeling: [41](#_ENREF_41), [37](#_ENREF_37), [42](#_ENREF_42) [7](#_ENREF_7), this paper  Epidemiology: [8](#_ENREF_8), [10](#_ENREF_10), [26](#_ENREF_26), [40](#_ENREF_40), [43](#_ENREF_43), [44](#_ENREF_44)  Lab animal: [22](#_ENREF_22), [29](#_ENREF_29), [30](#_ENREF_30), [45-52](#_ENREF_45)  In vitro:  Meta-analysis: | | Modeling:  Epidemiology: [5](#_ENREF_5), [11](#_ENREF_11), [31](#_ENREF_31), [53](#_ENREF_53), [54](#_ENREF_54)  Lab animal:  In vitro:  Meta-analysis: | |

\*slower than observed

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