Modelling adversarial dynamics in natural and artificial immunity

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A thesis submitted for the degree of
Doctor of Philosophy

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Abstract

Immunity is both a lens to understand the ecology of adversarial host-pathogen interactions, but also a lever for clinical intervention in combating infectious disease. This thesis uses mathematical modelling to interrogate both the function and effectiveness of natural immune systems, and how human interventions like vaccination can be best deployed. A defence of the value of this scientific approach in overcoming the empirical and interpretative challenges for these topics is provided in chapter 1.

The first two investigations consider the evolution and functional performance of natural immune systems. Chapter 2 proposes that immune adaptations can plausibly arise from Fisherian selection, and therefore could be maladaptive, and constructs a simple mathematical model of hosts and pathogens to examine this potential mechanism. Chapter 3 assesses the utility of a particular immune adaptation: fever. It models the impact of different proposed thermal strategies of fever in terms of suppressing pathogen temperature-dependent growth, and compares these to the calorimetric costs of heating.

The second two investigations consider how artificial immunity is best deployed, focusing upon vaccination strategies in the COVID-19 pandemic. Chapter 4 considers the risk and benefit of very early emergency use of a vaccine, before its safety and efficacy is known, finding this balance can favour such use for many individuals in the early stages of the COVID-19 pandemic. Chapter 5 investigates another emergency strategy for multiple dose vaccines, prioritising individuals for first doses and the expense of postponing individuals receiving subsequent doses, and when this strategy would be beneficial for public health in terms of risk reduction, disease transmission, and earlier relaxation of non-pharmaceutical interventions.

I conclude with a discussion of broader themes which span across these investigations, and suggestions for further research.

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This thesis is dedicated to the memory of Roger Carpenter (1945 - 2017)

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I remain most grateful for the love and support - in this and everything else - of my father, Nigel; my mother, Elizabeth; and my sister, Marissa.

Declarations

Statement of originality

I declare that this thesis was composed by myself and the work contained within is my own work except where expressly stated otherwise in the text. This work has not been submitted for any other degree or professional qualification.

Gregory Lewis
Hilary Term 2022

Statement of authorship

Chapter 2 is my own work, supervised by Michael Bonsall.

Chapter 3 is my own work, supervised by Michael Bonsall. This work has been published as: Gregory Lewis and Michael B. Bonsall. "Modelling the Efficacy of Febrile Heating in Infected Endotherms" In: *Front. Ecol. Evol.* 9 (17 September 2021). URL: https://doi.org/10.3389/fevo.2021.717822

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Chapter 5 is my own work, supervised by Michael Bonsall. During its production I began a collaboration with Nikos Bosse, William Waites and colleagues at the London School of Hygiene and Tropical Medicine, who were investigating similar topics, with the intention of preparing a joint paper combining our work. However, all work presented in Chapter 5 is solely my own independent creation.

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1 Introduction

Contents

Immune systems are both objects of scientific investigation and acute clinical interest. From an ecological perspective, they are both a result of, and driver influencing, the complex adversarial co-evolution between hosts and parasites.[1, 2] From a medical perspective, immune systems are key to defending against infectious disease, and a common clinical objective is to intervene on behalf of a host organism to aid its immune system in overcoming a pathogen infection.

This thesis applies mathematical modelling to better understand immune systems from both perspectives: on one hand, their evolutionary development in the context of biotic competition; on the other, how immune mechanisms are best exploited and assisted for medicine and public health. The work in this thesis

Interaction	Effect on Species A	Effect on species B
Mutualism	+	+
Commensualism	+	0
Neutralism	0	0
Amensalism	-	0
Competition	-	-
Parasitism	+	-

Table 1.1: Categories of species interactions. + indicates the interaction benefits a species, − indicates harm, and 0 no effect.

thus spans investigations of evolutionary mechanisms which give rise to natural immune systems, assessment of the performance of current immune adaptations, and analysis of vaccination, a means of artificially induced immunity, could have been best deployed in the ongoing COVID-19 pandemic. This introduction surveys concepts foundational to these investigations.

1.1 Parasites and pathogens

The interactions of species in a community can be categorized by whether this interaction benefits, harms, or is neutral for members of each species. All six possibilities are observed in nature (table 1.1).

Parasitism is one such interaction between individuals of different species characterized by harm to one (the host) and benefit to the other (the parasite). This interaction is antagonistic: the host benefits if it can avoid exploitation by the parasite, but this resistance harms the parasite in turn.

Pathogen is a term from infectious disease and microbiology for organisms which produce clinical disease.[3, 4] In clinical medicine, 'parasite' is typically reserved for pathogens which are helminths or protozoa, and not those of other taxa (e.g. bacteria, fungi, viruses);[5] in ecological terms, many of these pathogens are also (micro)parasites.

Clinically-defined *pathogens* and ecologically-defined *parasites* broadly but imperfectly overlap. Not all pathogens are parasites: many infectious diseases in humans are caused by organisms for which they are an accidental or 'dead-end'

host (e.g. West Nile virus,[6] *Gnathostoma* spp.[7]), incidental infections from free-living microorganisms in the environment (e.g. *C. Tetani*, *N. fowleri*, causative organisms of Tetanus and primary ameobic menigoencephalitis[8, 9]), or commensual organisms which can cause disease in abnormal circumstances (e.g. *S. epidermidis* and *C. acnes* in acne vulgaris,[10] gut dysbiosis due to upsets in the homeostasis of bacterial flora[11]). In these cases, the pathophysiology is not beneficial - and often harmful - to the pathogen itself. Although rarer, not all parasites are pathogens either, due to the harms caused by some parasites to their hosts being typically too insignificant to consider a disease: mosquitos and ticks are ectoparasites, but the principal interest they hold to medical science is their role as a vector of pathogen transmission rather than the direct injury they cause to their hosts.

This distinction leads to important differences for understanding the adversarial relationship between host and pathogen - including whether it is adversarial at all. Host organisms are fitter when they avoid the harm caused by pathogens (whether parasites or not), and so there is selective pressure for adaptations which better enable them to resist infection. The converse is not always the case: for pathogens which are not parasites, where infection is either neutral or sterilizing to the infective organisms, selection pressures for particular characteristics of disease or to counter host immune defences are absent. For pathogens which are also parasites, adaptations from the host to resist their infection would be expected to harm their fitness, and thus exert selective pressure for co-evolution of adaptations which counter host immune adaptations. However, as parasites are often dependent on the host life-cycle for their own reproduction and transmission, they may also be selection pressure for various particular disease characteristics, as well as variable disease severity. Although host immunity is under selection pressure to minimize pathogen virulence, parasites are not always selected to maximize it.[12]

1.2 A review of immune systems

Immune systems are defined as networks of biological processes which protect an organism from disease.[13] Such systems are ubiquitous in living organisms, from

CRISPR-Cas elimination of foreign DNA in bacteria to antibody production in humans. The designation of an immune system is demarcated more by grey areas than crisp lines: the biochemical and cellular responses to infection are clearly part of an immune system, the more biologically inert protections from surface barriers are typically included, whilst behavioural mechanisms (e.g. disgust, widely believed to have evolved to aid organisms to avoid risks of infection[14]) typically not.

Although the known detail of immune systems would fill many textbooks, relevant fundamental principles are surveyed here.

1.2.1 Recognition, blacklists, and whitelists

As host organisms are not perpetually diseased or infected, immune responses are typically induced. Thus immune systems typically have mechanisms for immune sensing to trigger appropriate responses to infection or injury.

One common approach to immune sensing is a molecular 'blacklist': an organism maintains pattern recognition sensors - receptors to molecules which derive either from pathogens (PAMPs - pathogen-associated molecular patterns, such as flagellin or lipopolysaccaride),[15] or injured host tissues (DAMPs - damage associated molecular patterns, such as heat-shock proteins and fibrinogen).[16] As the presence of these patterns are specific to disease, they can be used as a trigger for the immune response.

This approach is commonplace in 'innate' immunity: in vertebrates, this immune sensing is primarily performed by Toll-like receptors (TLRs),[17, 18] with the 10 receptors identified in humans sensitive to a variety of PAMPs and DAMPs. Another approach is seen in the adaptive immune system: in addition to a molecular 'blacklist', there is a molecular 'whitelist': cells present signals of normality, and adaptive immune sensing detects peturbations of this physiological picture which prompt a response.

In vertebrates, this system is an elaboration of two classes of protein: the major histocompatibility complex (MHC) and the T-cell receptor (TCR). MHC presents peptide fragments (antigens) sampled either from protein translation (MHC type 1,

expressed ubiquitously)[19, 20] or phagocytosis (MHC type 2, expressed primarily in antigen presenting cells and B-cells).[21, 22] In concert, this sampling produces an antigenic image of normal cell physiology and endocytosed material respectively.

TCRs are the sensors to detect changes in this image, and thus discriminate 'self' from 'non-self'. Each T-cell expresses one somatic variant of the TCR, which are extremely diverse due to genetic recombination of the receptor genes.[23] This essentially random variation means each TCR variant (and thus each T-cell) has essentially random affinities to peptides. This repertoire of TCRs is filtered during maturation to remove those with TCRs which no longer bind MHC (positive selection) and those which bind to MHC presenting self-antigen (negative selection).[24, 25] The resulting population of sensors are not specific for any particular PAMP, but for any molecular pattern which differs from the antigenic image of the host organism.

As always in biology, this summary is a simplification: the large variety of specific immunodeficiencies and auto-inflammatory diseases indicate immune sensing is neither perfectly sensitive nor specific for either black list or (non)-white list molecular patterns. Excluded mechanistic detail - such as the co-stimulation and 'Signal 2' in T-cell activation[26, 27] - have functional relevance: in the case of Signal 2, further verification after initial activation the T-cell is not auto-reactive.[28] Finally, vertebrate immunology in general, and immune sensing in particular, has mechanisms which straddle the division between innate and adaptive immune systems: natural killer cells of the innate system seem to respond to the absence of MHC ('missing self' as a DAMP/PAMP), but appear to have a diversity of subtypes specific to different pathogens, and show properties of immunological memory;[29] sub-populations of unconventional T-cells (e.g. natural killer T-cells, mucosal associated T cells, $\gamma\delta$ T cells) appear primed to respond to specific PAMPs through MHC-independent presentation.[30]

1.2.2 Response, tailoring, and memory

Sensing disease is necessary but not sufficient for protecting the host from it - the immune system needs to respond appropriately, for example by killing the pathogenic microbe, eliminating infected or cancerous host cells, or healing tissue injury and disruption.

In vertebrates, the initial mostly stereotyped response, aligned to innate immune sensing, is called inflammation. It comprises a multitude of self- and mutually reinforcing responses, targeted to the site of an injury, which span cascading systems of plasma proteins (e.g. complement and coagulation pathways), chemotaxis of specialized immune cells (e.g. neutrophils, macrophages) and vascular changes (vasodilation and increased permeability).[31] In addition to these localized effects, inflammatory signalling can prompt systemic physiological changes which appear to make the host body a more inhospitable environment to pathogens: fever and anaemia of chronic disease are two examples.[32, 33]

The adaptive wing of the immune system augments this response with additional specific effector mechanisms and sculpting the overall inflammatory response to better target the particular infection. The two primary additional effectors are cell-mediated immunity by CD8+ cytotoxic T cells,[34] and antibody production by B lymphocytes.[35] The former exploits the whitelisting of TCR to detect intracellular pathogens when their foreign peptites are sampled and presented on host class 1 MHC. When a CD8+ cell with binds strongly to this MHC-abnormal peptide complex, it activates, eliminates the host cell, and proliferates to eliminate other host cells similarly infected. The latter uses a variant of the TCR (the B cell receptor) which is distinct from the TCR in that it binds directly to whole antigens rather than peptide fragments, but shares the specificity and whitelisting immune sensing mechanisms mentioned previously. Similar to CD8+ T cells, B cells also activate and proliferate on an antigen binding to their receptor, although this activation prompts soluble variants of the B cell receptor (antibodies) being secreted.

Adaptive regulation and tailoring of the immune response is mainly provided by CD4+ 'helper' T cells (T_h).[36] Upon activation, these cells activate other immune

cells directly (e.g. B cell activation) and through secreting pro-inflammatory cytokines. The patterns activation and inhibition among T_h subpopulations sculpt the character of the inflammatory response: one polarity recognised is between type 1 and type 2 T_h cells, which tilt response towards cell mediated and humoral effector mechanisms respectively.[37]

Besides providing a tailored response to pathogens, adaptive immunity also provides immunological memory: after infection, although most of the activated B cell and T cell populations die, some persist as memory cells.[38] This primes the immune response to be more rigorous upon subsequent encounters with the pathogen. This mechanism is exploited by vaccination: by providing attenuated, killed, or subunits of a pathogen alone can provide a surrogate of immunological memory to benefit an individual if they subsequently become exposed to it.

Although adaptive immune responses described above are those of vertebrates, immune mechanisms with specificity and memory are recognised in other taxa. Lampreys and other jawless fish have a functionally and mechanistically analogous adaptive response, but with a distinct molecular architecture - their variable lymphocyte receptor, an analog to vertebrate TCR, is based on variable leucine rich repeats rathen than V(D)J recombination to produce receptor diversity.[39, 40] Specificity and memory in some insect species is also recognised, with an immunoglobulin-like protein (Dscram) characterized as a potential basis.[41] Although adaptive immunity is often characterized as more advanced development of innate immunity, one of the most ancestral recognised immune mechanisms, Crispr-CAS, which incorporate stretches of viral DNA in bacterial genomes to enable sequence-specific interference and degredation of viral genetic material, is also an adaptive immune system.[42]

1.3 Complications in assessing immunological performance

One natural question about immune systems is how effective are they (either a whole, or particular components) at their function of protecting the host from

disease. Although this question is straightforward to pose, it is conceptually and empirically challenging to answer.

1.3.1 Conceptual challenges

One issue is 'function' in biology is a fraught concept.[43] 'Function' and 'performance' typically imply goals, designs, and intentions: the *function* of a pen is to write; and pens *perform* better at the task of writing than a quill. Yet this implied teleology is absent in biology: organisms do not have immune systems *in order to* protect them from disease (nor do populations evolve *in order to* increase fitness) any more than gases mix *in order to* maximize entropy. It is simply a manifestation of the blind forces of genetic mutation and natural selection.

Despite this, function and other teleological terms are commonly used (and this use commonly criticised) by biologists. A couple of accounts have been offered to reconcile the concept of biological function with evolutionary theory.

One, more common in molecular biology and biochemistry, is to equate function with mechanistic effect:[44] for example, the function of an enzyme is to catalyze a biochemical reaction, and a mutated gene for this enzyme which produces a protein which no longer catalyses this reaction is 'non-functional'. The challenge to this account is many causal effects can be individuated: a human heart causes blood to circulate through the body, but it also causes an audible heartbeat and palpable pulse; even enzymes do not solely catalyse a chemical reaction, but (for example) increase osmotic pressure and alter pH when in solution. Intuitively, we wish to say these are byproducts or side-effects rather than functions, yet claims of what these biological objects are 'really for' seem necessarily teleological.

The other, more typical in ecology and evolution, is to define function in terms of evolutionary fitness. Although a trait may have many causal effects, the trait's function comprises those effects which led the trait to be selected for.[45] The heart's effect in circulating blood is its function as (unlike the noise or pulsatile arterial dilation it also effects) this enhances fitness. Statements like "Organisms have immune systems *in order to* protect them from disease" are convenient (if

apt to mislead) shorthand for, "Immune systems are traits which have the effect of reducing the expected severity of disease among organisms, and this effect makes organisms with an immune system fitter. Thus immune systems are selected for due to these effects of protecting organisms from disease."

1.3.2 Empirical challenges

This approach replaces an implicit teleology with an implicit pan-adaptationism: it remains controversial to what extent traits emerge and are fixed due to natural selection versus neutral mechanisms like genetic drift or constructive neutral evolution. Even if adaptive, precise understanding of what properties are (or were) subject to selection, and why these properties contributed to fitness is often elusive. To elaborate on these challenges in the context of immunity:

Pleiotropy, exaptation, and vestigality: Besides the difficulties in fully characterising the role a given immune gene or cell performs, interpreting their functional importance is also hard. Biological objects can serve multiple functions, these functions can be contributed to by multiple traits, and these mixtures can shift over time. A prior adaptation may be co-opted to serve a new function (*exaptation*), or an adaptation's function may no longer contribute to fitness (or its performance in that function is supplanted by another function), and so it atrophies (vestigiality). Thus selected effects of an adaptation (as well as its history of selected effect) depend on the shifting context provided by the organisms other traits.

TLRs serve as one illustration of these complications. Alongside their immunological role, TLRs also serve developmental functions in invertebrates,[46] and mammalian TLRs maintain neurobiological actions plausibly independent of their immunological functions.[47, 48] One interpretation of the above is, given the apparently more muted developmental role of TLRs in vertebrates versus invertebrates, is the TLRs principally serve an immunological function, an *exaptation* ancestral developmental role, albeit one where some residual developmental function remains.

This is not the only possible interpretation. Humans have 10 recognised TLR genes, whilst other invertebrate species have greatly expanded TLR repertoires.[49] Recognised primary immunodeficiencies in TLR-signalling and murine TLR knock-outs have relatively limited effects: conditions like MyD88 and IRAK4 deficiency, which mechanistically impair almost all TLR immune sensing, result in severe infections in childhood, but only from limited groups of pathogens, and this susceptibility declines with age.[50] Thus perhaps the role of TLRs in immune sensing remains important in invertebrates given the observed diversifying selection, but their immunological role in vertebrates has been supplanted by other mechanisms of immune sensing. Perhaps TLRs are maintained for their residual roles in development, but their immunological activity in vertebrates is vestigal.

Observational and experimental confounding in assessing contribution to fitness: As an outcome variable, fitness is challenging to measure directly in longer-lived organisms due to the necessity of measurement over multiple generations. Interpreting surrogate indicators (such as survival) can be complex: in the same way maximizing quantity of offspring is not the global optima of reproductive strategies (even if, all else equal, those who produce more offspring are fitter), traits that reduce mortality from disease may not be adaptive all things considered: insect species can show reductions in immunological activity upon transition to eusociality, with candidate explanations including substitution with communical behaviour ('social immunity') and changes in overall value of individual preservation for independent versus communal organisms.[51, 52]

Attributing differences in fitness to differences in immunological traits poses further complications. Observations are typically confounded by interactions between immune traits and non-immune traits, both of which weigh on the balance of overall fitness, such as the with the different explanations of reductions in immunity in some eusocial insect species mentioned above. Finding all relevant mechanisms (both pro and con) for an immunological trait, then determining why this balance favours or disfavours a given adaptation in a particular ecological context is typically

fraught: for example, the adaptive value of (heterozygous) Hb S in resistance to malarial infection would be difficult to infer from clinical cases of sickle cell disease.

Experimental manipulation is also typically confounded by the many-many inter-relationships between immune mechanisms and pathophysiology, complicating attribution of a specific mechanism to a specific protection from disease. Fever both stimulates and is stimulated by many other elements of inflammatory responses,[53, 54] thus interpretation a finding of increased mortality from an infection when fever is ablated is complicated by the possibilities other immunological side-effects of the ablation drove this result, or the relative importance of different mechanisms downstream of the febrile response.

Dynamics, equilibria, and mismatch The underlying environment for immunological phenotypes is largely a biotic one, and this can change rapidly. An immune system which offers effective protection to one set of pathogens and parasites may become ineffective if membership or relative prevalence within this group changes. Likewise, pathogens may co-evolve to negate or exploit particular immune adaptations in their life cycle.

Human activity may alter this environment on even more rapid time-scales. Thus 'evolutionary mismatch' is particularly relevant for human immunology, given the great change in prevailing environmental conditions in the last two hundred years. One example is the hygiene hypothesis, which suggests recent increases in prevalence of allergy and autoimmunity are owed to lower rates of infectious challenge in early life lead to worse entrainment of the developing immune system.[55]

Another is the potential for medical and public health interventions to substitute (or make redundant) the immunological function of various traits, making previous adaptations now costly to fitness on net. Traits like sickle cell or cystic fibrosis may now be under purifying rather than frequency dependent selection, owed both to the loss of the heterozygote advantage and increasing use of genetic counselling. A related possibility is for this substitution to mask traits which previously made significant contributions to survival. The argument made earlier that TLRs may be

vestigial due to the relatively modest impact of MyD88 deficiency can be challenged as i) diagnosis of MyD88 deficiency may be missed in individuals with the condition who die in infancy of an infection; ii) without vaccines and antibiotics, the condition would have a much greater mortality rate.

1.4 Evolutionary heritage and clinical utility

Given all of this, a deflationary pragmatism is appealing. The ground truth of biology is there are reproducing organisms which phenotypically vary, these variations in phenotype result in differences in survival and reproduction, and these variations are (imperfectly) inherited in the offspring of those organisms who reproduce.

Further language, even if not derivable from this ground truth, can be useful for the purpose of summary and categorization. In the same way there's no geological fact of the matter on what constitutes a peninsula, but is useful imprecise shorthand to label certain landmasses, 'species' likewise defies crisp definition, but it is a useful label to group similar reproducing organisms together and generalize amongst them. When the evidence favours a straightforward account of 'good designism', where a wide field of forms can be easily correlated to fitness effect, then function may be a helpful summary. Where the natural history is much more turbulent, and the fitness landscape may be spikier, with many putative local optima and path-dependency, it is less so.

Alongside this justification there is a practical one. Even if biology does not have purposes in mind, humans do: talk of cardiac function in medicine can be simply explained because both doctor and patient have the goal of avoiding asystole. Similarly, assessing immunological performance in terms of achieving humanitarian interests can guide how immunological mechanisms can be better exploited to achieve them, or when they can be complemented by other deliberate activity in medicine and public health.

1.5 The motivation for mathematical modelling

Given the formidable challenges above about gathering and interpreting relevant data, theory-led approaches are particularly attractive. They can aid both the explanatory project of understanding how natural immunological systems emerged, and the humanitarian one of understanding its strengths and weaknesss in combating infectious disease.

For the former, mathematical modelling may have insight for the underlying tectonic activity which govern particular fitness landscapes for immune adaptations and host-pathogen co-evolution. Underlying principles such as optimal virulence, 'Red Queen' dynamics and others may be easier to find by theoretical insight than adducing from the empirical record, yet aid understanding and interpretation of this data.

For the latter, the ability to extrapolate beyond past and present observations is valuable for planning and strategy. Modelling assessment of how well a given immune mechanism should be expected to perform can inform clinical decisions about whether it could be safely ablated or suppressed, anticipate which therapeautics are most beneficial, and assess public health strategy.

1.6 Thesis outline

This thesis integrates four pieces of research under the broad theme of applying mathematical modelling to adversarial dynamics seen in both naturally arising and artificially induced immunity. These are described in the next four chapters, charting a progression both from theoretical understanding of evolutionary mechanisms, to analysing and formulating public health strategy.

Chapter 2, "Immune adaptations as products of maladaptive runaway selection" proposes runaway selection as an alternative explanation for the evolution of immunological traits. This mechanism hypothesises that immune traits are initially adaptive (and selected for) when they are rare due to their immediate benefits in reduced pathogen load versus their co-specifics, but once they reach fixation

pathogen co-evolution removes this advantage. Although this trait may have persisting costs (e.g. energy expenditure) and no equilibrium reduction in virulence, it is nonetheless maintained in the host population as individuals without it are relatively immunocompromised and thus selected against. The chapter elaborates on this mechanism with a fuller verbal model, mathematical analysis, and investigates a cellular automata model of host-pathogen co-evolution.

Chapter 3, "Modelling the Efficacy of Febrile Heating in Infected Endotherms" focuses on fever as a test-bed for both the specific mechanism proposed in chapter 2, and a general illustration of the value of mathematical modelling to assess immune system performance. Unlike many other immune mechanisms, proxy measures for the costs of fever to both host and pathogen can be found for calorimetry (i.e. the energy cost required to heat the body in fever) and temperature dependent growth curves (i.e. the growth cost to the pathogen of elevated temperature) respectively. The chapter uses mathematical analysis of both to assess the efficacy of fever's antimicrobial heating through a number of potential mechanisms given the much narrower temperature increase of fever in endotherms versus ectotherms, and analyses whether 'spiking' or intermittent fever can be optimal for microbial growth restriction given a host energetic constraint.

Chapter 4, "Risk-benefit analysis of emergency vaccine use" applies a similar lens of mathematical assessment of performance to public health strategy rather than evolved immune mechanisms. One of the public health dilemmas faced in the COVID-19 pandemic was whether to license vaccine candidates for emergency use prior to even interim results from phase 3 trials: earlier emergency use benefits through earlier protection, balanced against the risk of administering an unsafe or ineffective vaccine. The chapter contributes a model of individual risk-benefit of emergency vaccine use in COVID-19, where the efficacy and safety of the vaccine are unknown values, across a field of baseline risk of COVID-19 given by the range of attack rates and infection fatality rates seen during the pandemic.

Lastly, Chapter 5, "Modelling the public health trade-offs of vaccine dose scheduling policy in the COVID-19 pandemic" undertakes a similar analysis for

a different dilemma in vaccine strategy: whether, for vaccines given in multiple doses, whether it is better to prioritise first doses to unvaccinated individuals versus additional doses to those already vaccinated. Similar to emergency use, there is a balance of risk versus uncertainty: where one dose brings more than half of the benefit of both doses, prioritising 'first doses first' provides greater protection across the population, against the risk these novel dose schedules worsen performance. The chapter provides a mathematical analysis of marginal vaccine efficacy (as well as distinguishing different types of vaccine efficacy) and constructs mathematical and epidemiological models to compare different scheduling strategies for COVID-19 vaccination.

2

Immune adaptations as products of maladaptive runaway selection

We hypothesize that a common dynamic in the evolution of immunity is one of maladaptive runaway selection: where immune adaptations offer no long-run advantage to the host species in host-pathogen conflict, and which ultimately are costly and maladaptive, can nonetheless reach fixation driven by intraspecific competition. We develop a cellular automata model for host immunity and corresponding pathogen virulence, which exhibits maladaptive runaway selection. We discuss the fidelity of the model to the biology it seeks to represent, and propose, despite its limitations, it provides a 'proof of principle' for this dynamic explaining parts of the natural history of immunity.

Contents

2.1 Introduction

Immune systems have their origin in host-pathogen conflict across natural history, thus martial analogies are commonplace: the immune system 'defends' the host from pathogens; it 'fights' infection; and it vies with pathogen species in a co-evolutionary 'arms race'.

Our understanding of host-parasite dynamics complicates such an account.[12, 56, 57] Virulence, roughly defined as fitness cost to the host imposed by the parasite,[58] tends to impose an indirect fitness cost to the parasite as well: for (biotrophic)

parasites, a dead host is a lost habitat. The hypothesis pathogens will be subject to selective pressure to reduce their virulence - 'unilateral disarmament' in the martial metaphor - was proposed over a century ago.[59]

> [...] there will be a selection in favour of those varieties which vegetate whence they can escape. The surviving varieties would gradually lose their highly virulent invasive qualities and adapt themselves more particularly to the conditions surrounding invasion and escape. That some such process of selection has been going on in the past seems the simplest explanation of the relatively low mortality of infectious diseases.

This 'avirulence hypothesis' later developed into a 'trade-off' hypothesis.[60, 61] This proposes that pathogens cannot jointly increase duration and intensity of infection without bound: a more intense (or virulent) infection of a host reduces its fitness, and consequently the resources available for the pathogen to exploit. Thus the pathogen faces a 'transmission-virulence' trade-off, of short-term fecundity versus long-term host 'habitat' degradation. The optimal balance for a pathogen to strike is not necessarily avirulence: individuals which produce shorter, more lethal, infections can be fitter than their less virulent conspecifics.

One virtue of the trade-off hypothesis, besides its simplicity, is it provides explanations of parasite virulence in terms of the ecological context of the host-parasite system. Modes of transmission that rely heavily on host fitness should be expected to favour less virulent parasites than those which do not. Thus vertically transmitted parasites (which require the host successfully reproduce) and directly transmitted parasites (which require the host to make contact with other members of the species) should be less virulent that those which use horizontal[62, 63] or vector transmission respectively.[61, 64, 65]

The primary challenge for the 'trade-off' hypothesis[66, 67] is that empirical data only equivocally supports the elegant theoretical predictions.[68] Some part of this gap may be explained by the challenges of marshalling compelling data[12] but another aspect may lie in multiplicity of other factors that may impact host parasite dynamics (and consequent parasite selection pressure) of which 'trade-offs' only play a part.

Alizon and colleagues note in their review that the "[G]reatest experimental and theoretical challenge for the trade-off hypothesis is now to better incorporate the immune system."[12] Whatever the optimal virulence of the parasite may be, the optimal virulence for its host is (by definition) zero. Immune systems reflect investment by host species into resisting parasite virulence: what influence do they have on host-pathogen systems?

We propose a major driver for immune adaptations is not co-evolutionary conflict between host and pathogen, but runaway selection within the host species. In this case, we suggest *intraspecific* competition among host species to reduce pathogen load can drive immune adaptations, even if in the long-run these adaptations disadvantage fitness by providing no lasting benefit to the host in host-pathogen conflict, but imposing independent costs in maintaining the trait. This now-costly trait is nonetheless stably maintained as its reversal penalizes fitness.

Immune adaptations which evolve in this manner are thus *maladaptive*: this adaptation leads to fixation of a trait which is stable and costly at equilibrium, thus individuals in this population are less fit versus a hypothetical where the adaptation never emerged.

We investigate this hypothesis in the following way: First, we survey the field of infection and immunity and suggest there is a general paradox: on the one hand, immune systems are surprisingly ineffectual; yet on the other, they are very stably maintained. Second, we outline how maladaptive runaway selection (similar to Fisherian runaway accounts in sexual selection) could resolve this paradox, and introduce a verbal model subsequently elaborated with mathematical analysis. Third, we develop a cellular automata model of hosts, pathogens, immunity, and virulence, and examine whether model behaviour confirms the initial verbal predictions. Last, we discuss the fidelity and limitations of our model, and point to distinctive predictions our hypothesis makes that could be tested empirically.

2.2 Motivation: Ineffectual yet indispensible immunity?

Although generalisation across biology is often imperfect, one trend we believe needs explanation is the apparent limitations of immune systems: they often seem to be ineffective investments of host resources to combat pathogenicity. To support this claim we draw on the following lines of evidence:

2.2.1 The success of 'hosts as habitats' models

Although our understanding of host-pathogen systems is incomplete, this understanding has progressed despite primarily considering the 'pathogen's point of view': the host is treated as a relatively static habitat with limited resources subject to harvesting by pathogen virulence. Yet hosts are not only a habitat for its pathogens, but also an adversary. Inter-species conflict can rarely be safely ignored: compare attempting to understand the complex dynamics of a predator species without regard to its prey or competitors.

2.2.2 Pathogens are often capable of much faster adaptation than than their hosts

Both theory and observation suggest (microbial) pathogen species commonly have a much greater adaptive velocity than their (macroscopic) host species.

In theory, microbial pathogen species usually possess (much) larger population sizes, shorter generation times, and greater mutability than their host species. Taking examples from human infectious disease:

- Titres from human bloodstream infections range from 0.1 to 100 colony-forming units per milliliter (mL);[69] for viruses, clinical detection limits for HIV and HCV lie around 100 copies per mL.[70, 71] These imply organism counts of 10^7 or more pathogens in a single infection given typical human blood volume is $5 \cdot 10^5$mL.

- Leggett and colleagues, surveying common bacterial pathogens in humans, find *in vitro* generation times ranging from 0.3 - 33 hours,[72] several orders magnitude shorter than humans.

- Human germline mutation rates are of the order of $1 \cdot 10^{-8}$ /bp/generation.[73, 74] Mutation rates in wild type bacteria range over $1 \cdot 10^{-4}$ to $1 \cdot 10^{-11}$ /bp/generation.[75] Viruses can show higher mutatability still: HIV-1 reverse transcriptase has an error rate of 10^{-3}.[76]

Direct observations tell a similar story. Clinically, genetic drift (and shift) in acute outbreaks,[77–79] the development of antimicrobial resistance, and the importance of combination therapy to control chronic HIV infection[80] are all examples of pathogen evolution on timescales shorter than a single human generation.

The lethality of recently-introduced pathogens

'Novel' pathogens to a host tend to be highly virulent,[81] whether the infection is from a zoonotic disease, an 'accidental' host, or by free-living microbes (e.g. *C. tetani*, *N. fowleri*, the causative organisms for tetanus and amoebic meningitis in humans).

One explanation is the 'novel' pathogen simply has not had time to adapt towards the optimal virulence for its host (which is presumed to be lower, although there are exceptions[82, 83]). What remains surprising is the prevalence of cases where the pathogen is initially 'too virulent'. In 'novel pathogen' cases, both host and pathogen species are naive to one another, yet in these circumstances pathogens often overwhelm host defences (free-living microbes are a stronger case, as many species are not even opportunistically parasitic, and thus should be expected to be minimally adapted to combat immunity).

2.2.3 Immunological costs

Alongside these limited benefits, immunity can impose concrete fitness costs to the host:

Energy Fever provides the easiest calorimetric measures of the energetic costs of immune responses. In humans, maintaining a mild fever is approximately 10% of basal metabolic rate.[84] Other aspects of immunity response impose further energetic costs (e.g. biosynthesis of immunoglobulins), both when 'active' or quiescent.

Autoimmune disease Immunity can misfire in the absence of infection. Anaphylaxsis, allergy, many of the arthritides, and the contribution of inflammation in the pathophysiology of chronic disease[85] are some examples.

Immunological exacerbation of virulence Immune responses can provoke pathophysiology in their own right, and so worsen the consequences of an infection. Perhaps the leading example is sepsis, whereby an infection over-stimulates the innate immune system, leading to a life threatening systemic inflammatory response syndrome (SIRS).[86]

2.2.4 Conservation of immune adaptations

In contrast to this mixed picture of functional performance, immune adaptations are strongly conserved. Toll-like receptors (TLRs) are ubiquitous across metazoans; a conventional adaptive immune system mediated by immunoglobulins and T cell receptors (TCRs) is found in all jawed vertebrates.

Two features of this conservation are worth highlighting. One is the distribution of immune adaptations is principally phylogenic: although there are cases of immune gene loss, ancestral immune adaptations are typically conserved in all phylogenic descendants despite radical variation in other aspects of their physiology, morphology, and ecological context. The other is the coexistence of species possessing facially more or less sophisticated immune systems.

These features are not straightforward to explain in terms of the adaptive value of the immune system. On one hand the strong conservation of immune adaptations imply they are near-universally valuable: no jawed vertebrate would gain a fitness advantage by dispensing with its adaptive immune system. On

the other, similar adaptations have not emerged in many species, despite their putative fitness advantage.

2.3 Maladaptive immunity and the runaway selection hypothesis

The motivation sketched above is not a decisive demonstration immune systems are not adaptive. Yet it suggests challenges to straightforward adaptationism as an explanation for immune traits. We explore the possibility of selection for *maladaptive* immune traits below.

2.3.1 Selection and fixation of maladaptive traits

Many traits are speculated to be suboptimal or functionally inefficient. Although confirming these speculations is difficult (in theory, traits often serve many functions, and thus apparent inefficiency with respect to one may be an efficient trade-off with others; in practice, manipulating traits and observing fitness in the natural environment is difficult), explaining such cases poses little challenge for evolutionary theory. Natural selection is myopic, and thus populations tend to traverse in the direction of greatest immediate fitness advantage, regardless of whether this path arrives at the global optima or a local one.

A greater paradox is seemingly *maladaptive* traits - not just inferior to some hypothetised alternative, but worse than nothing at all. Extreme sexual dimorphism with one sex developing extravagant ornamentation to attract the other are commonly proposed examples. A common explanation for these traits being stably conserved in a population is Fisherian or runaway selection. In sketch, when ornamentation also indexes mate quality, ornamentation (and selecting mates with ornamentation) provides both a competitive advantage in sexual selection alongside a direct penalty to fitness. The trait will be selected if the former outweighs the latter overall. However, as the benefit of the trait is a positional one, it is lost once it reaches fixation in the population whilst the (non-positional) penalty remains.

As yet-further ornamentation can be positively selected for by the same mechanism, there can be 'runaway selection' for traits which offer transient competitive advantages to individuals when they are rare, but are maladaptive at equilibrium once prevalent: although populations with the trait are less fit than those without, within any population individuals with the trait outcompete those without it (figure 2.1). This process only terminates when the marginal benefit of further enhancing the ornamentation are matched by the direct fitness costs, and the resulting equilibrium is stable as well as wasteful: even if all individuals in a population would be fitter if they invested less in ornamentation, individuals who deviate from the wasteful equilibrium suffer a fitness penalty.

2.3.2 Runaway selection of immune adaptations

We propose the key ingredients of Fisherian runaway selection can apply to host-pathogen coevolution. Even if immune adaptations do not provide persistent benefit to the host species in reducing the equilibrium virulence of a co-evolving pathogen, they provide transient competitive advantage to individuals versus their relatively immuno-deficient co-specifics. This can drive steady accumulation of immune adaptations in the host species population, even if the costs of these adaptations are no longer compensated with any benefit in pathogen resistance.

We offer this verbal model to illustrate the idea:

1. Suppose a static environment with a host population H and a pathogen population P, with P adapted to parasitise H at optimal virulence. Call this H/P.

2. Consider an immunological adaptation for H $(+)$. The effect of this is to provide increased resistance to infection by P, and although this has some other costs (e.g. energetic costs of biosynthesis of a new immune protein) this cost is less than the benefit in reduced disease from infection with P. In the H/P system Individuals (h_i, with i being an index) with + (h_i+) are selected for, and + achieves fixation in H ($H+$).

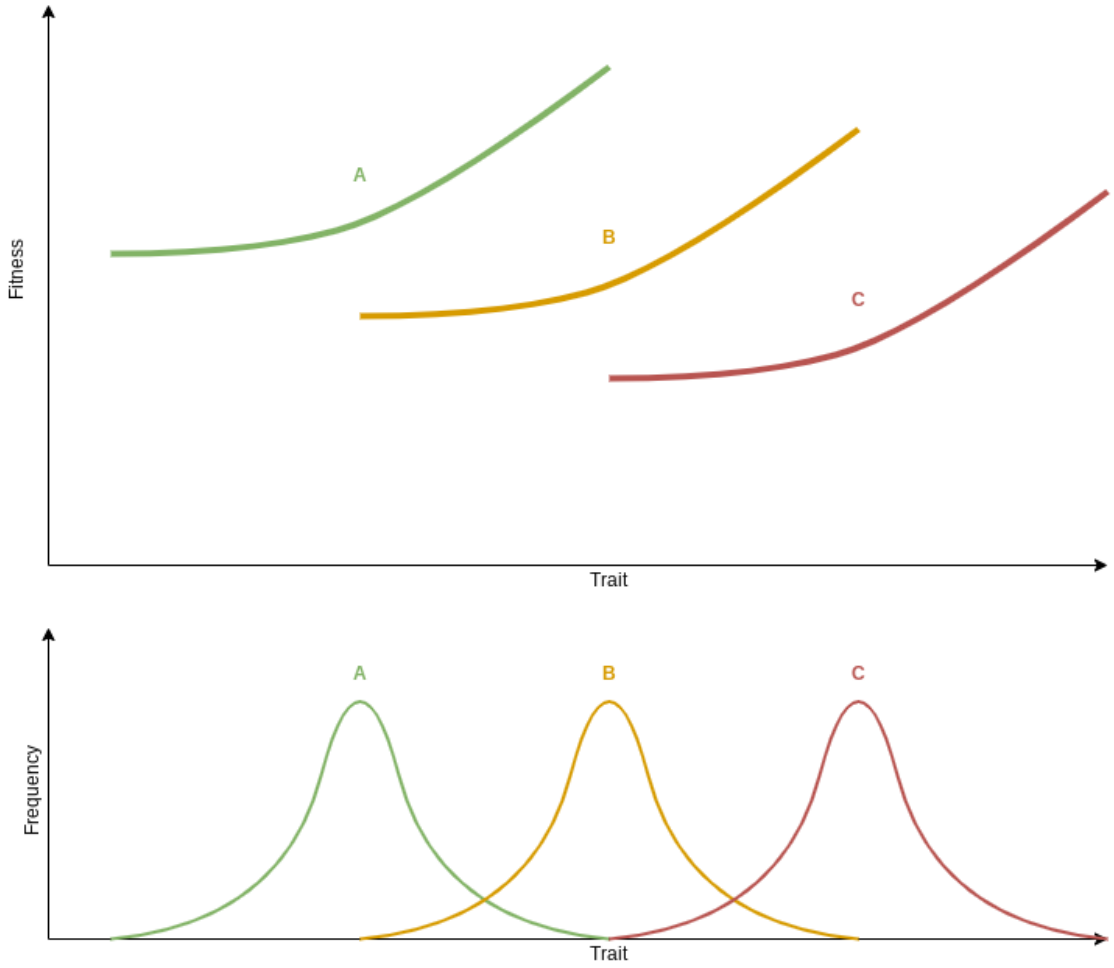


Figure 2.1: Schematic representation of runaway selection. The upper panel illustrates fitness landscapes for a (qualitative) trait hypothesized to impose a fitness penalty outweighed by the advantage it provides in intraspecific competition. These fitness landscapes depend on the population distribution of the trait (lower panel): e.g. individuals with greatest value of the trait in population A would be much less fit if they were transferred to population C. In all populations individuals with greater values of the trait are fitter than those without, and thus the trait is under positive selection in in populations. Yet its accumulation in the population reduces average fitness.

3. Imagine a virulence factor for the pathogen ($-$), which 'cancels out' $+$, and thus returns virulence for pathogens with this trait in $H+$ back to its previous optimum for H (and so $H+$ returns its prior rates of pathogen-associated disease). As $+$ approaches fixation, pathogens with $-$ are also selected for, and so this achieves fixation in the pathogen population in turn ($P-$).

4. Thus the original H/P population is replaced with an $H+/P-$ population, with the host population less fit than it was before: $H+$ suffers the same

virulence from $P-$ as H did from P, but it pays the additional costs of $+$ as well.

5. This cycle could repeat with a further adaptation $++$, leading to a $H++/P--$ population, and so on.

This account has several implications, and one assumption, worth highlighting:

Host-initiated inter-specific 'arms race' If P is already at its virulence optimum, there is no selective pressure for greater virulence: $-$ is at a selective disadvantage in H/P. There is only selective pressure for the pathogen to develop greater virulence in response to host immune adaptations. By contrast $+$ (or $++$) are always under selection pressure in H as (by definition) these are fitness enhancing.

Maladaptive runaway selection for host immunity Even though in the long-run immunological adaptations are deleterious (as the 'upside' of reduced infection from P is transient, and the 'downside' of a fitness cost to maintain this enhanced immune system permanent), these adaptations are nonetheless selected for.

Ratchet-like accumulation of immune adaptations Although $+$ is advantageous in an H/P system, *losing* $+$ is disadvantageous in a $H+/P-$ system (or $H+/P$): the H individuals suffer greater virulence from $P-$ (or P) than $H+$ individuals, and so are selected against.

No ratchet for accumulation of pathogen virulence Unlike $H+/P$, where $+$ remains under selection pressure, for $H/P-$, pathogens without $-$ would outcompete their too virulent $P-$ counterparts. Unlike H, P can be under selective pressure to down-modulate its virulence.

Maintenance costs as a mechanism for self-limiting and asymmetric runaway selection The verbal model implies adaptations and counter-adaptations can be added indefinitely. One could imagine this process self-limits - for example, the costs for further adaptations of immunity or virulence increase, such that at there is some maximum whereby further marginal increases to immunity and virulence are net-costly no matter their benefit with respect to host-pathogen competition. Second, these limits may not be symmetrical between host and pathogen: if one or the other species can escalate further, it could enjoy a stable advantage regardless of the other's coevolution.

2.4 Mathematical framework

Suppose a host species (H) is infected with a sole pathogen (P) species. Let individuals of H (h_i) have some variable degree of 'immunity' (I_i), which is a measure of its ability to avoid or repel infection by P. Let individual populations of P for each h_i (p_i) have a corresponding variable called 'virulence' (V_i), a measure of its ability to successfully infect H. The effect of this host-pathogen conflict to overall host and pathogen fitness are $F(h_i)$ and $F(p_i)$, respectively.

$F(h_i)$ and $F(p_i)$ are modelled as sum of respective 'contest' (c) and 'maintenance' (m) functions. The contest function represents the consequence of host-pathogen conflict for host (c_H) or pathogen (c_P) given the respective degrees of immunity and virulence. The maintenance function represents the cost to fitness (in terms of energy or otherwise) of immunological adaptation or virulence factors for host (m_H) and pathogen (m_P):

$$F_h(I_i, V_i) = c_H(I_i, V_i) - m_H(I_i) \tag{2.1}$$

$$F_p(I_i, V_i) = c_P(I_i, V_i) - m_P(V_i) \tag{2.2}$$

2.4.1 Stipulating the contest and maintenance functions

We stipulate c_H must be monotonically increasing with with I_i and monotonically decreasing with V_i (for any given value of V_i or I_i respectively). An alteration which makes the host more resistant to pathogen infection, or makes the pathogen effective at infecting the host, should result in increased host fitness.

Conceptually the impact of c_H on $F_h(I_i, V_i)$ should have a finite range, with zero as the upper-bound: h_i should not become fitter by being susceptible to nearly avirulent pathogen to which it can mount a very effective immune response versus being not susceptible at all. Similarly there should be a hypothetical lower bound for c_H at the extreme of a pathogen that instantly kills the host upon infection. One can introduce a 'monotonic wrapper' to c_H which is order-preserving yet has finite range. A (logistic) example could be:

$$F_h(I_i, V_i) = \frac{N}{1 + e^{c_H(I_i, V_i)}} - N - [m_H(I_i)] \tag{2.3}$$

With N as a constant, thus constraining the range of c_H's contribution to $F(h_i)$ to [-N, 0]. For simplicity, this will be omitted from our modelling.

For c_P, we stipulate for any value of I_i there should be a single maxima with respect to V_i, so capturing the idea of optimal virulence: there is some 'ideal balance' to be struck in the contest of immunity and virulence for pathogen fitness. Maintenance functions for host and pathogen (m_H, m_P) should be monotonically increasing with I or V respectively: 'more' immunity or virulence should cost more rather than less.

The are innumerable equation systems which satisfy these constraints. We select one of the simplest for the baseline case of our modelling, where $c_P = I_i - V_i$, $c_H = -(I_i - V_i)^2$, $m_H = 0.1 \cdot I_i$, and $m_P = 0.1 \cdot V_i$ (we will subsequently assess sensitivity to this parameter value for the maintenance functions) thus:

$$F_h(I_i, V_i) = (I_i - V_i) - 0.1 \cdot I_i \tag{2.4}$$

$$F_p(I_i, V_i) = -(I_i - V_i)^2 - 0.1 \cdot V_i \tag{2.5}$$

2.4.2 Initial analysis

Consider simplified versions of equations 2.4 and 2.5 where $m_H = m_P = 0$, thus:

$$F(h_i) = I_i - V_i \tag{2.6}$$

$$F(p_i) = -(V_i - I_i)^2 \tag{2.7}$$

These each describe a surface in 3-dimensional space (figure 2.2). $F_p(I_i, V_i)$ has a maxima on the line $V_i = I_i$: $\frac{\partial F_p(I_i,V_i)}{\partial V_i} = 2(I_i - V_i)$ (thus $\frac{\partial F_p(I_i,V_i)}{\partial V_i} = 0$ when $I_i = V_i$), $\frac{\partial^2 F(p_i)}{\partial V_i^2} = -2$. For a given value of I_i, $F_p(I_i, V_i)$ is maximised with respect to V_i when V_i takes the same value.

In contrast, $F_h(I_i, V_i)$ does not have a maxima: $\frac{\partial F_h(I_i,V_i)}{\partial I_i} = 1$. More immunity is always better: for a given value of V_i host is fitter with more rather than less immunity.

Consider the independent optimisation for $F_h(I_i, V_i)$ with respect to I_i and $F_p(I_i, V_i)$ with respect to V_i, representing the fact host fitness can select for changes in immunity among hosts, but not for virulence among pathogens (and vice-versa). Consider this joint optimisation as a vector field on $I_i, V_i \in \mathbb{R}$, defined by the vector-valued function $\vec{O}$ with unit vector components $\hat{\imath}$, $\hat{\jmath}$ defined by the partial derivatives of $F_h(I_i, V_i)$ with respect to I_i and $F_p(I_i, V_i)$ with respect to V_i respectively.

$$\vec{O}(I_i, V_i) = \left(\frac{\partial F(h_i)}{\partial I_i}\right)\hat{\imath} + \left(\frac{\partial F(p_i)}{\partial V_i}\right)\hat{\jmath} \tag{2.8}$$

For equations 2.6 and 2.7, this gives:

$$\vec{O}(I_i, V_i) = 1 \cdot \hat{\imath} + 2(I_i - V_i) \cdot \hat{\jmath} \tag{2.9}$$

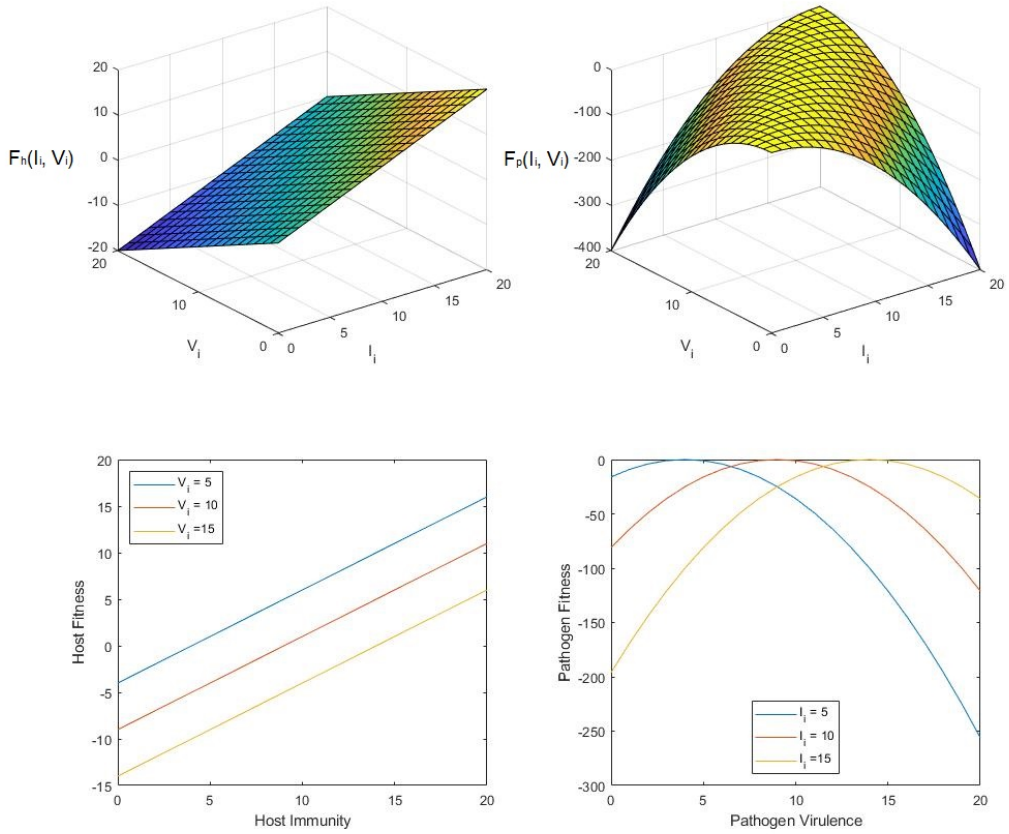


Figure 2.2: Host (left) and Pathogen (right) fitness landscapes from equations 2.6 and 2.7 respectively ([0, 20] for I_i, V_i), the lower panels are 'slices' through these surfaces at particular values.

As the coefficient for $\hat{\imath}$ is always > 0, $\|\vec{O}\| \neq 0$ for all (I_i, V_i) tuples. Thus there are no stable points, and $I_i \to \infty$. As the coefficient for $\hat{\jmath}$ is > 0 when $I_i > V_i$, if $I_i \to \infty$, $V_i \to \infty$. Figure 2.3 offers a visualization.

Now we return to the case where there are proportional costs to immunity and virulence for hosts and pathogens, as described by equations 2.4 and 2.5 ($F_h(I_i, V_i) = (I_i - V_i) - 0.1 \cdot I_i$; $F_p(I_i, V_i) = -(I_i - V_i)^2 - 0.1 \cdot V_i$).

This maintenance term does not introduce a maxima to $F_h(I_i, V_i)$ with respect to I_i, and $F_p(I_i, V_i)$ still has a maxima with respect to V_i (although the maintenance term introduces an offset from equality: $V_i = I_i - 0.05$), and the vector field of the joint optimisation is virtually the same. The crucial change is the equations

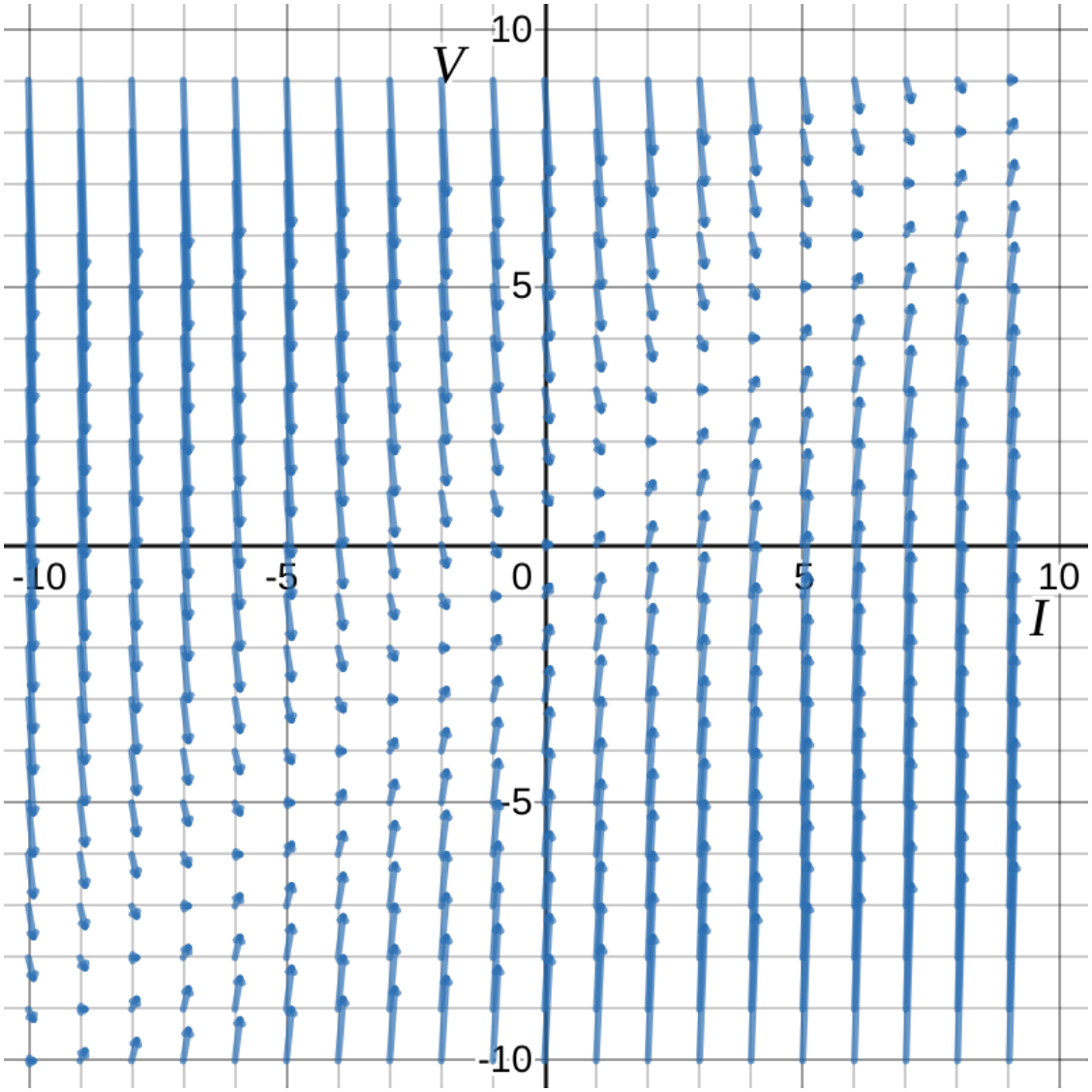


Figure 2.3: Vector field of $\vec{O}(I_i, V_i) = \left(\frac{\partial F_h(I_i,V_i)}{\partial I_i}\right)\hat{\imath} + \left(\frac{\partial F_p(I_i,V_i)}{\partial V_i}\right)\hat{\jmath}$, plotted for $-10 \leq I_i, V_i < 10$

are no longer invariant of translations of $k \cdot I_i + k \cdot V_i$ with $k \in \mathbb{R}$ (consider the substitution $A = I_i - V_i$ for equations 2.6 and 2.7).

Let $\vec{v}$ be the vector (1,1). The directional derivatives of this vector in equations 2.4 and 2.5 are:

$$\nabla_{\vec{v}}((I_i - V_i) - 0.1 \cdot I_i) = -0.1 \tag{2.10}$$

$$\nabla_{\vec{v}}(-(I_i - V_i)^2 - 0.1 \cdot V_i) = -0.1 \tag{2.11}$$

This suggests the potential for runaway maladaptive selection. In the fitness landscapes, independent optimisation for I_i and V_i lead towards mutual increases, but matched increases in I_i and V_i can reduce fitness for both host and pathogen.

This 'runaway' dynamic could be constrained if, for any value of V_i, $F_h(I_i, V_i)$ had some maxima with respect to I_i, instead of $I_i \to \infty$, $F_h(I_i, V_i) \to \infty$. One biologically plausible possibility would be that I_i has diminishing returns (or, equivalently, accelerating costs): perhaps further increments to immunological performance have increasing marginal energetic cost, or have accelerating likelihood of prompting autoimmune disease. Suppose $m_H = 0.1 \cdot I_i^2$, thus:

$$F_h(I_i, V_i) = (I_i - V_i) - 0.1 \cdot I_i^2 \tag{2.12}$$

As I_i increases the accelerating maintenance costs will outpace the linear conflict term in the fitness function. This can be seen graphically (figure 2.4) and shown algebraically:

$$F_h(I_i, V_i) = (I_i - V_i) - 0.1 \cdot I_i^2 \tag{2.13}$$

$$\frac{\partial(F(h_i))}{\partial(I_i)} = 1 - 0.2 \cdot I_i \tag{2.14}$$

Thus a maxima (as $\frac{\partial^2 F(h_i)}{\partial I_i^2} < 0$) at $I_i = 5$.

2.5 Cellular automata models

We extend this analysis by constructing cellular automata models to both confirm the analytical results in a stochastic model, and to investigate manipulations (e.g. ratcheting, effects of greater mutability) which are more difficult to express and analyse mathematically. All models share a similar outline:

1. Initialization of a grid of hosts and corresponding pathogen populations (i.e. the position (x, y) represents a host individual, and the pathogen population of that host). The grids are wrapped to a torus to give a uniform (edgeless) environment for both.

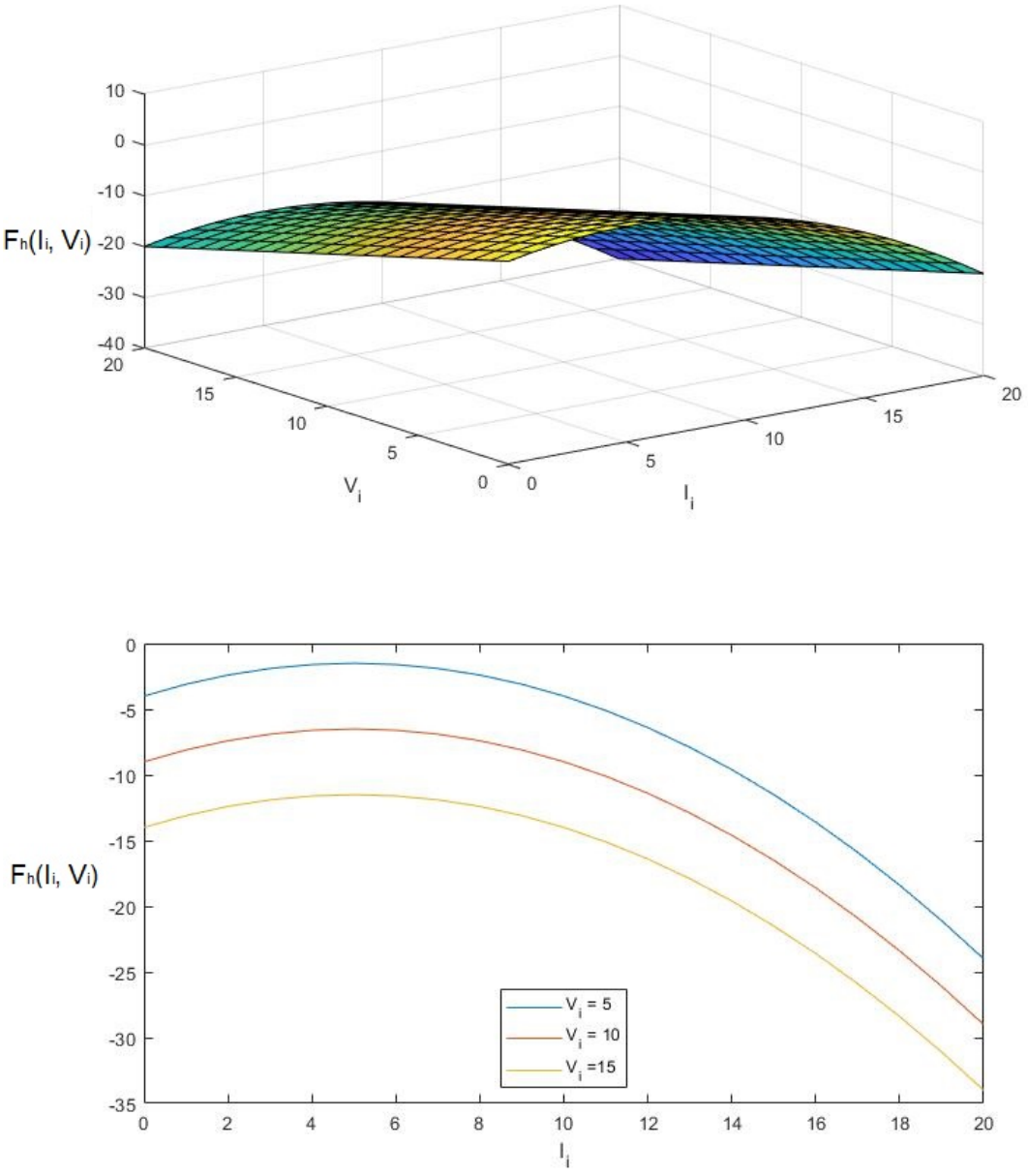


Figure 2.4: $F_h(I_i, V_i)$ landscape given I_i, V_i, and equation 2.12 (upper panel). Lower panel graphs 'slices' at $V_i = 1, 5, 10$, note the maxima at $I_i = 5$

2. A mutation stage, where unit increments of immunity and virulence are randomly added and/or taken away from hosts and pathogens, respectively.

3. For each position on grid, the host and pathogen fitness $F_h(I_i, V_i)$ and $F_p(I_i, V_i)$ is calculated from the its $I_{(x,y)}$ score and the $V_{(x,y)}$ score.

4. A competition stage: For each position on the grid, $F_h(I_i, V_i)$ and $F_p(I_i, V_i)$ are compared to the average fitness of its eight neighbours. Those with lower fitness than the average of their eight neighbours are replaced with the fittest neighbour (ties are broken at random).

5. 2-4 are iterated repeatedly.

2.5.1 Model set-up: baseline case and variations

The canonical parameter set for the baseline case is given in table 2.1. We then make a number of variations to the model. These variants can be split into three categories: first are tests of model fidelity, to see if it can give the expected performance in simple cases; second are sensitivity analyses; third are further investigations into both whether the model shows the features highlighted above in the verbal argument, and assessing the impact of mutation rate and the maintenance function on its behaviour.

Parameter		**Baseline case**
Grid size		10 by 10
Initial grid values	Immunity	0 for all elements
	Virulence	0 for all elements
Mutation stage	Immunity	1 per 100 of +1, 1 per 100 of -1
	Virulence	2 per 100 of +1, 2 per 100 of -1
Fitness equation	Hosts	$F_h(I_i, V_i) = (I_i - V_i) - 0.1 \cdot I_i$
	Pathogens	$F_p(I_i, V_i) = -(I_i - V_i)^2 - 0.1 \cdot V_i$
Iteration number		2000

Table 2.1: Parameters and baseline values for the cellular automata model

Model fidelity

The model should both assess host and pathogen fitness in the manner outlined above, and allow fitter organisms to displace less fit ones. We therefore develop simple test scenarios to check this:

1. 'Super-immunity': $I_{(x<6)} = 10$, $I_{(x>5)} = 0$, and all pathogens $V_{(x,y)} = 0$, with mutation of $V_{(x,y)}$ and $I_{(x,y)}$ disabled. We expect the host individuals with greater immunity to spread over the entire grid.

2. 'Super-virulence': $V_{(x<6)} = 10$, $V_{(x>5)} = 0$, and all hosts $I_{(x,y)} = 0$, with mutation of $V_{(x,y)}$ and $I_{(x,y)}$ disabled. We expect pathogen populations (p_i) to the region of lower virulence to spread over the entire grid.

We also test whether our model can show local effects with a 'split-optimal virulence' scenario: $I_{(x<6)} = 10$, $I_{(x>5)} = 0$. $V_{(x,y)} = 5$, mutation of $I_{(x,y)}$ (but not $V_{(x,y)}$) disabled. We expect those p_i in the region of the grid with higher-immunity hosts to maintain a higher virulence than those p_i in region with lower-immunity hosts.

Sensitivity analyses

Given the abstract nature of the model, different choices for parameter values in the baseline case are similarly reasonable. We therefore test variations of these to check the qualitative behaviour of the model is not sensitive to particular choice of parameter value. We vary:

Grid size Grid size: We repeat the model with a 1-by-2 (i.e. 2-cell) and 100-by-100 grids.

Mutation rates One test is of 'absolute rates' with two scenarios where in one the mutation rate for both hosts and pathogens are doubled, and another where they are halved. We also assess impact of changing the balance of 'positive' versus 'negative' mutations, by using two scenarios where we change the ratio

of additions:reductions in immunity and virulence from parity to 2:1 and 1:2, by doubling the rates of addition or subtraction, respectively.

Maintenance costs We modify the proportionate term for fitness costs for hosts and pathogens from 0.1 to 0.01, then in 0.1 increments from 0.2 to 1.1. We expect the model to behave similarly for all values save 1.1, where we expect the behaviour to switch: V and I should fall, whilst host and pathogen fitness should increase.

Further investigation

We develop further scenarios to test features of the verbal model highlighted above, as well as other explorations of the effect different mutation rates and cost functions can play.

'Host-initiated arms race' We use two scenarios, where the host or pathogen mutation step is modified to prevent mutations that increase I or V respectively. We expect V to remain at a steady value in the first case, but I to increase without bound in the second.

'Ratcheting' We use two scenarios. In the first, after 2000 iterations of the baseline case we modify the host mutation step to only allow immunity-reducing mutations. In the second, after 2000 iterations of the baseline case, we modify both the host mutation step as above but also reset I to zero for all grid positions. We expect in the first case I, V, $F_h(I_i, V_i)$, and $F_p(I_i, V_i)$ to remain at near their values for the first 2000 iterations; in the second, we expect V to fall and both host and pathogen fitness to increase.

Explorations of mutation rate and cost function

We focus subsequent exploration to cases where runaway selection dynamics can either be arrested, and/or offer hosts a stable fitness advantage. We investigate two broad hypotheses:

Mutation rate One case where we expect runaway not to be maladaptive is if the host is more mutable than the pathogen, and thus the pathogen cannot 'keep up' with host accumulation of immune adaptions. We test this with a scenario where the host's mutation rate is increased by a factor of ten. We expect both I and V to increase, and that host fitness steadily increases whilst pathogen fitness steadily falls.

Maintenance cost modifications One means of arresting the hypothesised 'runaway selection' dynamic discussed above could be to specify a concave rather than linear maintenance function (biologically, this could represent subsequent immune adapations of virulence factors being more costly, or having diminishing marginal returns). In this case, as c_H increases linearly with respect to I, $\frac{\partial^2 F(h_i)}{\partial I_i^2} < 0$, and thus there is a maxima for $F(h_i)$ (for pathogens, c_P is quadratically decreasing with respect to $|I - V|$, but if m_P grows faster with respect to V, $\frac{\partial^2 F(h_P)}{\partial V_i^2} < 0$). If the respective maxima differ for hosts and pathogens, initial runaway selection can stabilize into a steady states, and the range of steady states include those where the hosts are fitter than they were initially.

To test this, we first introduce quadratic rather than linear cost terms for both hosts and pathogens ($m_H = -0.1 \cdot I^2$, $m_P = -0.1 \cdot V^2$). Second, we modify the pathogen cost function again to be even more steeply increasing ($m_H = -0.1 \cdot I^2$, $m_P = -e^{V_i}$).

2.5.2 Technical details

All analysis performed in R (version 3.6.1). Analysis code and data are available at `https://github.com/gjlewis37/DPhil/blob/main/Ch2`.

2.6 Results

Throughout this section, we display the results of an arbitrarily chosen element of the grid (5,5). Plotting the average across the grid or from other positions gave essentially identical results (data not shown).

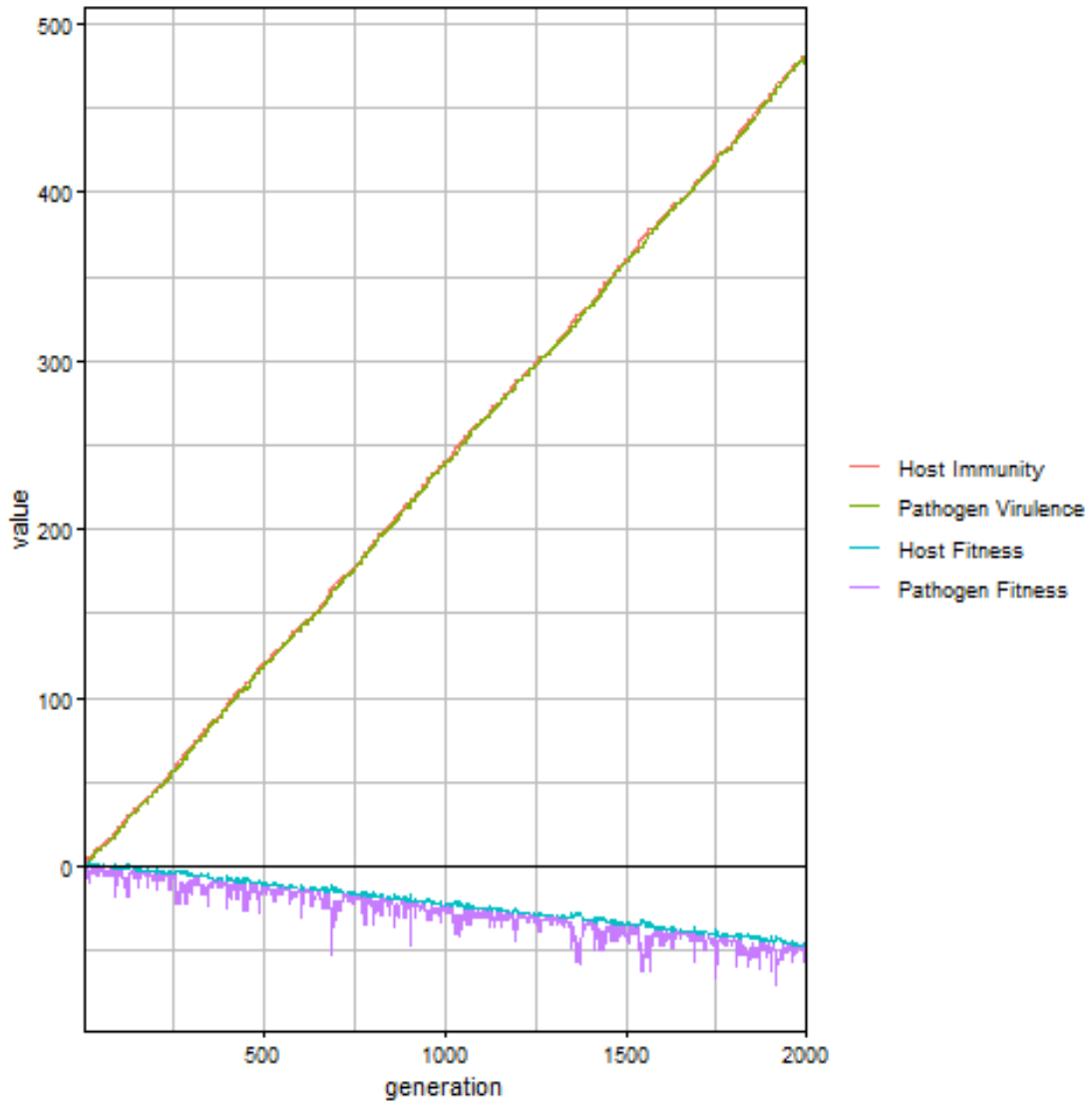


Figure 2.5: Baseline case: Virulence, Immunity, Host Fitness and Pathogen Fitness for the element in position (5,5) are plotted against generation time. Note approximately linear increases in I, V, but linear decreases in $F_h(I_i, V_i), F_p(I_i, V_i)$ - a maladaptive runaway.

2.6.1 Baseline case

In the baseline case, one observes runaway selection (figure 2.5). Throughout the grid, I_i and V_i increase, but $F_h(I_i, V_i)$ and $F_p(I_i, V_i)$ decrease, approximately linearly with number of iterations.

2.6.2 Fidelity tests and sensitivity analyses

These results were in line with our hypotheses: the qualitative effect of runaway selection was robust to varying the parameter values as described above, and the likewise the model demonstrated the behaviour we expected in the fidelity tests (see §2.8, supplementary results). The only minor divergence from our predictions were the 'switching' of *decreasing* I, V and *increasing* $F_h(I_i, V_i), F_p(I_i, V_i)$ occurred at $m_H = -1.0 \cdot I$ as well as $m_H = -1.1 \cdot I$ (discussed in supplementary results).

2.6.3 Further investigations

'Host-initiated arms race' In the case where hosts are prevented from developing positive increments of immunity in the mutation stage, the populations remain near their initial conditions - mutations that reduce immunity in hosts, and that either increase or decrease pathogen virulence are selected against when they emerge (figure 2.6). In the case where the pathogens are prevented from developing mutations that increase virulence, there is unbounded increase in I, with consequent increases in $F_h(I_i, V_i)$ and decline in $F_p(I_i, V_i)$ (figure 2.7).

'Ratcheting' We find ratcheting escalation of host immunity but not pathogen virulence. In the case where the final grid from the baseline simulation undergoes another 2000 iterations with the rules modified to exclude immunity-increasing (but not immunity-decreasing) mutations, both immunity and virulence stabilize. There is no mutual reduction in host immunity/pathogen virulence (figure 2.8). If the same process is repeated with the further modification that host immunity is reset to zero across the grid, V steadily falls to $V \approx 0$, with an overall improvement in both host and pathogen fitness (figure 2.9).

Mutation rate and 'outracing' In the case where the hosts have double the mutation rate than the pathogens, one sees similar runaway selection with unbounded increases in I and V, but as I increases faster than V, $F_h(I_i, V_i)$ increases whilst $F_p(I_i, V_i)$ falls (figure 2.10).

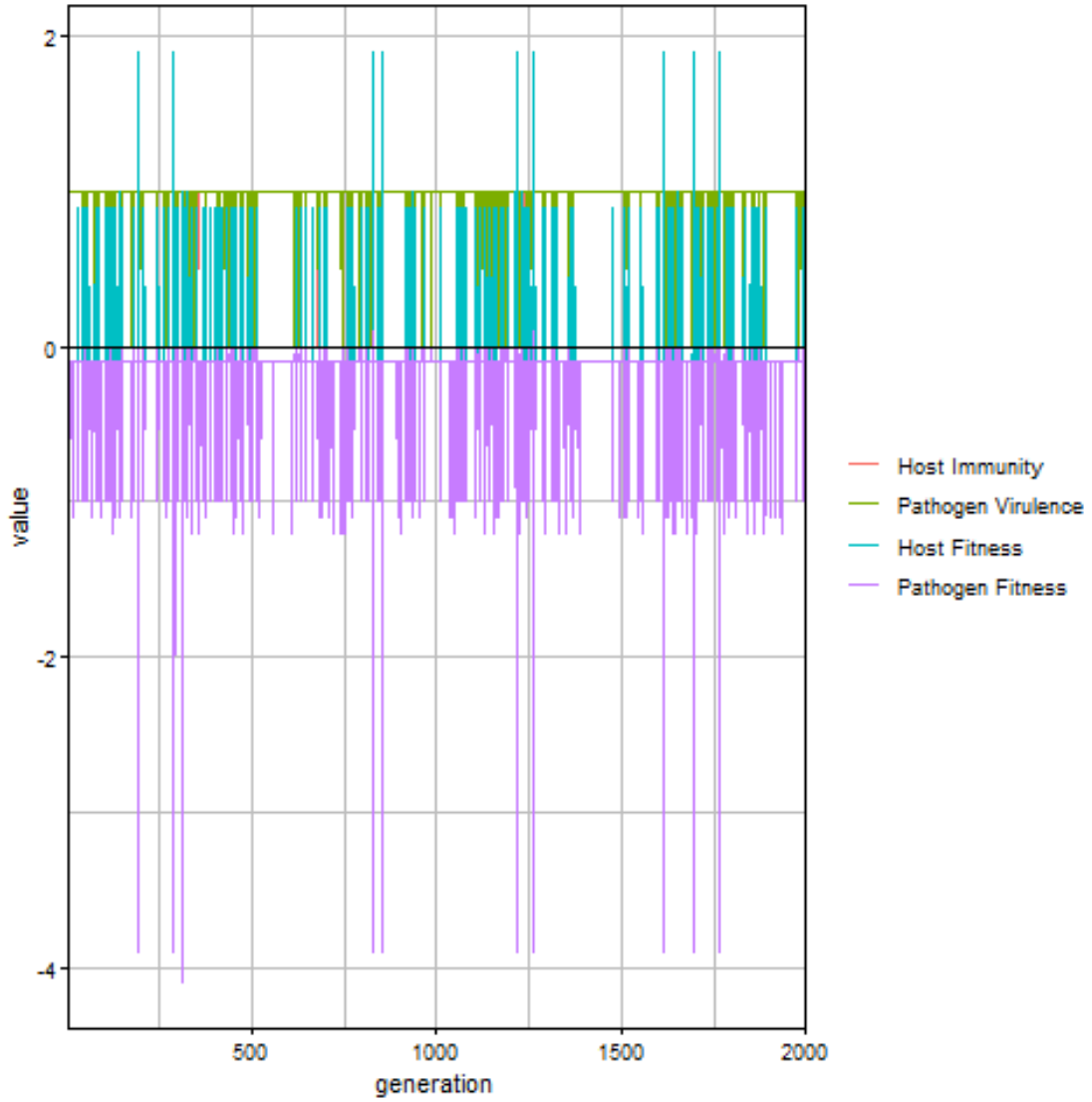


Figure 2.6: Disabling increases in host immunity: Virulence, Immunity, Host Fitness and Pathogen Fitness for the element in position (5,5) are plotted against generation time. Immunity and virulence remain constrained to their initial values ($I = V = 1$).

Maintenance cost function changes Modifying m_H and m_P to have quadratic rather than linear costs in I and V (i.e. $m_H = -0.1 \cdot I^2$, $m_P = -0.1 \cdot V^2$) resulted in stability rather than runaway behaviour (figure 2.11): I and V approached a stable value after ≈500 iterations, and remained there over the next 1500.

Modifying m_P with a steeply (exponentially) increasing cost term (i.e. $F_p(I_i, V_i) = -(I_i - V_i)^2 - 0.1 \cdot e^{V_i}$) alongside the quadratic maintenance cost in the host demonstrated both I_i and V_i approaching *different* steady state values (figure 2.12). *Post-hoc* variation of the constant terms in the host and pathogen fitness

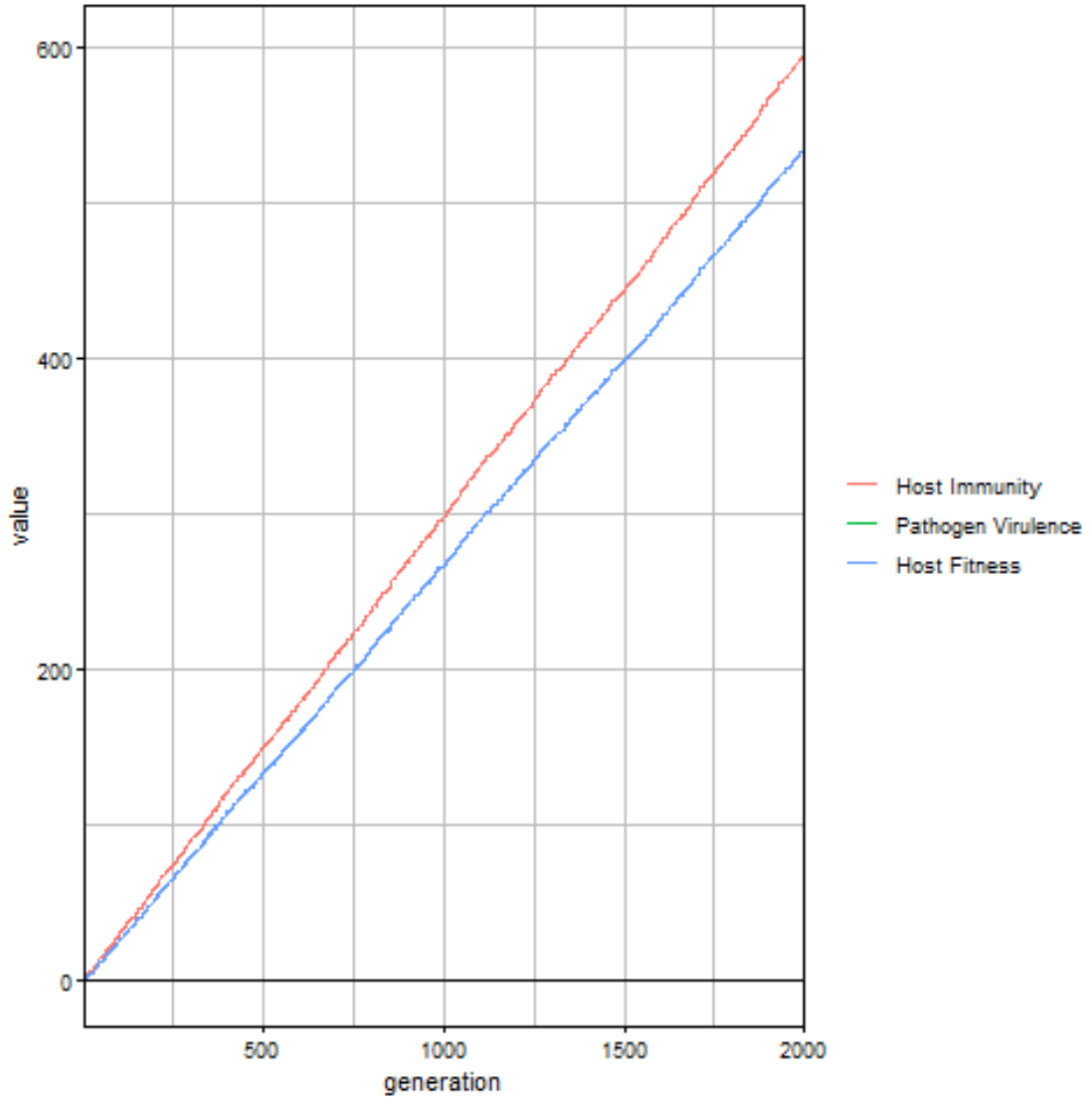


Figure 2.7: Disabling increases in pathogen virulence: Virulence, Immunity, and Host Fitness for the element in position (5,5) are plotted against generation time. Immunity and Host Fitness steadily increase. Pathogen fitness has not been plotted as it falls to highly negative values ($F_p(I_i, V_i) \approx -35000$ at the 2000^{th} generation).

equations (e.g. $F_h(I_i, V_i) = (I_i - V_i) - 0.05 \cdot I_i^2$; $F_p(I_i, V_i) = -(I_i - V_i)^2 - 0.05 \cdot e^{V_i}$) can change these stable values so that $F_h(I_i, V_i)$ is can stabilize at positive values (data not shown).

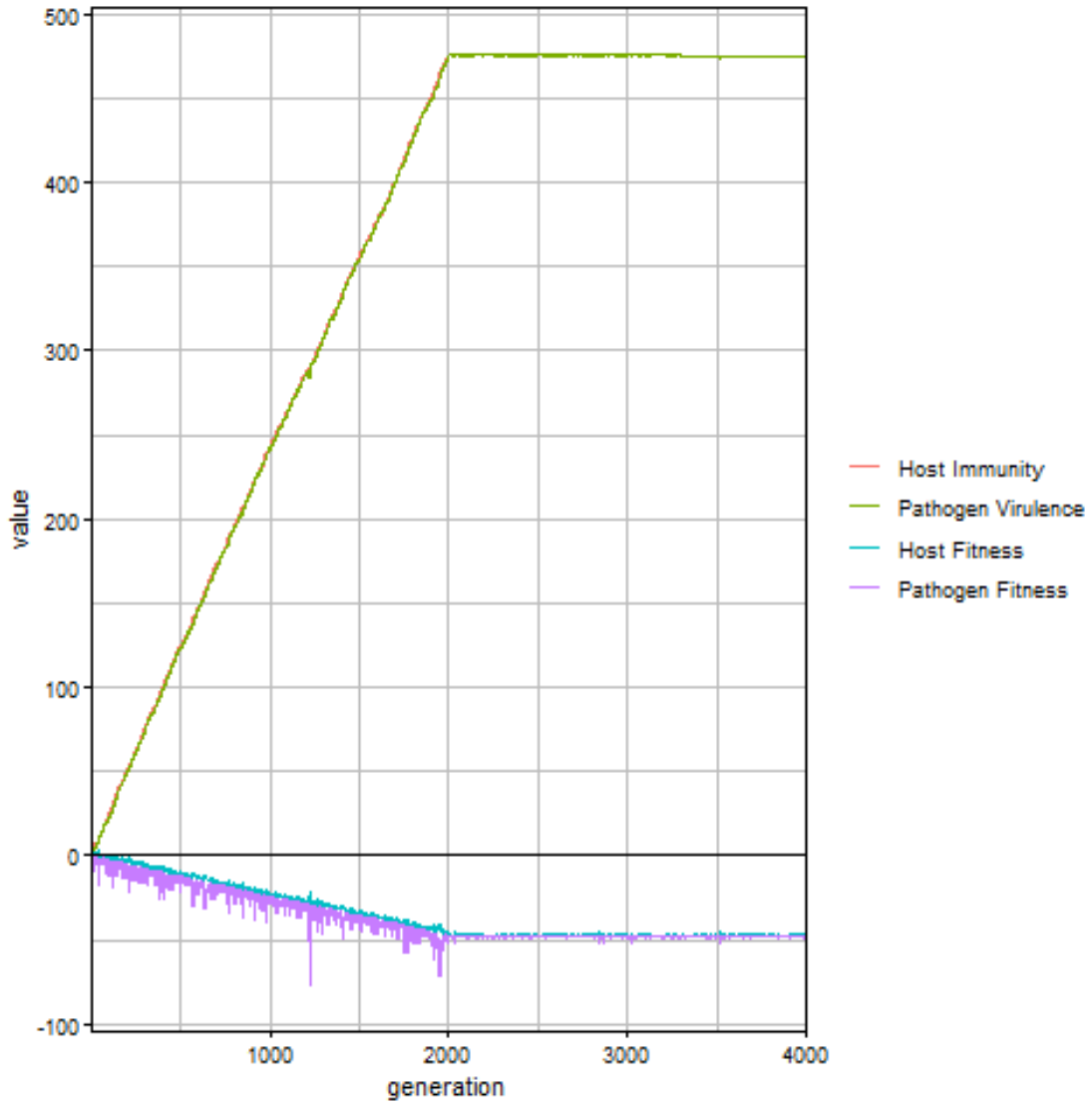


Figure 2.8: Halting immunity increases after 2000 generations: Immunity, Virulence, Host Fitness, and Pathogen Virulence for the element in position (5,5) are plotted against generation time. Note the steady linear trends halt and remain static once increases in host immunity are disabled.

2.7 Discussion

Here, we have developed a hypothesis which seeks to explain immune adaptations in terms of runaway selection. The cellular automata model we have produced broadly supports distinctive features of our hypothesis: the potential for runaway selection which is ultimately maladaptive, the 'race' being initiated unilaterally by host intra-specific competition, and the co-evolutionary escalation of immunity being ratchet-like for host immunity (but not pathogen virulence).

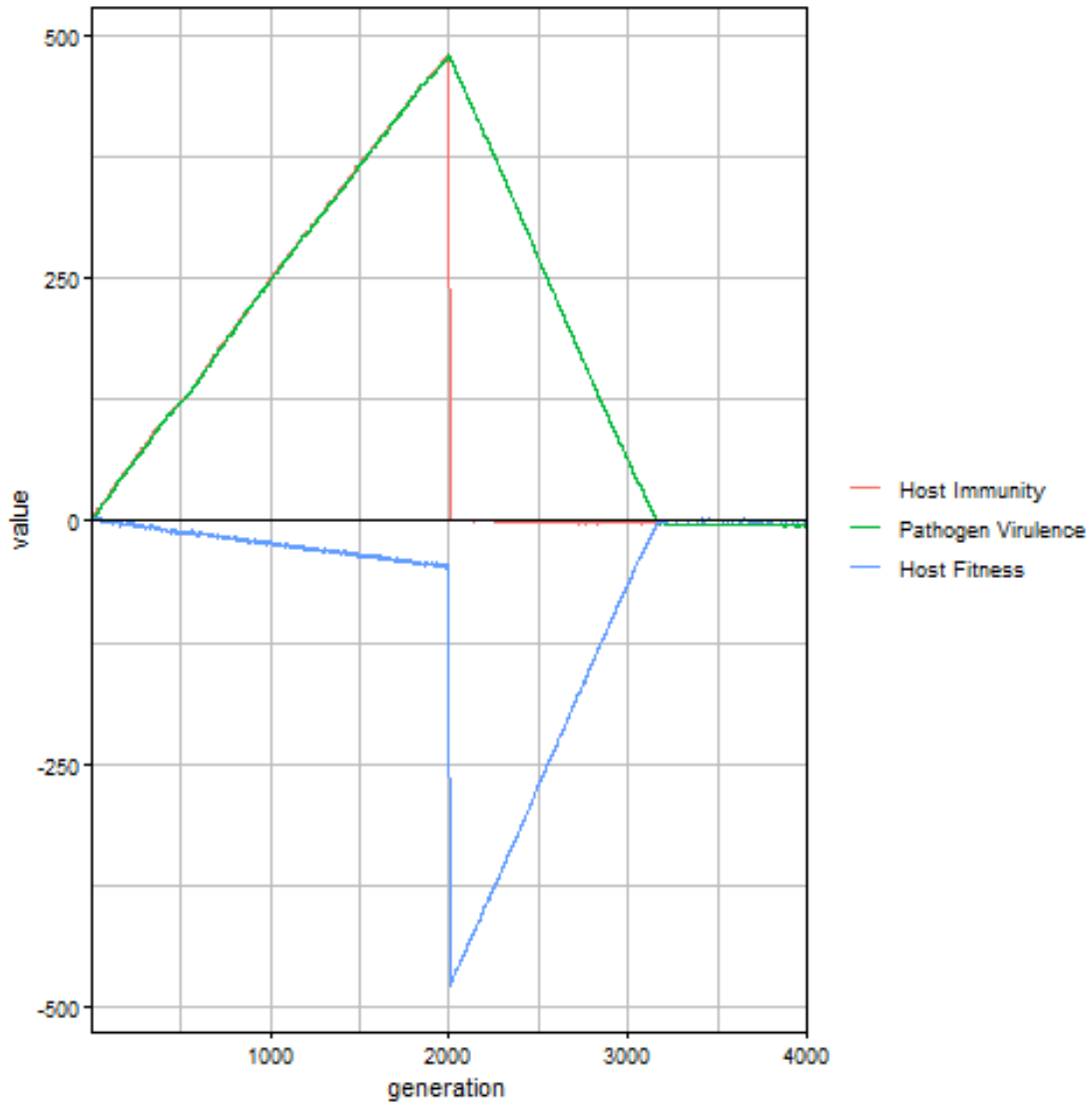


Figure 2.9: Halting immunity increases and resetting immunity after 2000 generations: Immunity, Virulence, Host Fitness, and Pathogen Virulence for the element in position (5,5) are plotted against generation time. Pathogen fitness has not been plotted as it drops to very negative values ($F_p(I_i, V_i) \approx -200000$) when host immunity is reset - it rises rapidly to $F_p(I_i, V_i) \approx 0$ at generation > 3170.

Our further investigations with this framework suggest the maintenance functions were key in determining qualitative behaviour. The runaway dynamic can be constrained when the maintenance costs (as a function of immunity or virulence) grow faster than the impact of 'extra' immunity or virulence on the effect of host-pathogen conflict. Differences between these maintenance functions between host and pathogens can also generate a stable adaptive advantage (rather than

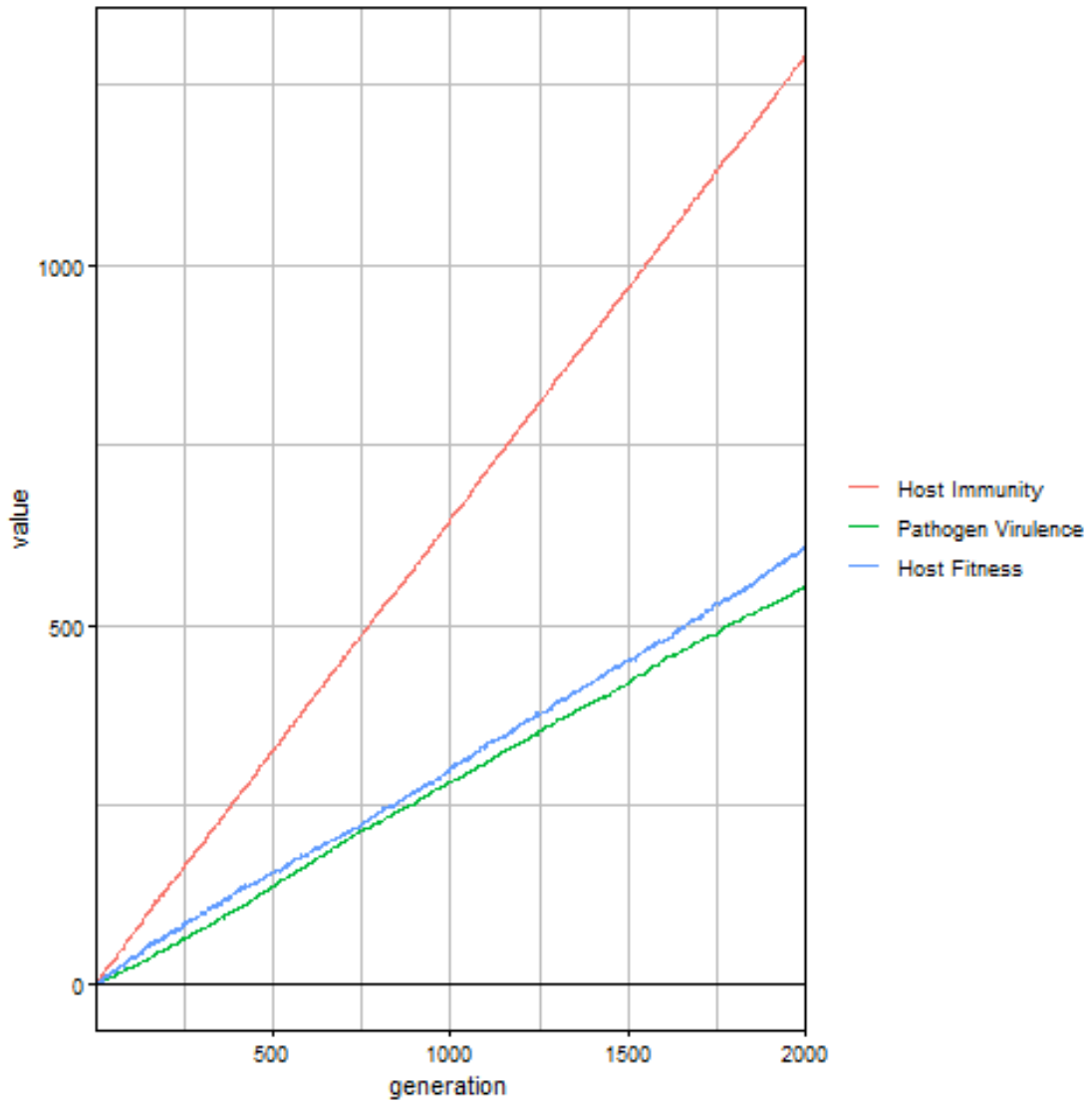


Figure 2.10: Outracing: Immunity, Virulence, and Host Fitness for the element in position (5,5) are plotted against generation time. Note divergence of I and V, and consequent minor improvements to $F_h(I_i, V_i)$. The dramatic quadratic fall of $F_p(I_i, V_i)$ (to -550000 at the final generation) has not been plotted.

disadvantage) to the host for immune adaptation.

Several elements of our hypothesis have been used in modelling host-parasite dynamics: that hosts and pathogens can invest resources in conflict with one another; that host susceptibility to infection can be in degrees rather than 'all-or-nothing'; investment in immunity or virulence can impose costs independent of its effect on the course of infection; host and pathogen 'investment' strategies can both co-evolve with 'arms race' or 'Red Queen' dynamics; and that these

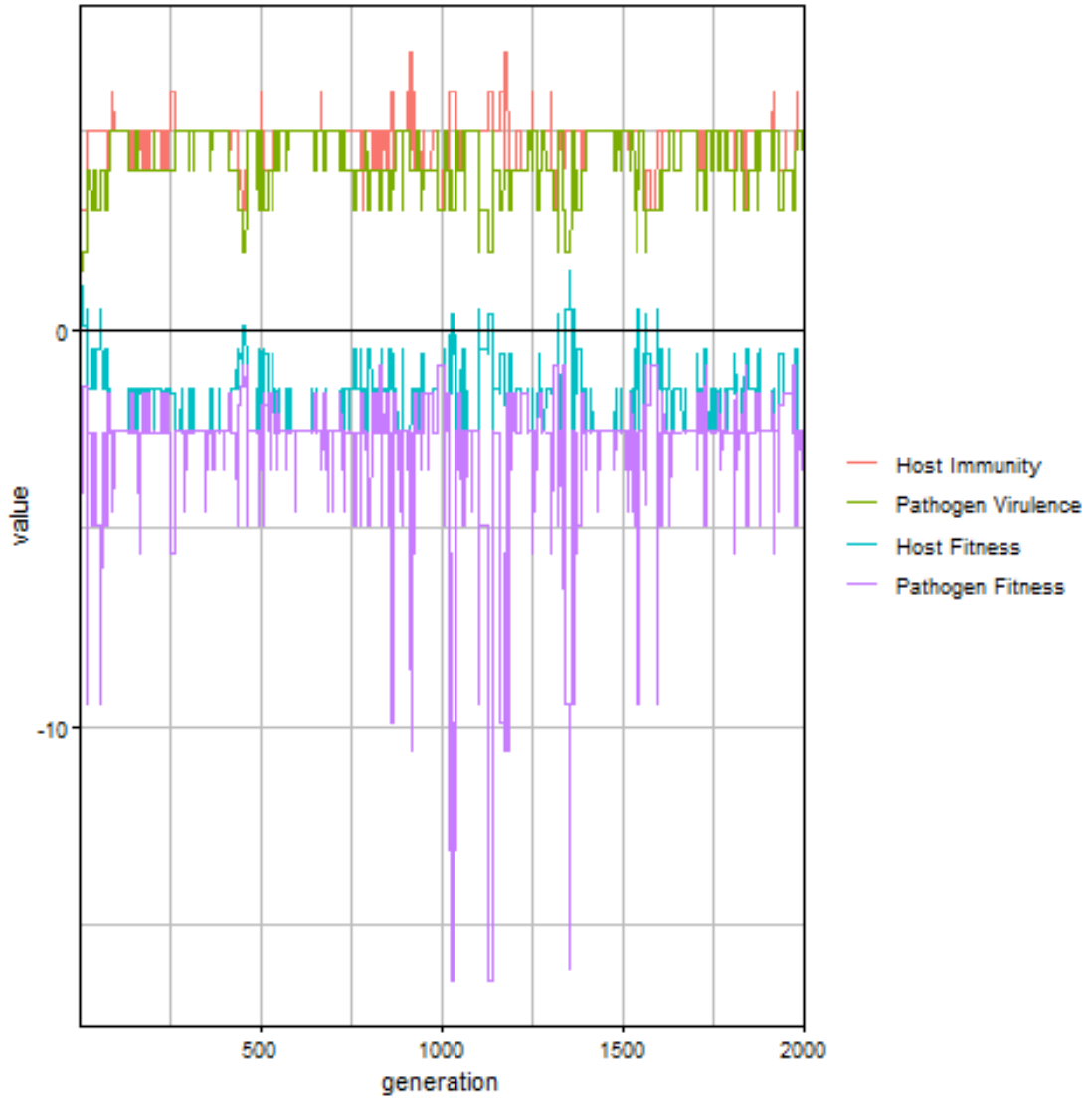


Figure 2.11: Quadratic costs: Immunity, Virulence, Host Fitness and Pathogen Fitness for the element in position (5,5) are plotted against generation time. Note stability at I, $V = 5$.

can be analysed using game theory.[87–93]

The novelty of maladaptive runaway selection suggests it emerges from the combination of these features. This follows from the verbal model given in section 2: if one of these factors are omitted (e.g. if immunity and virulence have hard limits,[89] or one of either hosts or pathogens are held static) the argument for maladaptive runaway selection would no longer follow.

It also suggests models which show maladaptive runaway selection need to have a particular structure. Often, theoretical approaches are used to find co-evolutionary

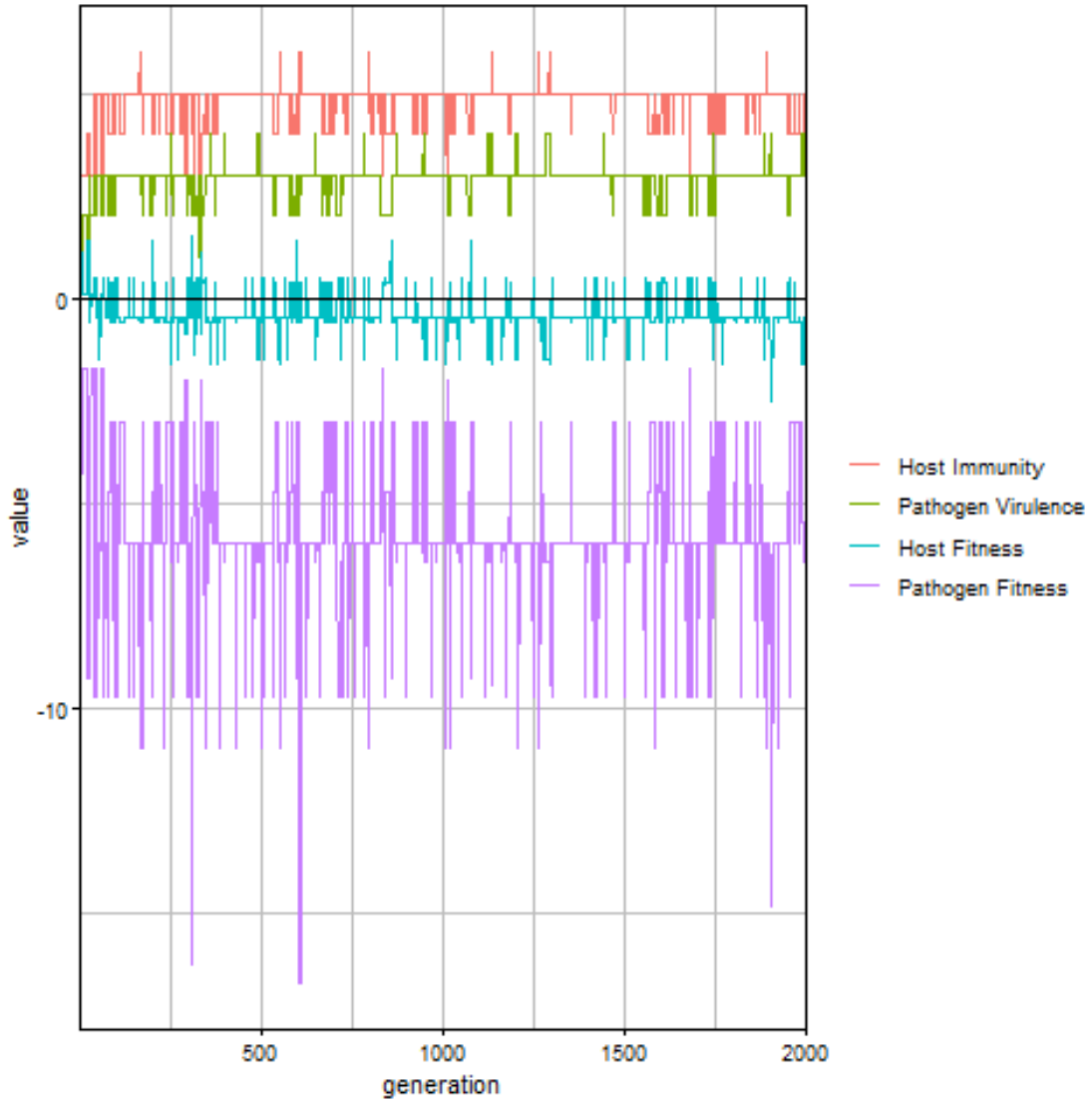


Figure 2.12: Quadratic costs for the host, exponential costs for the pathogen: Immunity, Virulence, Host Fitness and Pathogen Fitness for the element in position (5,5) are plotted against generation time. Note the rise and then stability around $I \approx 5$, $V \approx 3$.

stable strategies for host and pathogen, and thus use overall fitness rather than the contribution to fitness of immunity and virulence alone.[87, 93, 94] Although the former is necessary to understand whole-system equilibrium behaviour, our approach can highlight dynamics constrained around equilibrium states.

2.7.1 Limitations

The model used is highly simplified and abstract. Although this is useful in isolating a particular behaviour, it raises uncertainty around generality and external validity:

demonstrating a given behaviour in a mathematical model is not the same as a demonstration this behaviour occurs in nature. We structure our discussion of the limitations of this work in terms of the mathematical or modelling assumptions made.

Other factors to host and pathogen fitness Our model purely assesses fitness in terms of pathogen virulence and host immunity, excluding all other factors that typically contribute to fitness overall such as environmental constraints and inter-species competition.

Although isolating an aspect of fitness better exposes the mechanism of Fisherian selection for examination, it limits straightforward application to biological systems or natural history, as it can be entangled with (or overridden by) other factors in real scenarios.

This general point also applies to immune adaptations in particular, as these can have other functions beyond resisting pathogens: examples include cell-mediated responses in eliminating malignancy,[95] or authophagy's role in cellular maintenance.[96] Thus even if they confer no benefit at equilibrium in terms of pathogen resistance they may be adaptive overall when accounting for their other contributions to host fitness.

Survival, local competition and universal infection The use of superimposed and locally competing grids of persistent (i.e. individual elements can get arbitrarily 'unfit' without becoming extinct) hosts and pathogens was chosen for simplicity. Although this can loosely approximate some ecological contexts (such as a highly prevalent, contact-transmitted and chronic infectious disease) it's neglect of life-history dynamics and density effects make it a poor model for many others.

Further extensions to the mathematical analysis (e.g. mean-field approaches) and model construction (e.g. random rather than local selection from the pathogen grid, population models where fitness emerges from population changes rather than mathematical stipulation, and probabilistic infection with subsequent local infection). However, inclusion of these further factors should be expected to modulate, rather than eliminate, the main finding of runaway selection. For example, all else equal

immune adaptations have less benefit for a host population where individuals have a lower probability of infection, but they would still be selected for providing these discounted benefits outweigh their costs. This may change the point (if costs escalate) this process is checked, but not whether it occurs at all.

Immunity and virulence 'cancelling out' in equal increments Immunity and virulence are treated as single variables which can be totalled up and compared between host and pathogen. Although this monolithic treatment can parallel some mechanisms of host immunity and pathogen virulence (e.g. gene-for-gene relationships in plant resistance,[97, 98] aggregate production of toxins and anti-toxins), and although the representation is defensible at a sufficient level of abstraction (i.e. 'Immunity' and 'Virulence' representing overall investment of resources in host-pathogen conflict, thus for example the adaptive immune system can be modelled *en bloc* as a large investment in pathogen resistance), the gap between the two covers a vast diversity of pathophysiology.

One assumption of the modelling is that a given adaptation for immunity or virulence by can be cancelled out by a corresponding adaptation in the pathogen or host. There is no guarantee this would always apply: perhaps some adaptations for host and pathogen have no counter, or at least no counter accessible to natural selection. Runaway selection would not apply in these cases.

Another simplification is that immunity and virulence are unitary. In reality, hosts may contest pathogen infection through many different mechanisms, which may in turn provoke responses (and counter-responses) in a one-many way. Elaborating the model with multiple pathogen species (and multiple 'Immunities' which may cross apply to subsets of these) could prove an interesting further extension of this work.

Simple and uniform costs The diversity of mechanisms is - unlike our model - unlikely to have identical costs and benefits for host and pathogen. In the same way there is no guarantee there's an accessible counter-adaptation for every adaptation, there is no guarantee counter-adaptations have equivalent costs to the initial adaptation they are in response to. Particular contests of immunity and

virulence may give one party a structural advantage: perhaps a costly anti-microbial protein can be evaded with a functionally-irrelevant point mutation in the pathogen proteome; perhaps successful long-term evasion of the adaptive immune systems sets a hard constraint on overall pathogen fitness.

Similarly, the returns and costs of a given mechanism of immunity or virulence may not have linear returns with further investment. For example, perhaps it is cheaper for a pathogen to resist febrile temperatures than it is for hosts to mount higher fevers, thus further investment in higher fevers is increasingly counter-productive to the host. Our extensions with varying and non-linear cost functions (cf. §2.6.3) can begin to explore these dynamics, but there is a lot more ground that could be covered. One example is multiple mechanisms of Immunity and Virulence between a host-pathogen pair (i.e. $I_1 \rightarrow I_n$ with corresponding $V_1 \rightarrow V_n$) with different relative costs and scaling. One possibility is this will typically lead to sub-optimal investment by host across its potential mechanisms of immunity - investments in less effective or worse-scaling defences may crowd out development of more effective ones.

2.7.2 Implications and further work

Mathematical models also face a trade-off between concision and comprehensiveness;[99] the balance we strike is similar to other investigators. We believe our hypothesis of maladaptive runaway selection can be a credible mechanism for immune adaptation. This both offers new perspectives on ongoing debates, and also suggests new research directions.

Our work contributes to ongoing efforts to understand the host contribution to host-pathogen dynamics.[12, 100] Our account could be extended towards more sophisticated treatments of 'immunity', to better address the limitations discussed above, such as distinguishing constitutive elements which are always present versus those that can be induced in response to infection,[101] or a model where pathogen and host compete not only in how much to invest in virulence and immunity in total but where to allocate this total to exploit or defend against different approaches to pathogenicity.

One proposal from 'evolutionary medicine' is to control pathogens via 'sculpting' their co-evolution to lead them towards lower virulence or less resistance to therapeutics,[102] argued to be more effective than attempts at opposition which ultimately prove counter-productive. This proposal is broadly concordant with our hypothesis that immune adaptations themselves could be counter-productive and ultimately forlorn attempts by the host at eradication of the pathogen.[103, 104] However, our work also suggests cases where these attempting to 'fight' pathogens can benefit the host: when it can 'race faster', or where the costs of escalating conflict scale in its favour. Both are plausible hopes for human intervention: medical science could outpace microbial evolution; by modelling the 'offense-defense' balance[105] between host and pathogen, we may be able to 'choose our battles' in areas where the pathogen is at a fundamental disadvantage.

There are opportunities to test the hypothesis of maladaptive runaway selection empirically. The framework in our model could be mirrored *in vivo*, although ensuring the experiment starts with the pathogen at its virulence optima is a challenge. One approach would be to cultivate the pathogen on clones of the host population (allowing adaptation for the pathogen to occur, but not the host), before initiating the experiment where both host and pathogen populations can co-evolve. Subsequent competition experiments with each with their ancestor can establish whether this co-evolutionary period has made both less fit as our hypothesis predicts. Some of the details of our model (e.g. that host adaptation precedes pathogen counter-adaptation) could be assessed, and some of the adjustments in our framework could be replicated (e.g. whether pathogen virulence falls if the co-evolved host is replaced by clones of the original variety).

There are observations that can be sought that provide indirect evidence for or against our hypothesis. Finding immune responses that are costly for the host to erect but cheaply evaded by the pathogen provide some support for maladaptive runaway selection (and vice versa). Maladaptive runaway selection would also suggest higher values for the proportion of the 'energy budget' the host spends on immune systems. The 'ratchet-like' behaviour implied by our hypothesis could

be compared to any observations where a host population has been subject to a sustained reduction in pathogen load (with our hypothesis suggesting one should see immunological defences continue being maintained to a similar degree).

2.8 Supplementary results

2.8.1 Fidelity tests

Super-immunity

As expected, the region with $I = 10$ spread to cover the entire grid, displacing the $I = 0$ region (data not shown).

Super-virulence

As expected, the region with $V = 0$ spread to cover the entire grid, displacing the $V = 10$ region (data not shown).

Split-optimal virulence

As expected, the initially uniform virulence across the grid diverged into two regions, one with $V \approx 0$, the other with $V \approx 10$, matching the corresponding regions of $I = 0$ and $I = 10$ (figure 2.13).

2.8.2 Sensitivity analyses

Grid size

2 by 1 The qualitative behaviour with 2 cells is qualitatively similar: I and V steadily increase, $F_h(I_i, V_i)$, $F_p(I_i, V_i)$ steadily decrease (figure 2.14). The smaller changes in these variables can be explained by the small cell count, with consequently fewer mutations in both host and pathogen populations each generation.

100 by 100 With a 100 by 100 cell grid, the qualitative behaviour was similar to the baseline case (figure 2.15). The main quantitative difference between this and the baseline is the greater absolute rate of change, likely owed to the proportionately higher absolute number of mutations per generation.

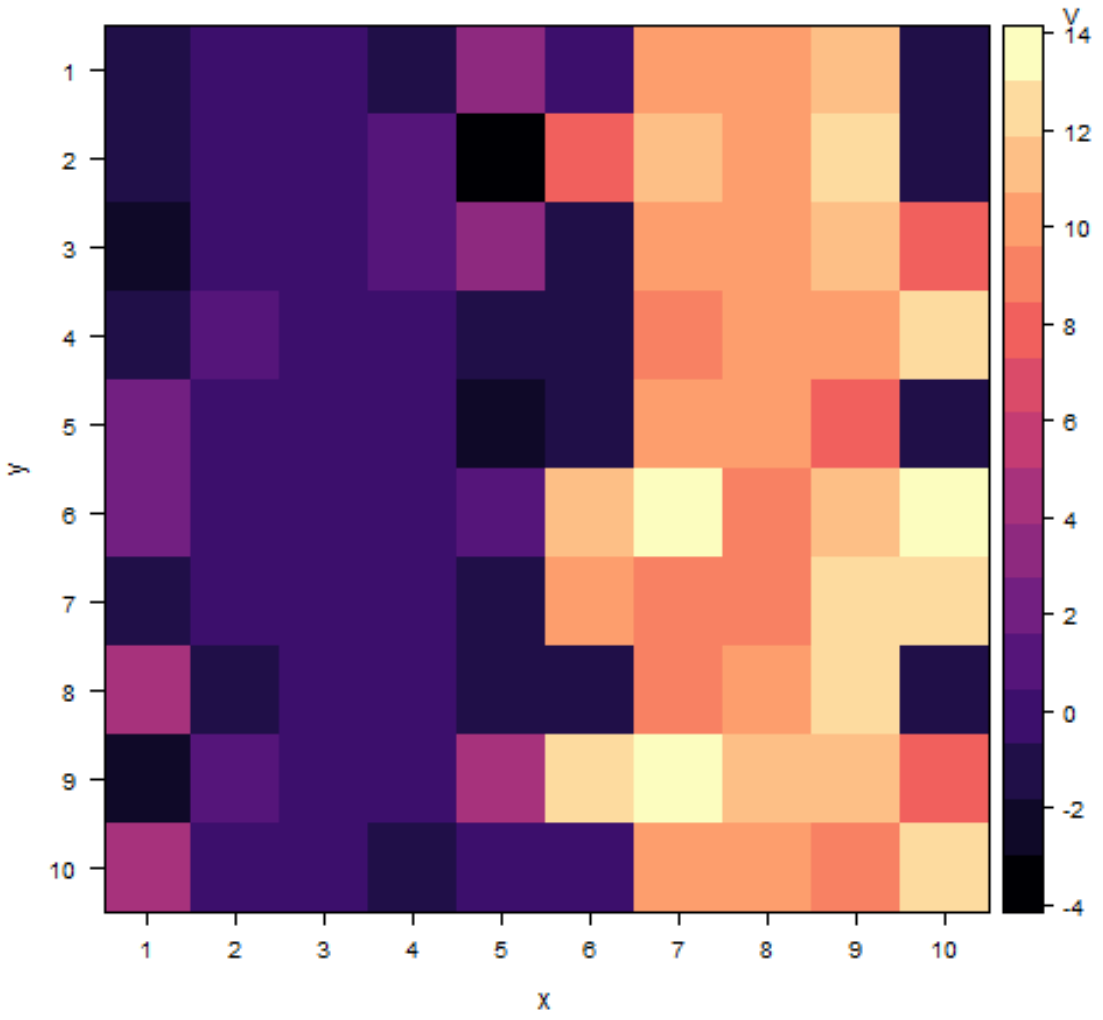


Figure 2.13: Raster plot of virulence scores at the 2000th iteration in the split-optimal virulence fidelity test. Note the two regions corresponding to $V \approx 0$, and $V \approx 10$, with intermediate values at the borders of each region.

Mutation rate

The sensitivity of the baseline case to mutation rate and the ratio of increasing versus decreasing mutations was assessed by doubling the mutation rate for both hosts and pathogens (figure 2.16), halving the mutation rate for hosts and pathogens (figure 2.17), doubling only the rate of mutations that increase I and V (figure 2.18), and doubling the rate of mutations that decrease I and V (figure 2.19). In all cases, the qualitative behaviour was unchanged, with greater absolute rates of

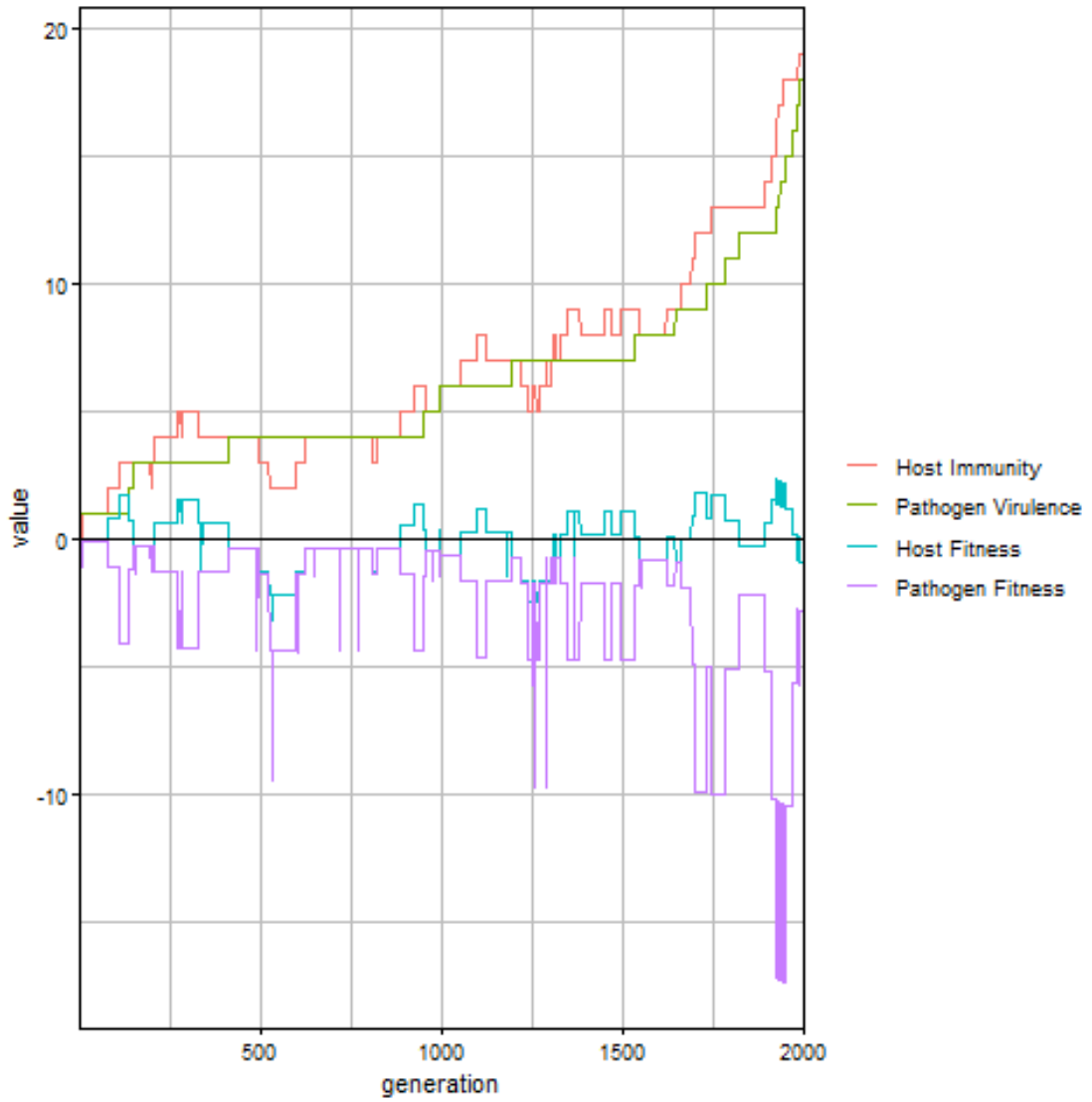


Figure 2.14: 2 by 1 grid sensitivity test: Immunity, Virulence, Host Fitness and Pathogen Fitness for the element in position (1,1) are plotted against generation time. Greater noise and lower absolute changes are likely attributable to much lower absolute rates of mutation in the entire (much smaller) populations.

change corresponding to doubling rates of all or increasing mutations, and lower rates with lower absolute rates or increased rates of reducing mutations.

Maintenance costs

$m = 0.01 \cdot I$ (or V). Changing the maintenance function parameter to a tenth of its baseline value did not change qualitative behaviour (figure 2.20), although the reduction in $F_h(I_i, V_i)$ and $F_p(I_i, V_i)$ were proportionately less.

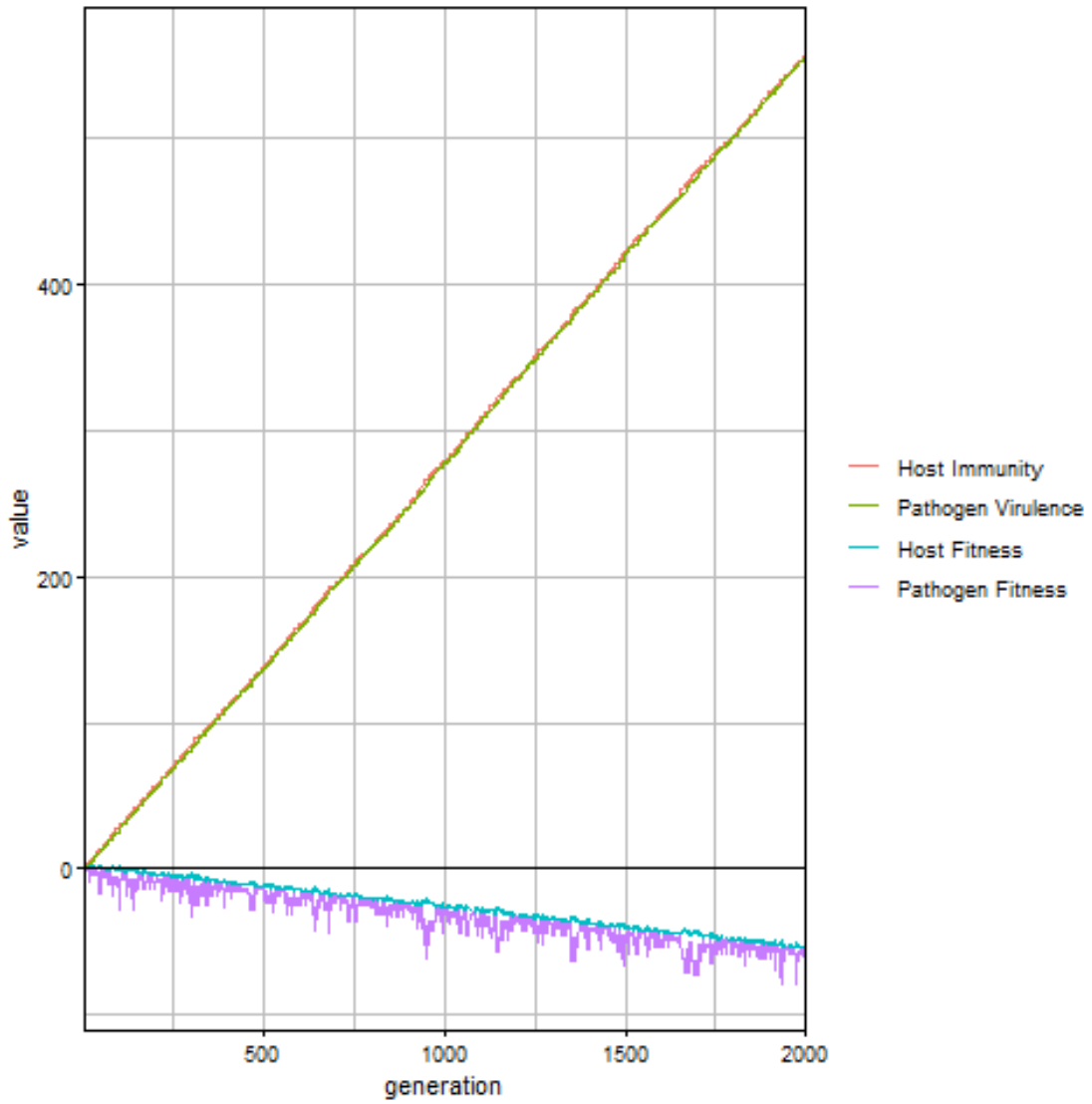


Figure 2.15: 100 by 100 grid sensitivity test: Immunity, Virulence, Host Fitness and Pathogen Fitness for the element in position (1,1) are plotted against generation time.

$m = 0.2 \rightarrow 1.1$ Increasing the maintenance constant (for both I and V) from 0.2 to 1.1 in 0.1 increments (figure 2.21) showed a gradual shift with the qualitative behaviour remaining the same up until $m = 0.9$ (but with quantitatively reduced rates of increase in V and I, and much greater volatility of $F_p(I_i, V_i)$), then inverting at $m = 1.0$ and $m = 1.1$ (i.e. V and I decrease, $F_h(I_i, V_i)$ and $F_p(I_i, V_i)$ increase.

That $m = 1.1$ 'flipped' the behaviour fits with predictions, as at $m_H = 0.1$ $\frac{\partial^2 F_h(I_i,V_i)}{\partial I_i^2} < 0$ for $I, V \in \mathbb{R}$. That this also occurred at $m = 1.0$ was surprising, as at this value $\frac{\partial^2 F_h(I_i,V_i)}{\partial I_i^2} = 0$ for $I \in \mathbb{R}$. This behaviour is likely explained by

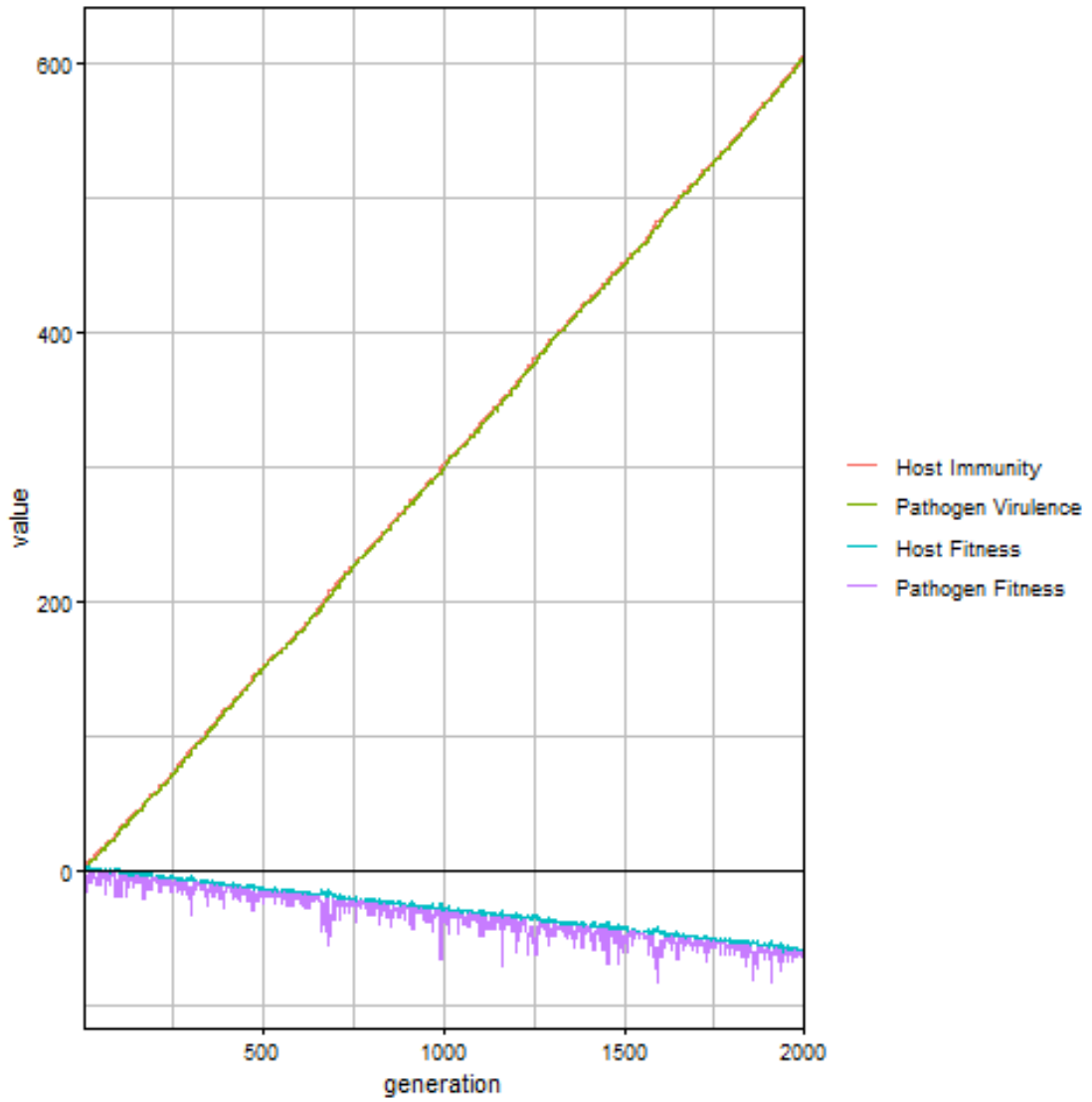


Figure 2.16: Doubling mutation rate sensitivity test: Immunity, Virulence, Host Fitness and Pathogen Fitness for the element in position (5,5) are plotted against generation time. The absolute rates of increase are greater than the baseline case, likely owed to the greater absolute frequency of mutations in the populations.

the possibility of collisions: if a immunity reducing mutation for a host coincides with an immunity reducing mutation for the pathogen, both host and pathogen increase their fitness.

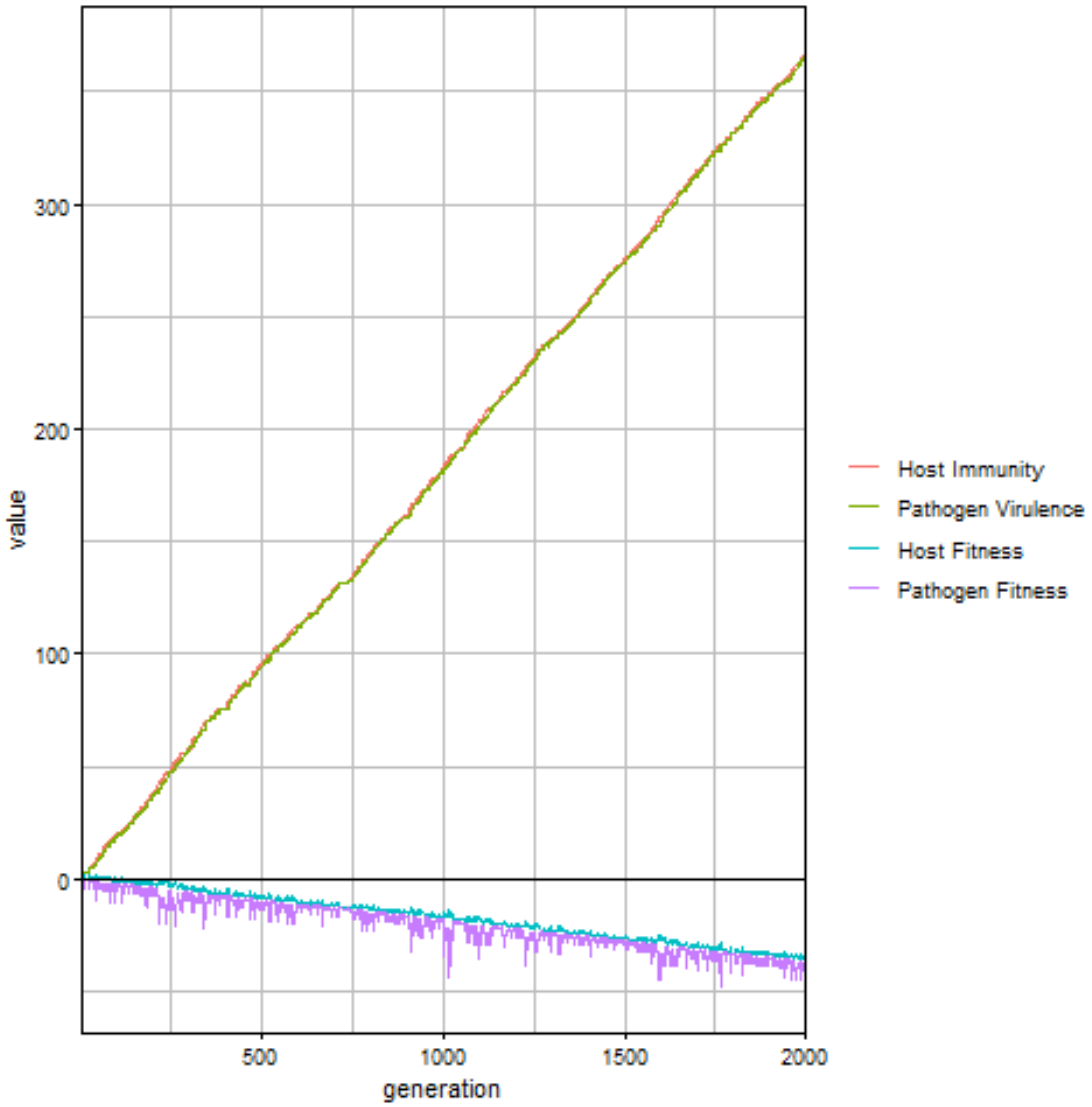


Figure 2.17: Halving mutation rate sensitivity test: Immunity, Virulence, Host Fitness and Pathogen Fitness for the element in position (5,5) are plotted against generation time. The absolute rates of increase are lower than the baseline case, likely owed to the lesser absolute frequency of mutations in the populations.

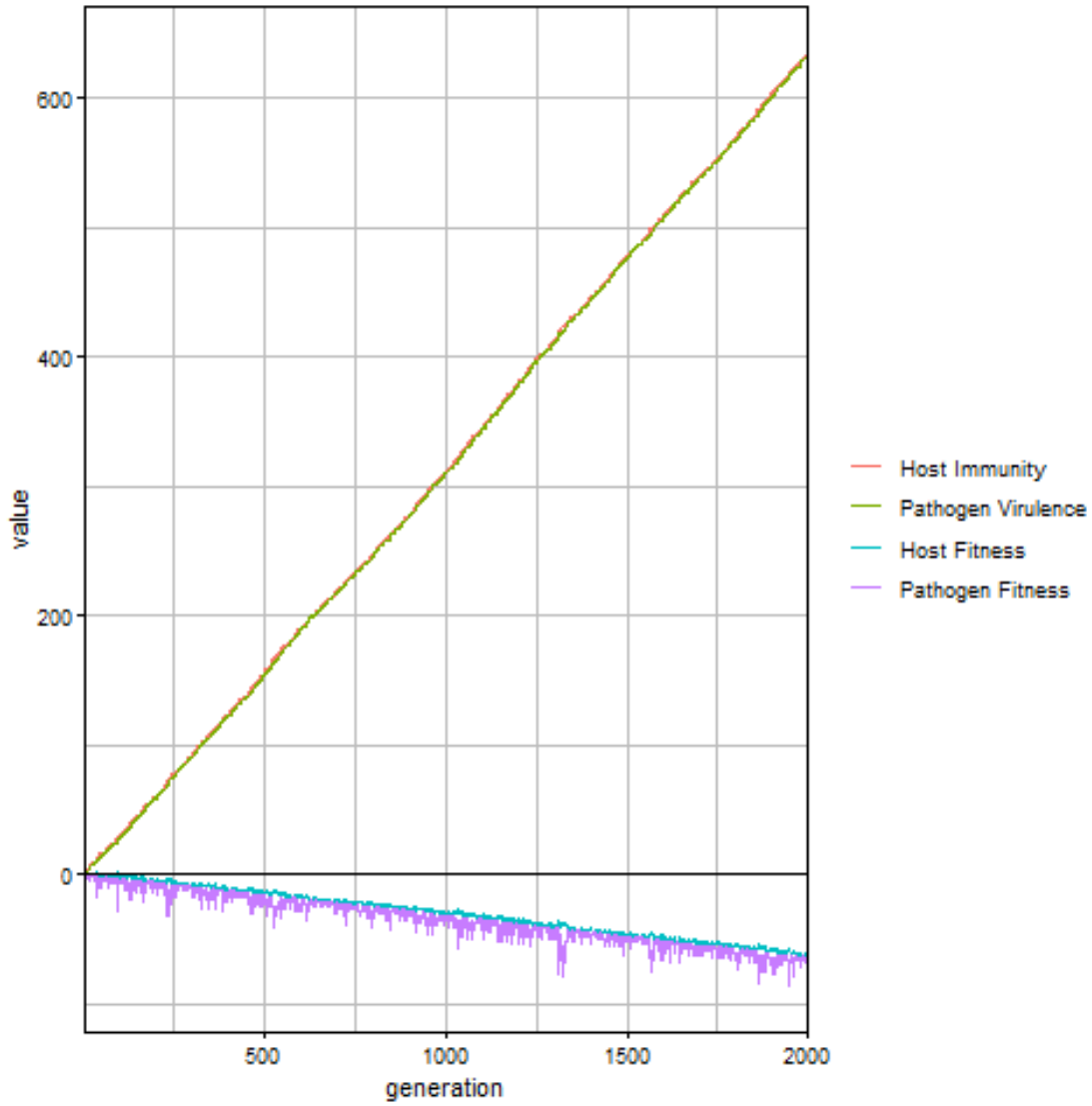


Figure 2.18: Doubling rate of mutations that increase I, V: Immunity, Virulence, Host Fitness and Pathogen Fitness for the element in position (5,5) are plotted against generation time. The absolute rates of increase are greater than the baseline case, likely owed to the greater absolute frequency of increasing mutations in the population.

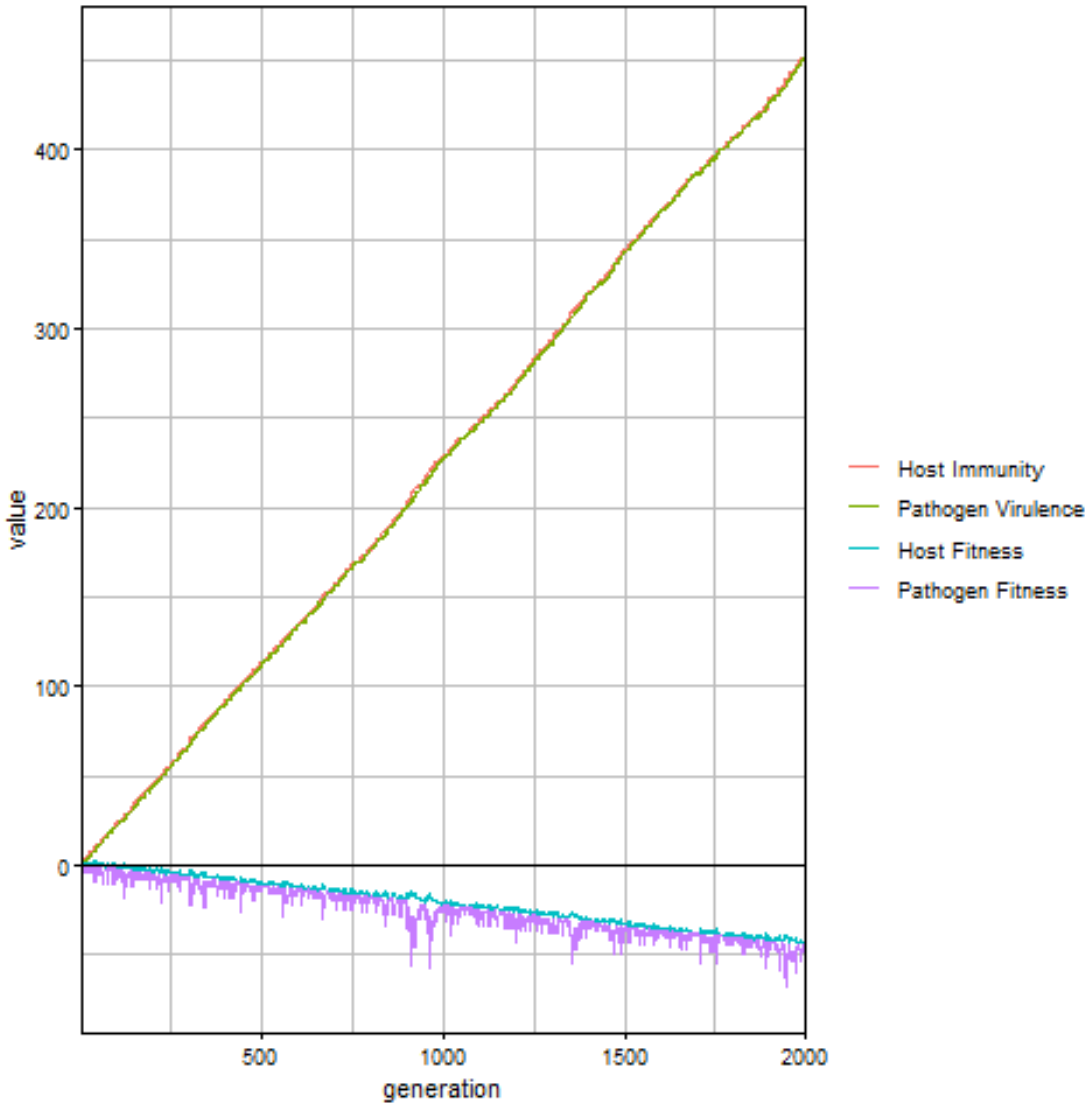


Figure 2.19: Doubling rate of mutations that decrease I, V: Immunity, Virulence, Host Fitness and Pathogen Fitness for the element in position (5,5) are plotted against generation time. The absolute rates of increase are greater than the baseline case, likely owed to the greater absolute frequency of increasing mutations in the population.

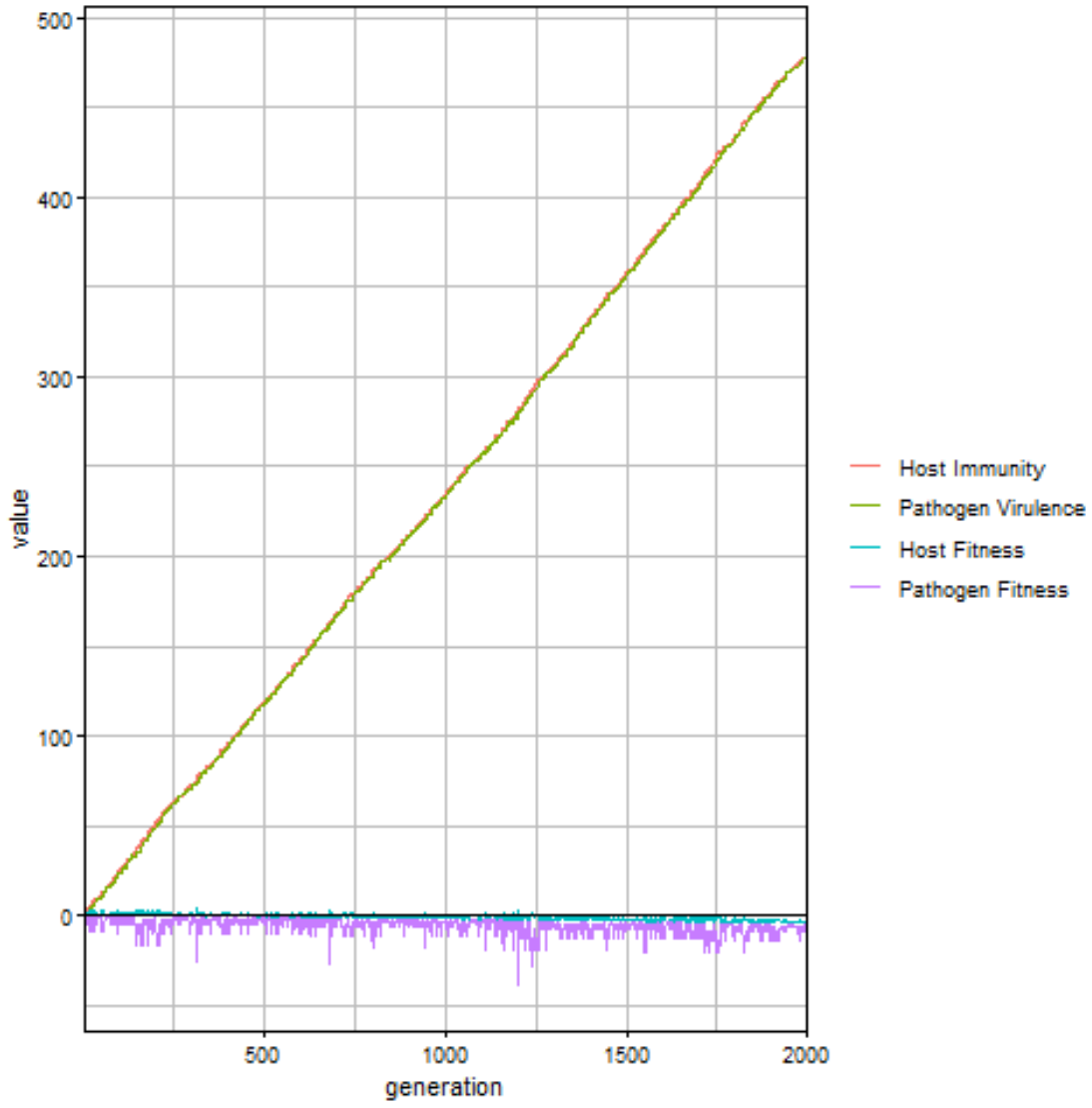


Figure 2.20: $m = 0.01$: Immunity, Virulence, Host Fitness and Pathogen Fitness for the element in position (5,5) are plotted against generation time. Host and pathogen fitness fall to negative values, although this is less than the baseline case.

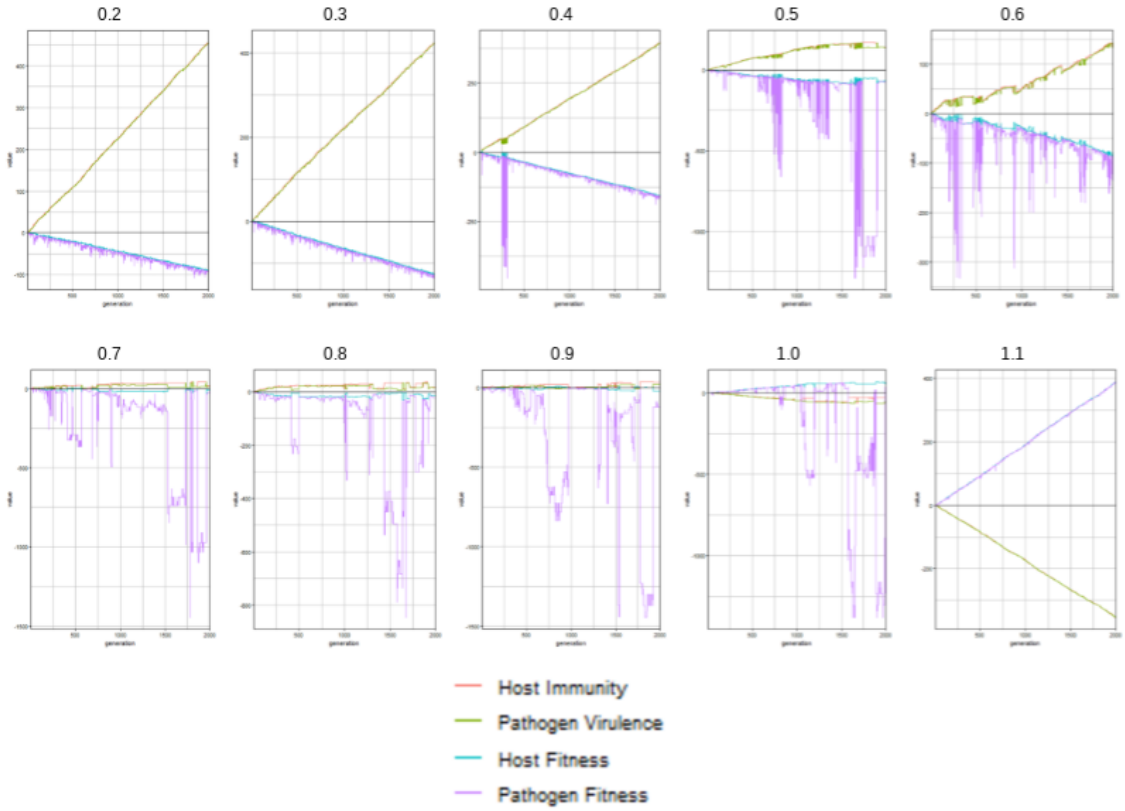


Figure 2.21: $m = 0.2 \rightarrow 1.1$: Variables for the element in position (5,5). Immunity, Virulence, Host Fitness and Pathogen Fitness for the element in position (5,5) are plotted against generation time for each sub-figure, the heading of each corresponding to the value of m. Note the decreasing absolute rates of change is m increases, leading to a switch in direction for all variables at $m = 1.0$ and $m = 1.1$

3

Modelling the efficacy of febrile heating in infected endotherms

Fever is a response to infection characterised by an increase in body temperature. The adaptive value of this body temperature increase for endotherms is unclear, given the relatively small absolute temperature increases associated with endotherm fever, its substantial metabolic costs, and the plausibility for pathogens to adapt to higher temperatures. We consider three thermal mechanisms for fever's antimicrobial effect: 1) direct growth inhibition by elevating temperature above the pathogens optimal growth temperature; 2) further differentiating the host body from the wider environment; and 3) through increasing thermal instability of the pathogen environment. We assess these by modelling their effects pathogen on temperature dependent growth, finding thermal effects can vary from highly to minimally effective depending on pathogen species. We also find, depending on the specification of a simple physical model, intermittent heating can inhibit pathogen growth more effectively than continuous heating with an energy constraint.

Contents

3.1 Introduction

Fever is a response to infection characterised by an increase in temperature. Whether (and how) this response benefits the infected organism is unclear.

3.1.1 The heating hypothesis

One plausible mechanism of how fever is a beneficial host response to infection is that elevated body temperature has a direct antimicrobial effect.[106] Pathogens are sensitive to the temperature of their environment. Fever, by heating the host body, alters the temperature of the pathogen environment, and inhibits pathogen growth.

There are three distinct mechanisms altering temperature can inhibit pathogen growth. One is a *direct effect*: If a pathogen grows optimally at a given absolute temperature, raising this temperature results in sub-optimal pathogen growth. The second is *environmental filtering*: Fever may also confer benefit by the *difference* in host body temperature from the wider environment. The elevated body temperature of the host body makes it a distinct ecological niche, which pathogens adapted to prevailing environmental temperatures are disadvantaged. The third is *dynamic variation*: Fever increases the *thermal instability* of the host body: no matter

which temperature a pathogen grows optimally at, this variability means it endures periods of sub-optimal growth.

The heating hypothesis can draw on a large body of circumstantial evidence for ectotherms.[107–110] Fungal pathogens provide the clearest example. Almost all fungal pathogens share a similar pattern of temperature dependent growth: very few species grow effectively when temperatures rise above 30°C.[111] Fungal pathogens inflict relatively little disease in non-hibernating endotherms (whose body temperatures are higher than 30°C), but much more in ectotherms or hibernating endotherms during their hibernation period. Increasing the body temperature of animals infected with prevalent fungal pathogens, either by placing them in a warm environment[112] or terminating hibernation[113] is sufficient to clear many fungal infections. These observations have also prompted the hypothesis that a major evolutionary driver for endothermy are these anti-fungal protective effects.[111]

3.1.2 The challenge of fever in endotherms

The heating hypothesis is less persuasive for fever in endothermic organisms. The principal challenge is the limited temperature increase of fever. In humans, a fever is classified as a temperature greater than 37.5 - 38°C (with 'normal' body temperature as 37.0°C), and temperatures increasing above 40°C are cause for increasing clinical concern. These small absolute increases make the mechanisms outlined above less plausible.

First, there is little reason to believe non-fungal pathogen species have similarly hard ceilings on their maximum (or optimum) growth temperature: many bacterial species out-range eukaryotes (let alone animals) with respect to high-temperature extremophilia. For endotherms, their non-febrile temperatures tend to be already too hot for fungal pathogens to tolerate, yet they cannot themselves survive body temperatures which would prohibit non-fungal pathogen growth. Second, the small absolute difference in temperature an endotherm's fever can generate also challenges a significant environmental filtering effect. Intuitively, if a pathogen can adapt to grow optimally at 37°C, adapting to a temperature a couple of degrees higher

seems unlikely to be a significant further obstacle. Third, an endotherm's body is typically a very temperature *stable* environment, especially when compared to ectotherm bodies and many environments free-living organisms inhabit. Fever in endotherms, with its small absolute changes, does not add enough variation to change this overall picture.

Across the scales from uncertainties as to how fever benefits an endotherm, there are clear costs. The most salient is energetic: fever is estimated to have an additional energetic cost of between 10% to 30% of basal metabolic rate in humans.[114–117]

Direct evidence on the benefit of fever in endotherms is also equivocal.[118] In some animal studies, inducing fever in infected mammals can enhance survival, and inhibiting it can reduce survival;[119, 120] yet in others, the opposite effect is observed.[121] Clinical observational studies in humans are also mixed, with varying direction of association between height of fever and anti-pyretic administration on survival.[122]

A key challenge in interpretation is fever is not only an increase in body temperature, but elaborated with a panoply of immunological and behavioural changes.[53, 54] Both observational and experimental approaches therefore struggle both to isolate and manipulate body temperature independently from the wider febrile response, and also to attribute any beneficial effects of fever to thermal effects in particular, versus other effects for which the increase in temperature may be a mediator or confounder.

Thus opinion is divided on whether fever is an effective host response for endotherms.[123–126] Clinically, fever - even in the context of infection - is typically treated by anti-pyretics by medical staff for their patients,[127] and parents for their children,[128] implying an overall judgement fever is not beneficial. It was not always so: inducing fever as a therapeutic intervention for particular infections was practiced in the pre-antibiotic era.[129] 'Abnormal' body temperatures can be a therapeutic target in the management of some critical illnesses (e.g. therapeutic hypothermia in cardiac arrest), and there is a renewed interest in 'thermal therapy'

(either localized or systemic) as a possible adjunct treatment for infectious diseases given the challenge of antimicrobial resistance.[130, 131]

3.1.3 Hypotheses for endotherm fever

We can distinguish a few alternative explanations for the evolution and adaptive value for fever in endotherms.

The heating hypothesis. Even if heating is a less effective means of host defence for endotherms than ectotherms, it may still exert some antimicrobial effect. These benefits, even if smaller than in ectotherms, may still be worth their metabolic costs, and so remain adaptive.

Fever is adaptive, but heating plays an indirect role. Elevated body temperature may no longer provide an important direct antimicrobial action in endotherms, but retains adaptive value by inducing other responses which do. On this hypothesis, fever may be an exaptation: although directly antimicrobial for ectothermic ancestors, in endotherms it now serves an indirect role orchestrating an effective immune response.

Even if temperature elevation is a key stimulator of innate immune responses to infection, it may be an inefficient one. Raising temperature across the entire body seems a less energy-efficient signal than synthesizing an interleukin: in principle, the energy of heating will be distributed across the entire body rather than targeted to the receptors; in practice, it is hard to imagine biosynthesis of a single protein could comprise 10-30% of basal metabolic rate. Yet even if so, the ancestral reliance on temperature to provide this signal during the evolutionary history of the organism makes it impossible to replace.

Fever is generally maladaptive. A trait that was once adaptive but now maladaptive may be conserved if reversing it poses a fitness penalty. In host-pathogen co-evolution, immune adaptions could be beneficial for host individuals before they reach fixation in the host population, maladaptive after they reach fixation (and subsequent pathogen counter-adaptation), yet host individuals who reverse the adaptation are selected against, and thus the adaptation is stably maintained.

Temperature elevation as a credible signal in host-pathogen co-evolution. As fever is metabolically costly, an increased body temperature is an honest signal both of immune activation and risk of the host dying from infection. This signal is perceptible in the pathogen environment. Pathogens may face a trade-off between intensity and duration of infection,[12] some pathogen reproductive strategies could be enhanced by reduction in growth at febrile temperatures, as this may favour longer infections and greater fitness overall.

Thus fever could benefit the host indirectly. By providing a honest signal to the pathogen, the host exerts selection pressure for pathogens pursuing prolonged infection strategies to respond to the signal of fever with reduced growth. As this response also enhances host fitness alongside pathogen fitness, responsive pathogens also exert selection pressure on the host species to preserve this honest signalling mechanism.

3.1.4 Motivation and aims

Whether (and when) fever is beneficial is important in two respects. The first is clinical relevance. If fever is broadly beneficial for endotherms like humans, then the common practice of administering anti-pyretics could be unwise. For fevers which arise from infection and where the fever itself is not a threat to health, anti-pyrexials could worsen the course of the infection.[124, 132] Further, it suggests inducing fever, as was done in the pre-antibiotic era, may be a useful adjunct therapy for infectious disease worthy of renewed consideration.

The second is fever can be a useful test case for exploring host-pathogen co-evolutionary conflict. It is typically challenging to infer the original benefit or current value of a given adaptation when observing it after the fact of protracted host and pathogen adaptation and counter-adaptation.

This challenge is compounded by the 'ground truth' of fitness difference attributable to the adaption being near-impossible to observe directly, and challenging to isolate experimentally. Febrile heating is a promising target for theoretical

approaches, as crisp (albeit imperfect) measures of fitness costs of changing temperature for both host and pathogen are accessible in terms of calorimetry and growth rates respectively.

Here, we investigate temperature dependent growth to assess the utility of heating as a mechanism of fever in endotherms using a set of mathematical models. First, we conduct a static analysis of how growth deteriorates for microbial pathogens as temperature is elevated above body temperature, comparing this to host metabolic investment in maintaining these temperature increases. Second, we assess how valuable additional thermal differentiation from the environment could be. Third, we investigate the idea that the variation in temperature that inducible fever provides poses an intrinsic cost on the pathogen no matter its coevolutionary response to this source of thermal instability, and evaluate the magnitude of this effect as a coevolutionary stable strategy. Finally, we construct a simple physical model of heating, to compare the energy efficiency of intermittent versus continuous heating for inhibiting pathogen growth.

3.2 Modelling temperature dependent growth

The archetype of a microbial temperature dependent growth curve is growth rising beyond a minimum growth temperature T_{min}, reaching an optimal growth temperature T_{opt}, and then a steep decline from this optimum to a maximum growth temperature T_{max} (figure 3.1). This archetypal shape is widely observed across microbial organisms (e.g. phytoplankton,[133] bacteriophages,[134] and fungi[135]); we are unaware of any exceptions among pathogenic microbes.

By elevating body temperature, the host inflicts an energetic cost to the pathogen, by inhibiting its growth, and to itself, by increasing its metabolic rate. In this conflict, the strategy of elevating body temperature seems more effective the more disproportionate the costs are for the pathogen than for itself.

Energetic costs to the host of elevating temperature scale linearly with ΔT, given the heat transfer equation:

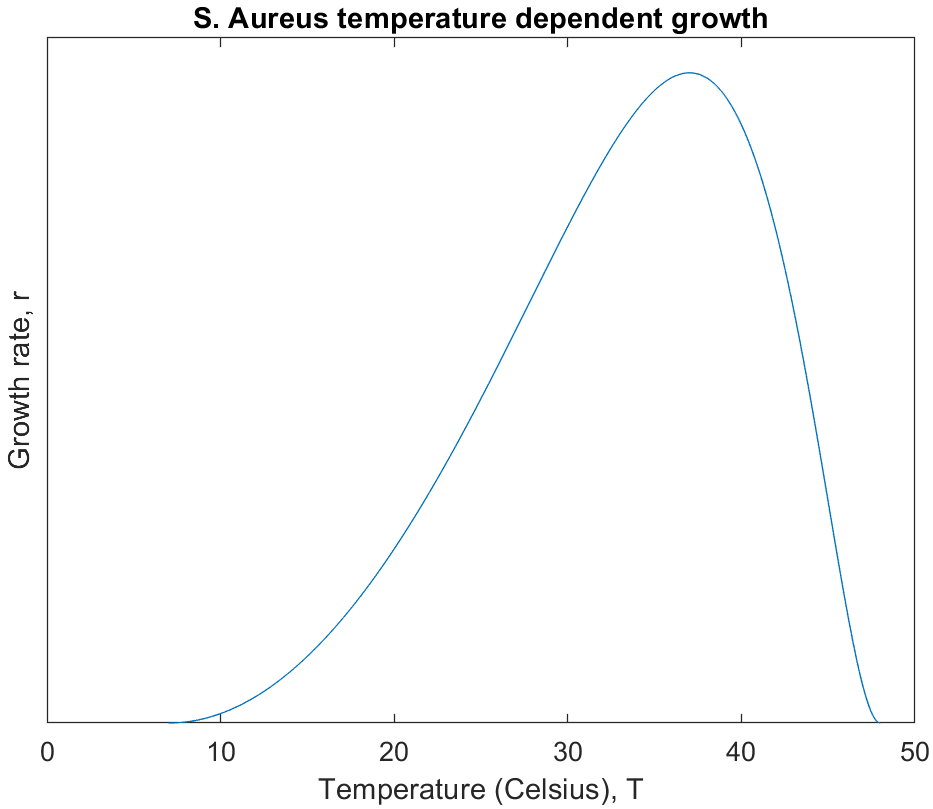


Figure 3.1: *S. Aureus* growth curve ($T_{min} = 7°C$, $T_{opt} = 37°C$, $T_{max} = 48°C$) modelled with the modified Ratkowsky equation ($\sqrt{r} = (T - T_{min}) \cdot (1 - e^{0.16 \cdot (T - T_{max})})$. Equation plotted in the domain $T_{min} \leq T \leq T_{max}$.

$$Q = h \cdot A \cdot \Delta T \tag{3.1}$$

Where Q is the energy flux, h is the coefficient of heat transfer, A the surface area, and ΔT the difference in temperature.

There are a variety of mathematical models for temperature dependent growth inhibition and inactivation in microorganisms.[136] Some are more empirically-driven, whilst others are theory-led. These models nonetheless share steep and non-linear (typically exponential) declines in growth as temperature exceeds T_{opt}. For example, the modified Ratkowsky equation:[137]

$$\sqrt{r} = b \cdot (T - T_{min}) \cdot (1 - e^{(c \cdot (T - T_{max}))}) \tag{3.2}$$

Where r is the growth rate, b a scaling parameter, and c a constant. For this equation, the growth rate penalty to the pathogen scales approximately $\propto e^{\Delta T}$ as T increases above T_{opt}.

A strategy where costs scale linearly for the host but exponentially for the pathogen would be an effective host strategy if the host could increase its temperature without limit. Yet endotherms tend to be less thermally tolerant than their pathogens. For body temperature increases tolerable to the host, the impact on pathogen growth could be much more modest.

Although human pathogens have optimal temperatures around 37 °C, they substantially vary in their T_{max}. We take two exemplars: *S. dysenteriae* has a T_{max} of 40°C, in the range human fever can reach; *E. coli* has a T_{max} of 45 °C, much higher than safe limits on human body temperature.[138] We would therefore expect *S. dysenteriae* to be more 'fever-sensitive' than *E. coli*, with its growth inhibited more at febrile temperatures.

To assess this quantitatively, we model the temperature-dependent growth of each pathogen by fitting the modified Ratkowsky equation to the observed values of T_{min}, T_{max}, and T_{opt}, for each pathogen finding the c coefficient numerically by computing T_{opt} for $0 \leq c \leq 2$ in increments of 0.001, selecting the value of c for which T_{opt} is closest to 37 °C. For *S. dysenteriae*, c is 1.247; for *E. coli*, c is 0.260. For *S. dysenteriae*, the modelled growth equation is:

$$\sqrt{r} = (T - 4) \cdot (1 - e^{1.247 \cdot (T - 40)}) \tag{3.3}$$

And for *E. coli*, it is:

$$\sqrt{r} = (T - 10) \cdot (1 - e^{0.260 \cdot (T - 45)}) \tag{3.4}$$

These curves are plotted in figure 3.2. We calculate from these equations the relative growth (where 1 is the optimal growth rate) at febrile temperatures (table 3.1). Febrile temperatures inhibit *S. dysenteriae* much more effectively than *E. coli*. Not only at 40 °C (the T_{max} for *S. dysenteriae*, where *E. coli* still grows at 85% of

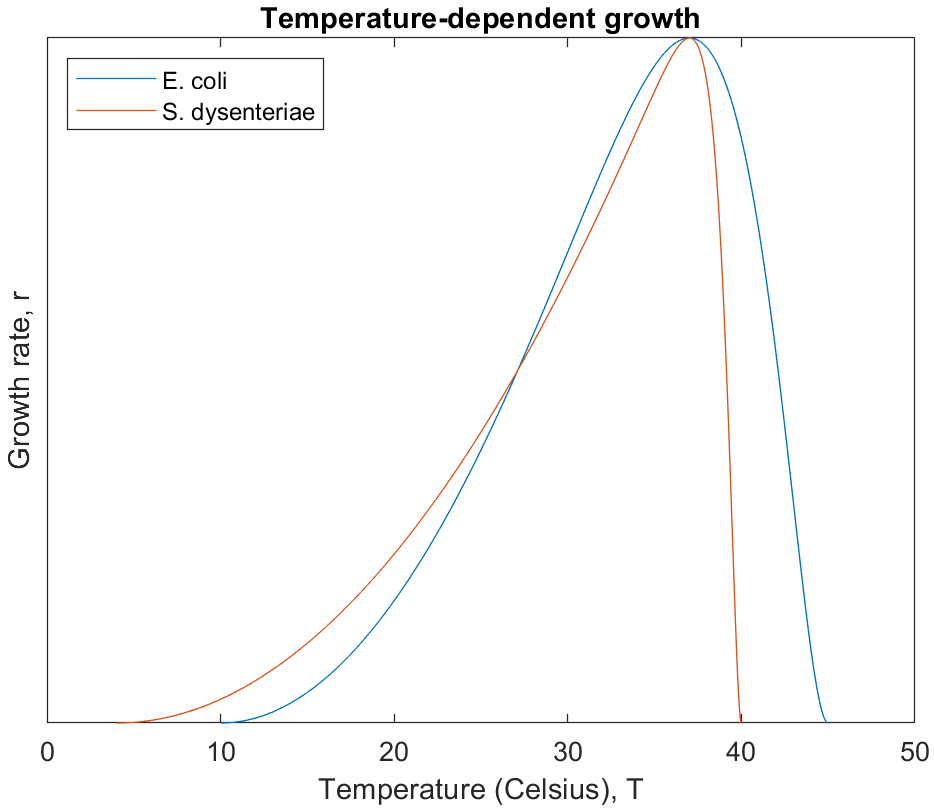


Figure 3.2: *S. dysenteriae* and *E. coli* temperature dependent growth curves, modelled with the modified Ratkowsky equation. Note the much steeper relative decline in growth for *S. dysterentiae* at temperatures > 37 °C

		Temperature			
Species	Temperature range	37	38	39	40
S. Dysenteriae	4-40	1	0.94	0.60	0
E. coli	10-45	1	0.99	0.94	0.85

Table 3.1: Relative growth ($T_{opt} = 1$) at febrile temperatures for *S. dysenteriae* and *E. coli*, modelled with the Ratkowsky equation.

its optimal growth, but also at milder fevers: a 'high fever' of 39°C almost halves *S. dysenteriae* growth, but only reduces *E. coli* growth by 6%.

The plausibility of a direct thermal effect is much more credible for *S. dysenteriae* than *E. coli*. The substantial metabolic cost to the host of heating its body is much more easily justified when this inflicts substantial or complete growth inhibition (*S. dysenteriae*) compared to when this inhibition is very mild (*E. coli*), and could only become significant at body temperatures which are life-threatening

to the host in their own right.

Many human pathogens, like *S. dysenteriae*, are sensitive to febrile temperatures (e.g. *N. gonorrhoeae*, *S. typhi*); and many human pathogens, like *E. coli*, are resistant to them (e.g. *S. Aureus*, *V. comma*). Thus the direct efficacy of febrile heating may depend on the pathogen causing the infection.

3.3 Marginal environmental filtering

For endotherms that are commonly already warmer than their environment, a further elevation in body temperature through fever may have much greater effect restricting growth of pathogens adapted to environmental temperature than those adapted to body temperature. At the extreme, febrile temperatures above a pathogen's T_{max} thermally exclude it. The steep decline in growth above T_{opt} but below T_{max} means that small temperature increases in this range can have a out-sized effect in inhibiting pathogen growth.

To examine this, we construct a hypothetical scenario of a pathogen adapted to an environment of 37°C, with an identical temperature dependent growth curve to *E. coli*. We then consider endotherms with body temperatures higher than this environment, and then assess the relative impact on microbial growth of a fever which elevates body temperature further still. For example, the marginal effect of a 2°C fever for a host with a body temperature of 38°C is the value of the growth curve at $T = 40$°C divided by the value of the growth curve at $T = 38$°C: 0.87, corresponding to 13% growth inhibition (versus 6% for a 2 degree temperature increase from 37°C to 39°C.

For 37°C $\leq T \leq$ 43°C, in the model, the equation for the relative growth of a 2°C further increment is given by:

$$\frac{r(T+2)}{r(T)} = \frac{((T-8)\cdot(1-e^{(0.260\cdot(T-43)})))^2}{((T-10)\cdot(1-e^{(0.260\cdot(T-45)})))^2} \tag{3.5}$$

We plot this curve (alongside those for a 1 degree and 3 degree increase) in figure 3.3. With increasing body temperature, the additional increment exerts a

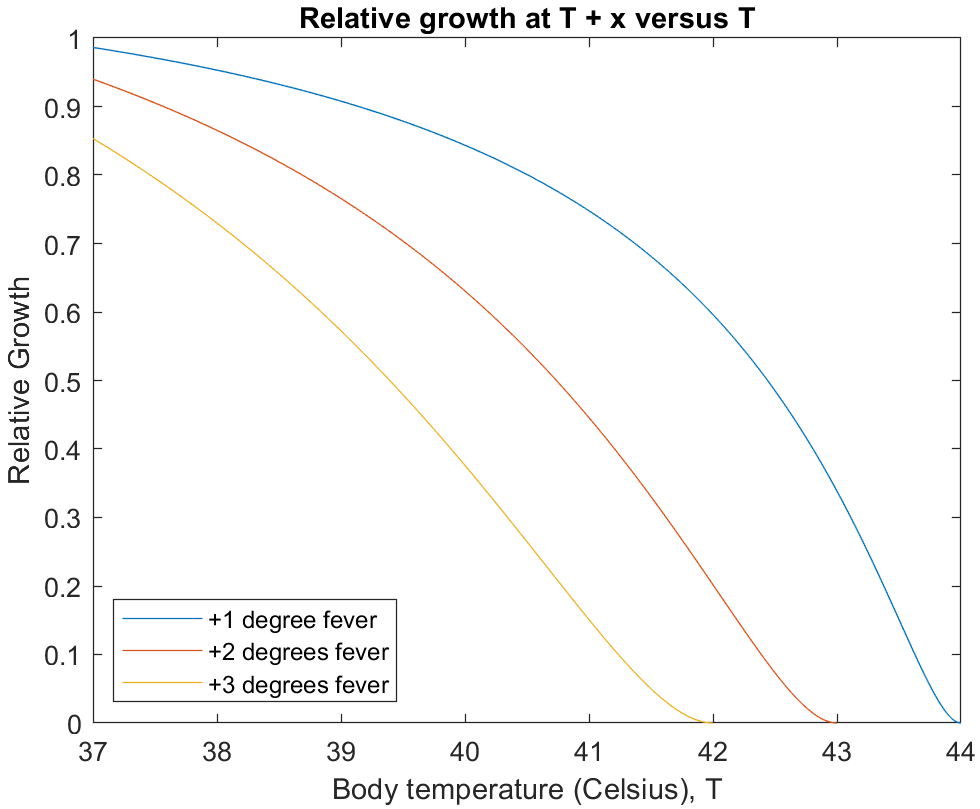


Figure 3.3: Each curve gives the relative ratio of growth rate at T+x°C (blue 1 °C, red 2 °C, yellow 3 °C versus a body temperature of T, modelled with the *E. coli* temperature-dependent growth curve. For example, the leftmost point of each curve corresponds to the impact of raising temperatures at 37°C of 0.99, 0.94, and 0.85 respectively (cf. table 3.1). Note each curve reaches zero when $T + x = T_{max}$

greater relative reduction in pathogen growth. At the extreme, this gives complete thermal restriction (relative growth = 0) when the sum of body temperature and increment equals T_{max} (44°C, 43°C, and 42°C for 1-3°C fevers respectively).

However, as body temperature climbs further, the returns of incremental febrile heating diminish as it becomes increasingly redundant for *environmental filtering*. In our scenario a host with an (afebrile) body temperature greater than 45°C already thermally excludes the pathogen without any additional febrile heating.

In essence, these potential *environmental filtering* benefits of fever only apply to a narrow range of host body temperatures where the host body is somewhat (but not greatly) hotter than the environment: if body temperature $> T_{max}$, febrile heating is redundant. In the modelling scenario, this is for body temperatures $<$ 8°C

warmer than the 37°C environment. Endotherm body temperatures of 35-40°C are more than 20°C greater than mean global temperature, and few microbes have $T_{max} > (T_{opt} + 10)$. This suggests ecological contexts where fever exerts a significant additional *environmental filtering* effect for endotherms are uncommon.

3.4 Dynamic temperature variation as a robust thermal strategy

Even if a pathogen can adapt to grow optimally at any given temperature, optimal growth across a range of temperatures results in slower growth versus a single temperature. Thus fever may benefit the host through introducing thermal instability into the pathogen environment. Such a mechanism may only be incompletely mitigated by pathogen co-evolution, and so could prove a beneficial thermal strategy for the host robust to pathogen counter-adaptation.

To investigate, we consider the average growth ($\bar{r}$) over a *range* of temperatures: this would amount to the average of the growth at these temperatures, weighted by the proportion of time the pathogen spends at these temperatures. In the simplest case where this time is uniformly distributed over a continuous temperature interval, $\bar{r}$ is the average height of the function across this interval (analytically, the definite integral divided by the width of the interval).

To isolate *dynamic variation* effects from *direct* effects we consider the maximum $\bar{r}$ that can be achieved for a temperature range k: for an interval of width k, what value of T gives the greatest definite integral between T and $T + k$ for the temperature dependent growth curve.

We then analyse the relationship between $\bar{r}$ and k: as the variation in temperature increases, how much does average growth fall.

To make this analysis more tractable, we replace the Ratkowsky equation with a gamma distribution function ($Gamma(2, 1)$, $y = \frac{x \cdot e^{-x}}{2}$), which is algebraically simpler and can approximate Ratkowsky growth curves when reflected, stretched and scaled (figure 3.4). In terms of this new function $y = \frac{x \cdot e^{-x}}{2}$, the point (0, 0) is the pathogen T_{max}, and positive values of x correspond to temperatures below

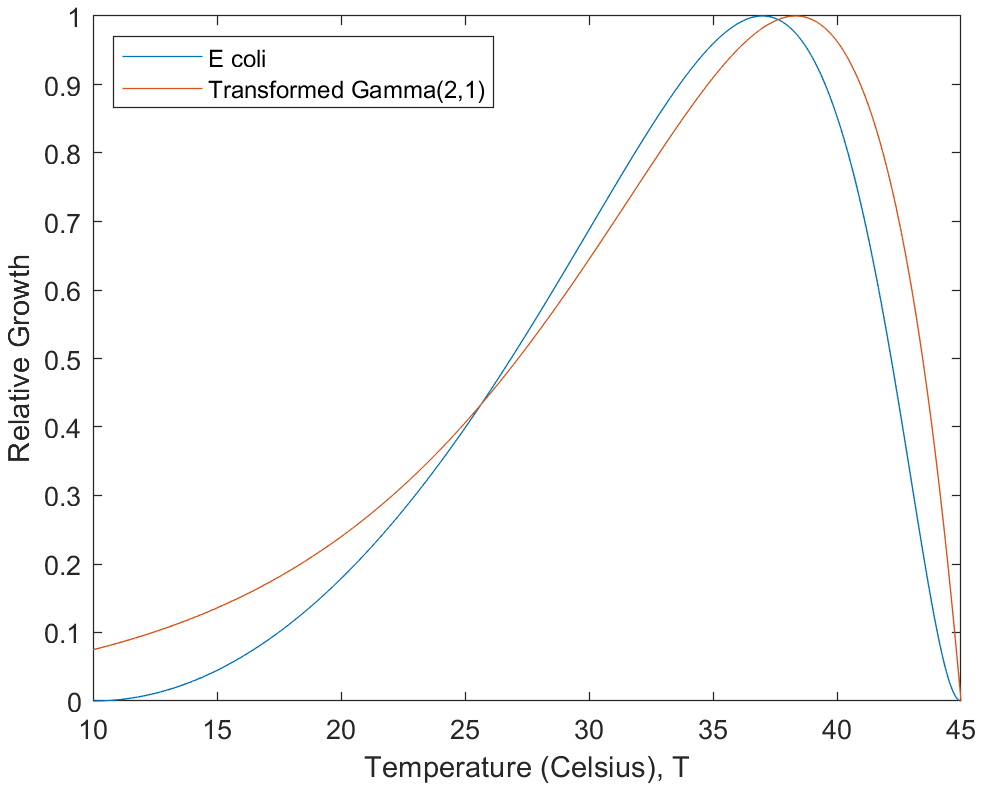


Figure 3.4: Illustrating similarity between Ratkowsky equation and Gamma distributions. The blue line is the modelled growth curve for *E Coli* (see equation 3.4). The red line is a reflected, scaled, and stretched Gamma(2,1) distribution, the equation being $r = 0.15(45 - t) \cdot e^{-0.15(45-t)} \cdot e$. The fit is approximate, but serves to illustrate the fundamental similarity in shape between these two families of functions.

T_{max}: the point (1, 2e), the maxima for the function, corresponds to T_{opt}, which is lower in temperature than T_{max} by one arbitrary unit.

To find the maximum $\bar{r}$ that can be achieved for a temperature range k, we find the maxima of the definite integral of this function between T and $T + k$:

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}T}\left[\int_T^{T+k} \frac{T \cdot e^{-T}}{2} \mathrm{d}T\right] &= \frac{(T+k) \cdot e^{-(T+k)}}{2} - \frac{T \cdot e^{-T}}{2} \\ &= e^{-k-T}\left(\frac{k}{2} + T\left(\frac{1-e^k}{2}\right)\right) \end{aligned} \tag{3.6}$$

This equation has a single root at $T = \frac{k}{e^k - 1}; k > 0$. As the interval k increases, T decreases, and $\lim_{k \to 0^+}(T) = 1$. In more concrete terms, for a uniform temperature

distribution across an interval of k units, the highest $\bar{r}$ is observed when the upper limit of this range is $\frac{k}{e^k-1}$ units lower than T_{max}.

The value of this maximum $\bar{r}$ for an interval of k is given by taking the integral with these bounds, and dividing by the interval width k:

$$\bar{r} = \left[\int_{\frac{k}{e^k-1}}^{\frac{k}{e^k-1}+k} \frac{T \cdot e^{-T}}{2} \mathrm{d}T \right] /k = \frac{(e^k-1) \cdot e^{\frac{e^k \cdot k}{1-e^k}}}{2k} \tag{3.7}$$

These values can be normalized by dividing by the maxima of this function ($\frac{1}{2e}$). Normalized $\bar{r}$ is plotted against k in figure 3.5. This shows a sigmoidal response of $\bar{r}$ with increasing k: the reduction in average growth is initially small, accelerates, and tends to complete restriction at the extreme ranges of temperature variation ($\lim_{k\to\infty}(\bar{r}) = 0$).

This modelling suggests even in the best case, thermal variation inflicts a growth penalty on the pathogen versus a single temperature. Further, increasing this variation inflicts a greater penalty to best case thermal performance of the pathogen.

How robust this thermal strategy is to pathogen co-evolution depends upon how it can adapt in response to thermal variation. Implicit in our analysis above is the pathogen growth curve is essentially fixed: a pathogen may be able to transpose its growth curve along the temperature axis to optimise thermal performance across an interval, but not alter its shape or width. Although the general observation of the archetypal growth curve (e.g. figure 3.1) rules against dramatic shape changes, smaller changes in shape or width are credible,[139] although these may incur other trade-offs.

Also, the absolute effect size of thermal variation appears small when translated into concrete biological terms. The interval width k is currently in arbitrary units, with 1 unit corresponding to the temperature difference between T_{opt} and T_{max}. For *E. coli*, this corresponds to 8°C; for *S. dysenteriae*, 3°C.[138] In our simplified model, thermal instability of 3 degrees impedes pathogen growth by 1% in the first case, and 4% in the second.

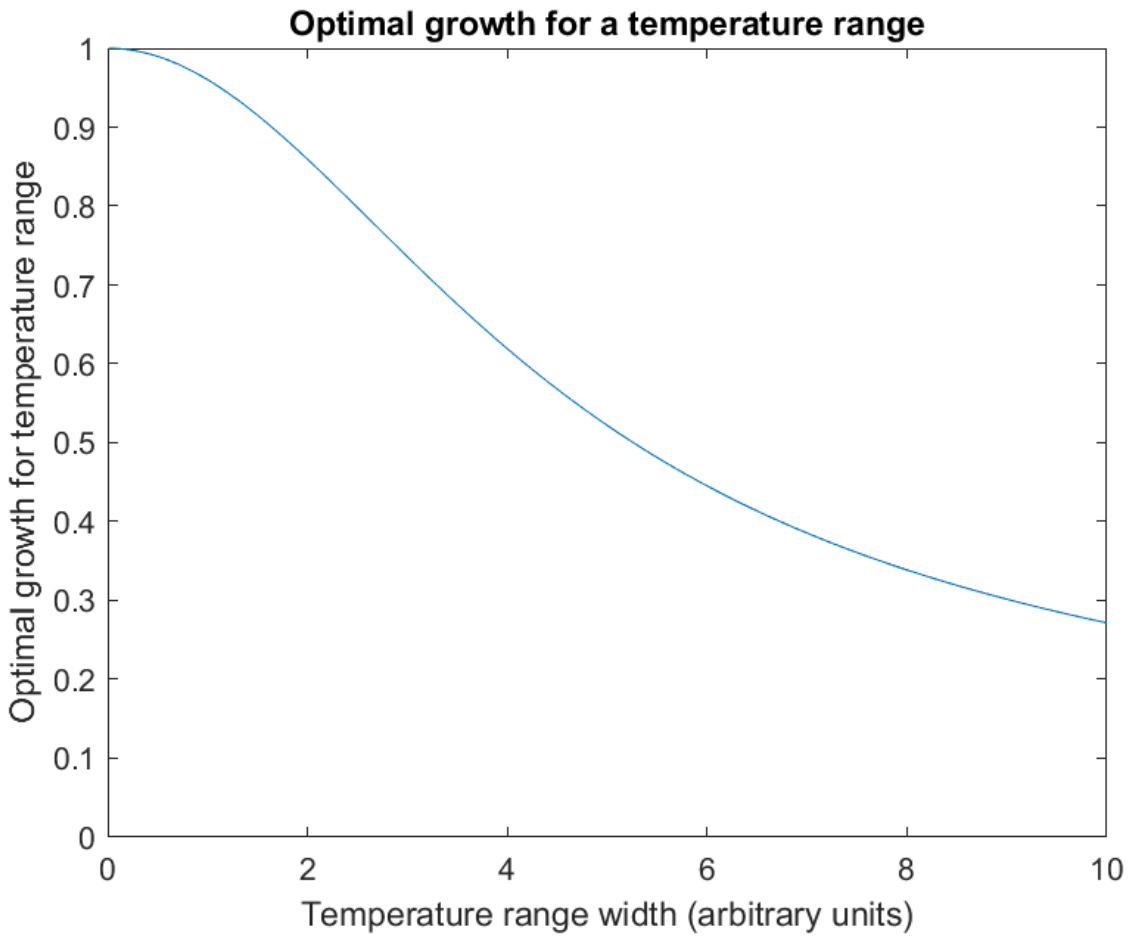


Figure 3.5: Optimal growth for a temperature range. The optimum solution for mean pathogen growth rate for uniform temperature variation is plotted against the width of this range (k in the text), for $0 \leq k \leq 10$. This is normalized to optimal growth at a single temperature (thus is 1 when the temperature range is zero - i.e. a single point). As the temperature range increases, the optimal growth across this temperature range falls sigmoidally compared to growth at a single temperature.

3.5 Intermittent fever and optimal thermal restriction

Fever is not always a sustained elevation in temperature. Transient ('spiking') or intermittent fevers are common clinical observations. We explore whether intermittent heating can be superior to constant heating for an infected host given a limited energy budget.

As a concrete model example, suppose a 1kg mass of water (heat capacity 4200 J/kg/°C) at an environmental temperature of 25°C is heated to maintain a

temperature of 37°C, with a heat transfer coefficient of 10 J/s/°C/m^2 and a surface area of 1m^2 (these latter two values are chosen for concreteness; as scaling constants, the comparative dynamic behaviour we investigate is insensitive to their particular value). Heat transfer from the water to the environment is, from equation 3.1:

$$10\text{J/s/°C/m}^2 \cdot 1\text{m}^2 \cdot (37\text{°C} - 25\text{°C}) = 120\text{W} \tag{3.8}$$

From the first law of thermodynamics, the water must be heated at 120W to maintain a temperature of 37 °C. We now compare two strategies of using additional energy to further increase this temperature. First, instantaneous heating to 40°C with subsequent cooling to return to 37°C. Second, using this energy of instantaneous heating to give sustained heating over the same period.

For the first strategy, the cooling equation is:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \frac{[120\text{W} - 10\text{J/s/°C/m}^2 \cdot (T - 25\text{°C})]}{4200\text{J/kg/°C}} \tag{3.9}$$

Solving for temperature as a function of time, with $T(0) = 40$:

$$T = 3 \cdot e^{\frac{-t}{420}} + 37 \tag{3.10}$$

The water has cooled to near its initial temperature (37.1°C) at $t \approx 1430$s. The time integral gives the overall temperature elevation:

$$\int_0^{1430} 3 \cdot e^{\frac{-t}{420}} \mathrm{d}t \approx 1220\text{s°C} \tag{3.11}$$

To compare to the second strategy of sustained heating, we take the energy required for instantaneous heating of this mass of water by 3°C (12600J), and instead use it to provide additional continuous heating over this period of 1430s (8.81W). The temperature equilibrium that would result is given by:

$$\begin{aligned} 120\text{W} + \frac{12600\text{J}}{1430\text{s}} &= 10\text{J/s/°C/m}^2 \cdot 1\text{m}^2 \cdot (T\text{°C} - 25\text{°C}) \\ T &= 37.88\text{°C} \end{aligned} \tag{3.12}$$

The benefits of elevated temperature to inhibit pathogen growth are non-linear with temperature. We transform the temperature into 'Utility' (U) with the temperature dependent growth curve of the pathogen, normalized to their maximum growth rates:

For *S. dysenteriae*, this is (cf. equation 3.3):

$$U = 1 - \frac{\left[\left((T-4)\cdot\left(1-e^{(1.247\cdot(T-40))}\right)\right)^2\right]}{1037.929} \tag{3.13}$$

U is zero at maximum pathogen growth (T_{opt}) and 1 at zero pathogen growth (T_{max}, T_{min}). The overall utility to the host gained with the 'burst heating' strategy is, by substitution:

$$\int_0^{1430} 1 - \left[\frac{\left(\left[3\cdot e^{\frac{-t}{420}}\right]-4\right)\cdot\left(1-e^{1.247\cdot\left(\left[3\cdot e^{\frac{-t}{420}}\right]-40\right)}\right)^2}{1037.929}\right] \mathrm{d}t \approx 183\mathrm{Us} \tag{3.14}$$

'Us' is a unit of pathogen growth restriction: 1 Us is equivalent to completely halting pathogen growth for one second. The utility to the host with the sustained heating strategy is:

$$\int_0^{1430} 1 - \left[\frac{(37.88-4)\cdot\left(1-e^{1.247\cdot(37.99-40)}\right)^2}{1037.929}\right] \mathrm{d}t \approx 65\mathrm{Us} \tag{3.15}$$

The same procedure for *E. coli*, gives (cf. equation 3.4):

$$\int_0^{1430} 1 - \left[\frac{\left(\left[3\cdot e^{\frac{-t}{420}}\right]-10\right)\cdot\left(1-e^{0.260\cdot\left(\left[3\cdot e^{\frac{-t}{420}}\right]-45\right)}\right)^2}{558.23}\right] \mathrm{d}t \approx 28\mathrm{Us} \tag{3.16}$$

Versus sustained heating:

$$\int_0^{1430} 1 - \left[\frac{(37.88 - 10) \cdot \left(1 - e^{0.260 \cdot (37.99 - 40)}\right)^2}{558.23} \right] \mathrm{d}t \approx 15\mathrm{Us} \tag{3.17}$$

In these models 'burst heating' accrues more two to three times more utility in terms of pathogen growth inhibition than sustained heating with a fixed energy constraint. In absolute terms, the benefits still depend on the thermal sensitivity of the pathogen. For *S. dysenteriae*, burst heating is roughly equivalent to halting pathogen growth for 3 minutes out of every every 22 (versus 1 minute with sustained heating); for *E. coli*, this is 30 seconds every 22 minutes versus 15.

These results are sensitive to the 'cut-off' value for what counts as near the initial temperature of 37°C (table 3.2). Lower or higher values (e.g. 37.01°C, 37.5°C) alter the total time period of analysis ($\approx$ 2400s and 750s respectively) and so alter the temperature generated by a continuous heating strategy. Repeating the analysis for these different values are given in table 3.2. At the higher cut-off value (37.5°C), continuous heating slightly surpasses burst heating for both *S. dysenteriae* and *E. coli*.

		Cut-off value (°C)		
		37.01	37.1	37.5
S. dysenteriae	Intermittent heating	184	184	181
	Continous heating	33	65	184
E. coli	Intermittent heating	28	28	28
	Continuous heating	9	15	31

Table 3.2: Intermittent versus continuous heating impact on pathogen growth reduction (in arbitrary units) with different temperature cut off values for the analysis. For intermittent heating, the total impact is mostly insensitive to the cut off value, as most growth reduction occurs at the initially higher temperatures. In contrast, continuous heating shows progressive improvement, as a higher cut-off value reduces the time period for analysis, and so increases the effective power that can be used for continuous heating. For both *S. dysenteriae* and *E. coli*, continuous heating slightly surpasses intermittent heating at the highest cut-off value of 37.5°C, a borderline febrile temperature for humans in its own right.

This suggests the optimal strategy depends on the host's energy budget for febrile heating: although the energy used is identical across all scenarios in table 3.2, the effective power for continuous heating approximately doubles between

37.01°C, 37.1°C, and 37.5°C, as the interval this energy is being deployed over approximately halves. Intermittent heating may be more effective than continuous heating with a stricter energy constraint, but continuous heating can be more effective with a more generous one.

3.6 Discussion

We have outlined three distinct mechanisms which could underlie the hypothesis that the temperature elevation of fever in endotherms directly inhibits pathogen growth. The first through simply elevating temperature to a point on the pathogen's temperature dependent growth curve in which it grows poorly (a direct effect). The second by further increasing the temperature difference between the host body and the environment, so pathogens adapted to environmental temperatures are poorly adapted to the host body environment (a *environmental filtering* effect). The third by increasing the temperature volatility of the host body environment, impeding pathogen growth no matter what temperature they are best adapted to (a *dynamic variation* effect).

Mathematical investigation of the relationship between the cost of temperature elevation to the host (in terms of energy) versus the costs inflicted to the pathogen (in terms of growth restriction) share similar patterns. In theory, each mechanism can be a highly effective host strategy in the limit of unbounded febrile temperatures. The same applies for large temperature increases accessible to ectotherms.

In endotherms, where fever elevates body temperature by much smaller magnitudes, the picture is more equivocal. In terms of direct effects, febrile body temperatures still substantially inhibit growth for some species (like *S. dysenteriae*), and so plausibly justify the metabolic cost of fever alone. Other pathogens (like *E. coli*) are much more resilient to febrile temperatures: although there is still some growth inhibition, this benefit looks much smaller when balanced against the energetic costs to the host.

For both *environmental filtering* and *dynamic variability*, these mechanisms also have limited value whether or not the pathogen is fever-sensitive: in the first case,

because it only applies in very limited temperature range where an environmental pathogen is not already thermally excluded by normal body temperature, but is by one a few degrees higher; in the second, although thermal variation imposes some residual inhibition of pathogen growth (even if the pathogen has adapted to grow optimally across this temperature range) this only amounts to a few percent worse than optimal growth for a single temperature.

We also assessed the potential value of intermittent or 'spiking' fever by comparing using the same energy budget to heat in bursts versus a sustained temperature elevation over time in a simple physical model. Our findings are that heating in bursts is substantially more effective in terms of delaying pathogen growth when the energy constraint is stricter, owed to the non-linear effects of temperature on pathogen growth inhibition.

3.6.1 Limitations

All mathematical modelling strikes a balance between fidelity and simplicity. The modelling of marginal thermal restriction and intermittent fever are very simple. It is hoped this degree of abstraction is better than a more richly detailed model given the latter would likely become highly specific to the modelling scenario, and make general principles harder to infer from its behaviour.

Limitations to data also pose challenges: the pathogen growth curves are fitted on data-book values for species in laboratory conditions. The values of T_{max} etc. may vary from these due to factors like strain and local environment. Our analyses are also sensitive to how small changes in temperature between T_{opt} and T_{max} are modelled: whether, for example, a pathogen 0.2 °C above its optimal growth temperature grows sub-optimally to the degree inferred from the Ratkowsky equation. The purpose of the examplar species is to demonstrate the range of possible behaviour, and the overall range is unlikely to be sensitive to this uncertainty.

We have deliberately isolated febrile heating from the wider fever response. Extrapolating our findings from the former to the latter requires caution. We

have not assessed the impact of other mechanisms by which fever could protect an endotherm from infection, nor their relative importance versus febrile heating.

Our scenarios for modelling were focused on two bacterial pathogens in humans at core body temperature. Extrapolating from this to other endotherms, other pathogens (such as non-bacterial microbes), and other host body environments (e.g. skin surfaces) should be done cautiously. We hope the broad principles used in constructing these models (e.g. basic thermodynamics, the Ratkowsky equation) make the broad trends in results have reasonable external validity.

3.6.2 Conclusions and further work

The heating hypothesis. Whether febrile heating is an effective mechanism for endotherms overall depends on the relative prevalence of fever-sensitive and fever-resistant pathogens. Even if febrile heating is sometimes ineffective, providing infections from pathogens which it is effective against are common enough, a host strategy which responds to infection with heating 'by default' can have positive expected value, and thus adaptive overall.

Quantitative assessment of when these mechanisms are effective versus when they are not is very challenging: a given host typically susceptible to a wide number of pathogens, relative prevalence is often environmentally dependent, and the relative burden of disease attributable to different pathogen species is typically opaque. A lower-resolution qualitative assessment may still give good support for this hypothesis: for example, demonstrating fever sensitivity is sufficiently common among pathogens known to infect humans, or that a significant fraction of global human burden of disease can be attributed to pathogens which are sensitive to febrile temperatures.

The clinical value of fever. These results are not sufficient to resolve the clinical controversy around suppressing fever. Yet our results suggest febrile heating alone could have significant clinical utility for some infections.

Although this supplies cause for caution in suppressing fever, the overall clinical judgement in the context of a given infection needs to assess more than the

plausibility of the heating hypothesis. For a given patient and a given infection, fever may be unwise to suppress even if febrile heating serves little purpose: its immunomodulatory effects may be crucial to combating the infection. The opposite could also be the case: for example, for an individual with limited physiological reserve the additional stress of fever may be harmful overall even if its thermal effect on the infection is significantly beneficial.

One approach to gain further insight would be to better understand what triggers different 'types' of fever: 'spiking', undulating, or continuous fever are all clinically observed.[140] One hypothesis could be fever is recruited for different purposes depending on the status of infection: a competing explanation for 'spiking' besides the energy efficiency we explored is that spiking principally serves as an immunological signal, whilst continuous fever is reserved for more severe infection where antimicrobial heating is resorted to. Understanding fever's correlates and mechanisms may inform which biological mechanisms are important in which circumstances, and thus give a principled rationale on when to intervene.

For the clinical question, inference from first principles is inferior to trial data. This data is scant: there are a small number of small trials which vary in their findings, and systematic reviews typically give inconclusive results.[141–143] Perhaps the best infection to investigate further would be Malaria, given parasite growth is significantly inhibited at febrile temperatures *in vitro*,[144] expert opinion varies, and the data is equivocal.[145, 146] Given both the disease and anti-pyretic therapy are prevalent, resolving this uncertainty may bring significant humanitarian benefit.

Fever is indirectly adaptive. Our results also provide suggestive evidence for febrile heating being an exaptation. The mechanisms of thermal elevation are all in principle much more effective when temperature can vary in the range of ectothermic organisms. One hypothesis could be that raising body temperature in response to infection was highly adaptive in ectotherms, and ancestral immune systems co-adapted to be partly triggered by higher temperatures. After the development of endothermy (perhaps in part driven by the value of continuously, rather than intermittently, occupying a different thermal niche to avoid infection

from environmental microbes[147]) the direct antimicrobial value of raising body temperature faded, but this mechanism was preserved due to ongoing reliance of the immune system on a temperature signal.

For this hypothesis, as well as fever being maladaptive, accessible evidence is unlikely to be better than suggestive. Even if one can rule out the thermal mechanisms of fever as an effective host response, isolating and assessing other mechanisms by which fever could combat infection is harder still. One may compare courses of fever between species: whether some endotherms can raise their body temperatures in fever much higher than others, and exploring what antimicrobial effects this has.

Fever as credible signal. Our exemplars, *E. coli* and *S. dysenteriae* are close phylogenetically, similar pathophysiologically, yet differ markedly in their sensitivity to febrile temperatures. What could explain the differences observed between endotherm pathogens in how they tolerate febrile temperatures?

One possibility is physiological differences: perhaps some aspect of *S. dysenteriae*'s metabolism imposes a temperature restriction versus *E. coli*. Another could be differences in lifecycle: perhaps *S. dysenteriae* spends more time in colder environments outside the host than *E. coli*, and so trades a lower T_{min} for a lower T_{max}.

One interesting hypothesis is sensitivity to febrile heating, and lower growth at febrile temperatures, could sometimes enhance pathogen fitness. If there are 'trade-offs' between length and intensity of infection, pathogen species adapted to longer milder infections may be advantaged if they respond to the host's credible signal of immune activation and threatened host death by reducing growth. Pathogens which lower the risk of earlier termination of their infection by host death or immune clearance may be at a selective advantage. Such a hypothesis is complicated by both intra- and inter-specific within-host competition. Responding to signals of imminent host death with accelerated rather than diminished growth could provide a competitive advantage for an individual pathogen (producing more offspring in the limited remaining time should the host die) even if deleterious for the pathogen

population as a whole (by increasing the likelihood of host death). Likewise for pathogen species whose typical host environment is one of multiple concurrent infections with other species, restrained growth in response to a fever caused by another species pursuing a 'greedier' reproductive strategy may be maladaptive.

This hypothesis can be examined both theoretically and empirically. Theoretically, one can attempt to build upon prior theoretical work on the co-evolution of honest (and costly) signalling in predator-prey or aposematic contexts:[148, 149] whether initially adaptive febrile heating can be maintained as a co-evolutionary stable 'inducible aposematism', whereby it is adaptive for hosts to thermally signal their physiological compromise, and for pathogens to respond to this with slower growth. Empirically, this hypothesis predicts pathogens which generate acute infections should tend to be less responsive to febrile temperatures than those which produce chronic infections.

4

Risk-benefit analysis of emergency vaccine use

Emergency vaccine use requires weighing a large number of uncertain risks and possible benefits. In the COVID-19 pandemic, decisions about what evidence is necessary to authorize emergency use have proven controversial, and vary between countries. We construct a simple mathematical model of the risks and benefits of emergency vaccination to an individual, and apply this to the hypothetical scenario of individual decision-making between emergency use of a COVID-19 vaccine without safety and efficacy data, versus waiting for efficacy and safety to be established. Even with conservative modelling assumptions and uncertainty distributions for vaccine efficacy (mean expectation = 17%) and serious adverse event risk (mean expectation = 0.3%), high risk individuals (e.g. those who are elderly and have a household contact with COVID-19) are better off using the 'emergency vaccine' rather than waiting for more information (absolute risk reduction for mortality up to 2%). Given these benefits, very early emergency authorization of vaccines despite very limited data may be the better public health strategy when confronted with a dangerous emerging infectious disease.

Contents

4.1 Introduction

Vaccination is rarely an emergency. Most vaccine candidates target an endemic and well-characterised infectious disease. In these cases, there is time to perform a rigorous vaccine candidate trial to establish a vaccine is safe and effective before it is offered for routine clinical use.

Emerging infectious diseases can be exceptions to this rule.[1] For instance, in Guinea in 2016 and the DRC is 2017, Ebola vaccines still in phase 3 trials were used to combat Ebolavirus disease (EVD) outbreaks.[150, 151] The ethical rationale was the risks of administering a vaccine which was not proven to be safe and effective was outweighed by the potential benefit of protection from a highly lethal infectious disease.[152] The WHO's Emergency Use Listing (EUL) procedure, first developed in response to this EVD experience, is explicit about this trade-off:[153]

> The EUL is a special procedure for unlicensed vaccines, medicines and in vitro diagnostics in the event of a PHE [Public Health Emergency] when the community/public health authorities may be willing to tolerate less

[1] Seasonal influenza vaccines are also a partial exception. Influenza vaccines differ season by season, as they are updated to match influenza strains predicted to pose the greatest danger. The track record over a long history of use provides strong evidence seasonal influenza vaccines are safe and effective *in general*. Yet direct evidence the current seasonal influenza vaccines *in particular* are safe and effective only arrives after administration has begun.

> certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the lack or paucity of treatment, diagnosis/detection or prevention options

The EUL also countenances emergency use of a vaccine candidate even when no human data on efficacy is yet available:[153]

> If preliminary human data showing some efficacy are not available for the vaccine under consideration and if not imminently available for other vaccines being concurrently developed, WHO will consider whether the preponderance of evidence from the non-clinical, and early human studies justifies considering the immunogenicity data as a potential surrogate that is thought to be reasonably predictive of clinical efficacy.

Navigating these uncertainties are complex, as they typically apply not only to the vaccine candidate but to the emerging infectious disease itself: at the early stages of an outbreak, infection fatality rate, risks of long-term health consequences, infectiousness, and even mode(s) of transmission can be uncertain or unknown.[154, 155] An individual offered emergency vaccination in such circumstances has to choose between two very unclear risks: whether, in their situation, the risks of the vaccine are greater or less than those of remaining susceptible to the disease.

For policy-makers deciding on emergency use authorisation, the benefit/risk to the individual is further complicated by population-level risks and benefits. One complex decision would be, if the vaccine impedes transmission, earlier use could lead to greater herd immunity, so reducing the final size of the epidemic;[156] another would be the risk of, if the vaccine is less safe and effective than hoped, damaging public confidence in subsequent vaccination campaigns for the diseases, and potentially vaccination programs for other diseases as well.[157–159]

The COVID-19 pandemic has brought these challenges to global attention. Regulatory practices varied between countries for vaccine licensure. Many regions (e.g. US, UK, Australia, Europe) accepted interim phase 3 trial results as sufficient for a vaccine candidate to be deployed, but their requirements differed: some needed to see an early signal of efficacy across the population, sometimes with a threshold of at least 50% vaccine efficacy; whilst others required efficacy and safety data

specifically for subgroups 'first in line' for administration. Both China[160] and Russia[161] have offered their vaccine to their population or for international sale before phase 3 results were available.

All approaches, whether more aggressive or more conservative, have proven controversial. Although most candidate vaccines now have extensive clinical data available, the dilemmas around emergency use remain live. These issues include: how should regulation treat modified existing vaccines (or modified schedules of existing vaccine administration) addressed to deal with emerging COVID-19 strains; how can new vaccine candidates which may reduce global COVID-19 vaccine shortfall be deployed; and what are the best approaches for constructing policy for future emerging diseases.

These challenges of decision-making under uncertainty are widely appreciated in medicine and public health.[162–164] The dilemma of emergency vaccine use - whether to act now on limited knowledge, or wait for more information to become available - is similar to problems about health economics in assessing the value of further information in medical research or decision support.[165, 166] Although mathematical evaluation of all ramifications of emergency vaccine use may be intractable, analyses restricted to individual risk-benefit can be informative: if individuals should expect significant benefit or harm if they elected for emergency vaccination, this argues strongly for or against it being offered in the first place.

This paper attempts this evaluation. We first construct a simple mathematical framework of individual risk-benefit for vaccine use. We then adapt this for emergency vaccination for the COVID-19 pandemic by using epidemiological parameter ranges of this pandemic alongside vaccine safety and efficacy track records. Our modelling then explores the scenario of an individual being offered an emergency vaccination for COVID-19, where the vaccine candidate has demonstrated encouraging early results, but the phase 3 trial is ongoing and interim data is not yet available. This situation allows us to assess an approach similar to that used in China and Russia, and arguably different than used in most other countries.

4.2 Methods

4.2.1 A model of vaccine risk-benefit

We use the following equation to evaluate the risks and benefits to an individual from being vaccinated:

$$\text{Utility} = \text{P(I)} \cdot \text{IFR} \cdot \text{VE} - \text{SAER} \tag{4.1}$$

Where P(I) is the probability of infection, IFR is the infection fatality rate (i.e. p(Death|Infection)), VE is the vaccine efficacy, and SAER is the serious adverse event risk. The first three terms give the benefit in terms of mortality risk reduction from the disease; the last term gives the risk increase accrued through vaccination. Utility ≤ 0 if any of the first three terms are zero: one cannot benefit from vaccination where one will certainly not acquire the infection, or certainly not die from the infection, or where the vaccine is certain to confer no protection.

This equation underestimates the net-benefit of vaccination in two respects. First, many infections (including COVID-19) can result in significant morbidity even they do not kill, but potential benefits from vaccination in avoiding these other sequelae are not included. Second, the great majority of serious adverse events in vaccines, whether clinical or experimental, are not fatal, yet equation 1 treats these events as equivalent to dying from the disease.

4.2.2 Emergency use

We consider a simplified scenario of an individual being offered an emergency vaccine whose safety and efficacy are currently unknown, but will be discovered subsequently. For concreteness, this could correspond to an individual being offered a vaccine like Pfizer/BioNtech after the publication of the phase I/II results (in August 2020), but prior to interim Phase III data (reported 4 months later in December). We compare two choices:

1. **Go.** The individual takes the vaccine early, taking an uncertain risk from vaccination for the uncertain benefit of potential earlier protection from the disease.

2. **Wait.** The individual waits for firm data on vaccine safety and efficacy, taking an uncertain risk from remaining fully susceptible to the disease until this is established.

We now adapt equation 1 to compare 'Go' versus 'Wait'.

$$\text{Expected Utility} = \widehat{\text{P(I)}}_{(t(e),t(k))} \cdot \widehat{\text{IFR}} \cdot \widehat{\text{VE}} - \widehat{\text{SAER}} \tag{4.2}$$

If the Expected Utility is positive, then emergency use is superior to waiting, and vice versa. The first change is this equation now represents a forecast rather than a point calculation of risk. The expected utility is a function of the expected values of P(I), IFR, VE, and SAER. The second change is greater precision on what is meant by 'probability of infection': an individual who opts not to take an emergency vaccine, preferring to wait for a vaccine which is firmly established to be safe and effective, is not deciding to remain susceptible to infection permanently. The risk of infection is therefore the probability of infection in the interval between the time they could have taken the vaccine as an emergency ($t(e)$) and the time when the vaccine's safety and efficacy are known ($t(k)$). (For brevity, this will be simply 'P(I)').

This approach is also conservative. The serious adverse event risk would still apply if the vaccine was taken at $t(e)$ instead of $t(k)$. This risk is only a penalty of emergency use for individuals who elect for the vaccine at $t(e)$ but who subsequently (at $t(k)$) have better options than this vaccine available to them.

4.2.3 Application to COVID-19

We now consider a parameterization of equation 2 in light of the COVID-19 pandemic (table 4.1).

IFR and probability for infection over a given period for COVID-19 can vary dramatically between individuals: a twenty year old woman living alone in China

Table 4.1: COVID-19 vaccine emergency use modelling parameters

Variable	Values
Probability of Infection (p(I))	*Range*: 0 to 0.4
Infection Fatality Rate (IFR)	*Range*: 0 to 0.2
Vaccine Efficacy (VE)	*Distribution* Conservative: $p = 1/3 : \text{VE} = 0$; $p = 2/3 : \text{VE} = Beta(1, 3)$ Optimistic: Uniform(0,1)
Serious Adverse Event Risk (SAER)	*Distribution* Conservative: $Beta(1, 301)$ Optimistic: log-uniform (10^{-6}, 10^{-3})

may have an $\widehat{\text{P(I)}}$ and $\widehat{\text{IFR}}$ three orders of magnitude lower than an 80 year old man who becomes a household contact of an active case. Given this variation, we use plausible ranges rather than point estimates. For $\widehat{\text{P(I)}}$, we consider the range (0, 0.4) the lower limit approximating someone living in a very low incidence environment (e.g. New Zealand, which had a total cumulative COVID-19 incidence of $\approx$ 35 per 100 000 n 2020[167]), the upper limit in the region of estimates of secondary attack rate for household contacts.[168] For $\widehat{\text{IFR}}$, we consider the range (0, 0.2), corresponding to the range of age-specific infection fatality rates estimated by Brazeau and colleagues.[169]

SAER and VE have less dramatic between-individual variation, but the 'typical' true value of VE and SAER of an unproven vaccine are uncertain. We consider the random variables $\widehat{\text{SAER}}$ and $\widehat{\text{VE}}$, estimators of VE and SAER, and construct both 'conservative' and 'optimistic' distributions for each.

For $\widehat{\text{SAER}}$, our conservative estimator ($\widehat{\text{SAER}}_c$) is based on the rate of vaccine-attributed serious adverse events observed in earlier studies of the vaccine candidate. For vaccines in phase 3 trials, the typical number of adverse events previously observed in phase 1 and 2 trials are zero. We use a conservative prior ($Beta(1, 1)$) and update this based on N consecutive observations of no serious adverse event ($Beta(1, 1 + N)$). We use $N = 300$, thus a conservative uncertainty distribution of $Beta(1, 301)$, with an expected value ($\text{E}[\widehat{\text{SAER}}_c]$) of roughly 0.3%. This is consistent with the rates of adverse events seen in Phase 1 studies, reviewed by Johnson and

colleagues.[170] They found 15 serious adverse events attributable to the agent being trialled in 24988 participants in the treatment arms of studies reviewed. They also report vaccine trials had a higher rate than other study types (incident ratio of 6.21). This gives $\mathrm{E}[\widehat{\mathrm{SAER}}_c] \approx 0.4\%$.

This approach is conservative as $\widehat{\mathrm{SAER}}_c$ does not use the knowledge that vaccines are typically much safer, with serious adverse event rates typically 1/10000 or less, and that vaccine candidates which reach later trials are selected for safety out of all candidates tested in earlier stages. Our 'optimistic' estimator ($\widehat{\mathrm{SAER}}_o$) presumes the vaccine candidate is similarly safe to vaccines already used in routine practice. As adverse event rates for these vaccines can vary from one in millions to one in thousands, we use a log-uniform distribution from (10^{-6}, 10^{-3}).

For $\widehat{\mathrm{VE}}$, our 'optimistic' estimator ($\widehat{\mathrm{VE}}_o$) is the maximum entropy distribution for the interval (0, 1), the uniform distribution: we do not believe any given value for vaccine efficacy is more or less likely than any other; $\mathrm{E}[\widehat{\mathrm{VE}}_o] = 0.5$. Our 'conservative' estimator ($\widehat{\mathrm{VE}}_c$) is more pessimistic in two respects: first, there is a significant probability the vaccine candidate is completely ineffective (for Uniform(0,1), VE is almost surely > 0), and it is more likely to have poor efficacy (VE < 0.5) than good efficacy. We therefore use a mixed distribution where one third of the probability mass is VE $= 0$, and the remainder is distributed by $Beta(1, 3)$; $\mathrm{E}[\widehat{\mathrm{VE}}_c] \approx 0.17$.

4.2.4 Analysis

We model our emergency vaccine use scenario for COVID-19 by dividing the plausible range of P(I) and IFR into 21 equidistant points (i.e. for IFR: 0, 0.01, 0.02 ... 0.2; for P(I): 0, 0.02, 0.04 ... 0.4.). For each of these 441 combinations of (P(I), IFR), we draw values at random from an estimator of VE and SAER, and calculate the utility. We repeat this 10000 times and take the average to give the expected value.

We also take the proportion of samples with Utility > 0 to give a 'likelihood of expected benefit': the probability individuals at a given value of (P(I), IFR) would find they were better off in expectation for electing for emergency vaccination when the true values of SAER and VE are known. This is distinct from a straightforward

'likelihood of overall benefit'. For example, emergency use of a vaccine with VE = 0.1 and SAER = 0 is certain to provide expected benefit to any individual for whom P(I) and IFR > 0: this vaccine cannot harm, and may help should they be exposed to the infection. Yet the likelihood of benefit of taking the vaccine cannot be greater than the Vaccine Efficacy (0.1).

4.2.5 Data and code

Analysis was conducted on MATLAB (v. R2020a; Mathworks, Massachusetts). All code and data is available at: `https://github.com/gjlewis37/EUAVax/`

4.3 Results

4.3.1 Surfaces of equipoise

For a given value of SAER, equation 1 produces a surface of equipoise which is a three dimensional hyperbola with respect to P(I), IFR, and VE (figure 4.1). The threshold value for VE falls with increasing values of P(I) or IFR: intuitively, compensating for a given harm of vaccination (SAER) can be achieved by a greater risk reduction from a less dangerous disease, or a lesser risk reduction from a more dangerous one. Decreasing SAER in essence lowers this constraint, with correspondingly more of the unit volume above the surface of equipoise - that is, where vaccination would be beneficial.

This also means for a given SAER, the marginal returns to increasing VE in terms of the area of (P(I), IFR) where vaccination is beneficial are decreasing. The central case, SAER = 10^{-3}, is illustrated in a contour plot with IFR and AR restricted to the parameter ranges relevant to COVID-19: $0 \leq \text{P(I)} \leq 0.4$; $0 \leq \text{IFR} \leq 0.2$ (figure 4.2).

4.3.2 Risk-benefit of emergency COVID-19 vaccination

The model for risk benefit in emergency vaccination for COVID-19 is given in figure 4.3. Notably, even with conservative estimators for both VE and SAER, individuals subject to higher P(I) and IFR are expected to benefit from emergency vaccine

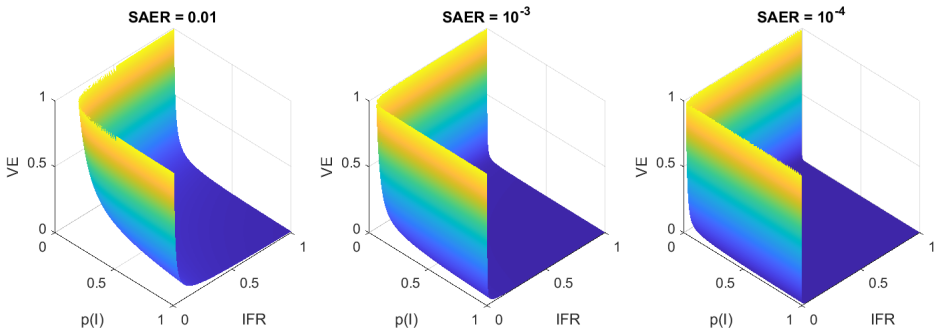


Figure 4.1: Surfaces of clinical equipoise for vaccination (Utility = 0) in terms of probability of infection (P(I)), Infection Fatality Rate (IFR) and Vaccine Efficacy (VE) for Serious Adverse Event Rate (SAER) = 0.01 (l), 10^{-3} (c), and 10^{-4} (r). The volume above this surface is where Utility > 0, thus vaccination is beneficial, and vice versa.

use. Those at lower risk of infection (and death conditional on infection) are more likely to be harmed by emergency vaccination, but this expected harm is relatively low (at most ≈ -0.003, matching $\mathrm{E}[\widehat{\mathrm{SAER}}_c]$). In contrast, the benefit of those at greatest risk are much greater: at the extreme of P(I) = 0.4, IFR = 0.2, and with 'conservative' estimators for VE and SAER the expected utility is ≈ 0.02. As the units for utility is probability of survival, this amounts to an absolute mortality risk reduction of 2%, thus a number needed to vaccinate of $\frac{1}{\text{Absolute risk reduction}} \approx 50$.

With more optimistic estimators for both VE and SAER, emergency vaccination offers both greater expected benefit and higher likelihood of net benefit across the range of P(I) and IFR (e.g. at p(I) = 0.4 and IFR = 0.2, the absolute risk reduction is ≈ 0.04). Emergency vaccination is consequently beneficial to individuals across a wider range of (P(I), IFR) values. The modelling scenarios of conservative estimators for VE alongside optimistic expectations for SAER (and vice versa) give results intermediate between those shown in figure 4.4, (supplementary material).

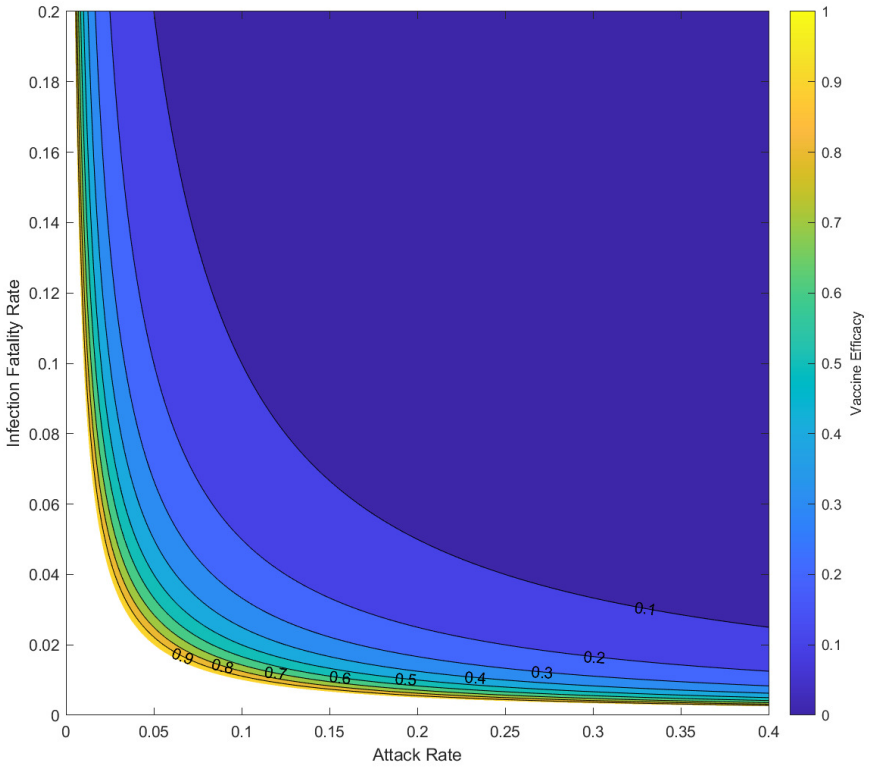


Figure 4.2: Contour plot of Vaccine Efficacy (VE) versus probability of infection (P(I)) and Infection Fatality Rate (IFR), for ranges of these parameters relevant to COVID-19 ($0 \leq \text{P(I)} \leq 0.4$; $0 \leq \text{IFR} \leq 0.2$), given a Serious Adverse Event Rate (SAER) of 0.1%. The VE = 0.1 contour includes more than half of this parameter region, and so Utility $>$ 0 for a vaccine efficacy of 10% in this region of values. Further increments of VE include progressively smaller additional proportions of this field of (P(I), IFR). Note the unshaded region is where vaccination is not beneficial even with a perfectly effective vaccine, given by $0.001 \geq \text{P(I)} \cdot \text{IFR}$: this is the region where the risk of disease is lower than than the (stipulated) SAER of the vaccine.

Likelihood of expected benefit shows a similar pattern to simple expected benefit, although the thresholds for equipoise in terms of (P(I), IFR) are lower, especially with 'optimistic' estimators for VE and SAER. This is owed to distributions for SAER being highly skewed, with the median or modal SAER being lower than the mean. Thus in regions of neutral expected benefit the majority of samples are positive expected value, with the minority distributed in a longer tail below zero.

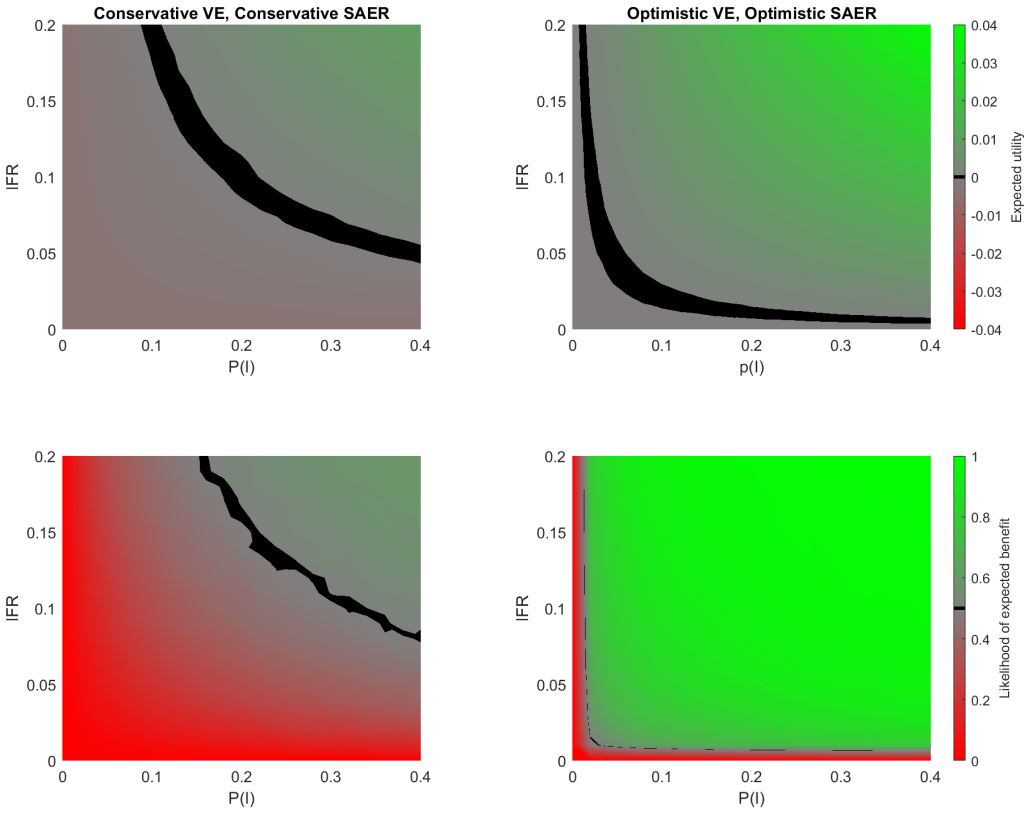


Figure 4.3: Expected utility (top row) and likelihood of expected benefit (bottom row), for the model of emergency COVID-19 vaccination with conservative (left column) and optimistic (right column) estimators for VE and SAER. Green denotes positive utility or likelihood of expected benefit > 0.5, and red the opposite. The black region corresponds to that of approximate equipoise between emergency vaccination or not: $-0.0005 <$ Expected Utility ≤ 0.0005 and $0.495 <$ Likelihood of expected benefit ≤ 0.505 respectively. The optimistic estimators result in emergency vaccination being beneficial across a greater proportion of the [P(I),IFR] parameter space. However, with either conservative or conservative expectations, those at high risk of COVID-19 - the top right region of these graphs - can expect significant benefit.

4.4 Discussion

Our mathematical analysis suggests that even relatively ineffective vaccines can be beneficial when the danger from disease is high enough: the benefit of a 10% risk reduction from a highly contagious and lethal infectious disease can outweigh the risks of vaccination, even if these are (by vaccine standards) relatively great. The hyperbolic nature of the relationships between net-benefit and VE also means, for a given SAER, that the thresholds for net benefit (in terms of P(I) and IFR)

fall further when moving from VE of 0.1 to 0.2 than from 0.5 to 0.9.

When we apply this model to emergency vaccination for COVID-19, 'gambling' on an uncertain vaccine can be the safer bet than accepting the dangers of prolonged susceptibility for those at high risk of COVID-19. This result occurs despite a very conservative approach in assessing the risks and benefits, and with conservative expectations of the emergency vaccine's safety and efficacy. With more optimistic expectations, both the magnitude of benefit and the range of (P(I),IFR) where emergency vaccination is expected to be beneficial increase.

Our model makes many simplifying assumptions. We assume no interactions between variables, despite older individuals (a greater IFR) often mount less effective vaccine responses (a lower VE).[171] An individual's 'Utility' may not simply be mortality risk-reduction: individuals may put particular weight on particular health states which may be more or less likely to result from disease or vaccination. We also ignore relatively minor costs of both vaccination and infection, such as the inconvenience of getting a vaccination, pain of injection, or an infection which gives a mild illness and complete recovery.

Our modelling scenario is a highly simplified 'snapshot' scenario, so neglects many of the dynamics which could attend emergency vaccine use in an evolving pandemic. Examples of these include: 1) The outcomes for individuals who go ahead with emergency vaccination may generate observational data to improve initial estimates of vaccine efficacy and safety for those making decisions subsequently; 2) IFR and P(I) may not only be uncertain but non-stationary (e.g. new variants or therapeutic breakthroughs may emerge); 3) P(I) itself may be sensitive to how widely emergency vaccination is offered and accepted.

Our model for COVID-19 does not account for many vaccine candidates being developed in parallel. Although our model is indifferent to an individual who waits for the safety and efficacy of the emergency vaccine to be known or for another proven vaccine to become available, we do not model the possible risk of 'vaccine-vaccine interference'.[172] Emergency use of a relatively ineffective vaccine

could compromise the protection the individual gains from being subsequently administered a more effective vaccine.

Our results are highly sensitive to the assumed distributions of $\widehat{\text{VE}}$ and $\widehat{\text{SAER}}$. Specifying their values risks a tautology: vaccine use is in expectation better than non-use as - by stipulation - the expected benefits are greater than the expected risks. However, these values were partly informed by historical data on vaccine trials. Furthermore, subsequent data on COVID vaccine efficacy and safety suggests, if anything, the assumed distributions of $\widehat{\text{VE}}$ and $\widehat{\text{SAER}}$ were not optimistic enough. The three earliest COVID-19 vaccine candidates reported interim results with VE > 0.5 (Pfizer/BioNtech,[173] Moderna,[174] Oxford/Astrazenica[175]). These are very surprising conditioned on our model of conservative expectations for VE ($p < 0.001$) - even more conservative expectations would find this outcome even more improbable. Our 'optimistic' uncertainty distribution for VE is less surprised by these results ($p = 0.125$), suggesting it is a more reasonable prior.

Similarly, the combined SAERs for these vaccines are much lower than 0.3% predicted by the conservative estimator for serious adverse event rate (e.g. $\approx 0.0002\%$ of thrombotic events following Oxford/Astrazenica vaccination,[176] $\approx 0.0001\%$ of myocarditis or pericarditis following Moderna or Pfizer/BioNtech vaccination[177]), and much more in the range of 'one in thousands' to 'one in millions' given by our 'optimistic' estimator. Wong, Siah and Lo, reviewing previous trials, find the likelihood of a vaccine candidates in phase 1 studies ultimately reaching approval for use is 33.4%, rising to 85.4% if the candidate reaches phase 3 trials.[178] This suggests a given vaccine candidate being subsequently found safe and effective is much more common than our conservative assumptions imply.

Much more significant is our model does not account for the possibility of vaccine-dependent enhancement of disease (VDE).[179, 180] Loosely, this can be thought of as a VE which is less than zero. Modelling this is particularly complex as the expected likelihood and degree of VDE either generally or in a particular scenario remains very poorly understood. However, this risk only qualitatively changes the results when it is so high the expected VE falls to very low values. In the

conservative model, the highest risk individuals only cease to benefit in expectation from emergency vaccination when the expected vaccine efficacy is ≈ 0.04 or less: a vaccine scarcely more likely to protect rather than enhance disease.

One should be cautious using models like these to guide individual decision-making around emergency use. For example, although age is the most significant predictor for COVID-19 IFR, a given individual's IFR would also depend on a number of other factors.[181–183] Similarly, an individual's P(I) depends on the time remaining until safety and efficacy is firmly established, the incidence in their environment (which can change over this time), and their own behaviour. All are challenging to assess.

Two misinterpretations are important to guard against. The first is although our modelling shows large proportions of the (P(I), IFR) parameter space favours emergency use, this does not mean most individuals in a population stand to benefit from it. Both P(I) and IFR are highly skewed distributions across individuals: although some would find themselves in the 'top right corner' (e.g. elderly individuals with an infectious household contact), most would find themselves closer to the bottom left. A P(I) of 1% is in the range of seroconversion estimates over 3 months in countries with poorly controlled epidemics; the IFR generally only begins to exceed 1% in those over 60 years of age.[169] Insofar as our model implies a recommendation for emergency use, it only applies to the fraction of the population at high risk, similar to those already assessed as highest-priority for vaccination under most vaccination deployment strategies.

The second is that individuals our model assesses as not benefiting from emergency vaccination would also not benefit from non-emergency vaccination. Our model only considers the benefit of potential short term protection (e.g. the interval between phase 2 and interim phase 3 data) in the context of uncertainty around VE and SAER. For non-emergency use, VE and SAER would be known much better, and the overall risk-benefit assessment would need to consider a much longer duration of protection (which may be lifelong), the probability of infection

over this much longer period, and that an individual's IFR increases as they age. Our model does not apply to this scenario.

Our model only assesses risk-benefit to the individual, and so does not include population-level factors such as the potential of risk compensation, herd immunity, or the potential of emergency use to enhance or undermine public confidence in vaccination. These factors are important to policy-makers contemplating whether to authorize emergency use, yet they are difficult to assess and weigh alongside the individual-level benefits to estimate the socially optimal policy. Yet although the aggregate individual-level benefits are not the only consideration in public health, they are commonly a crucial or leading one: most of the business of public health is to make members of the public healthier. We hope mathematically articulating the risk-benefit for individuals can inform these difficult decisions; on the face of it, the significant expected benefit at an individual level for those at high risk would require a lot to outweigh these gains.[2]

Our mathematical analysis underlines that risk reduction can involve trade-offs, and calculation cannot be done purely in qualitative terms of 'un/safe' or 'in/effective'. When one faces little risk of infection with a mild disease, the benefits of vaccination may not be worth even remote risks of harm. The opposite is also true: if confronted with a high likelihood of infection by a highly lethal pathogen, a vaccine which is 'ineffective' (e.g. a VE much lower than 50%) and - by vaccine standards - very 'unsafe' (e.g. an SAER of 1%) could still be better than nothing.

We also note the rationale for a '50%' efficacy threshold appears dubious. Not only would a hypothetical vaccine of (e.g.) 15% efficacy and a reasonable safety profile be better than nothing for many individuals, but such a threshold would rule out the great majority of primary and secondary prevention if it was applied

[2]There may be ethical concerns even in cases where it does, depending on the outweighing consideration. For example, denying emergency vaccine access to Alice, who (correctly) assesses emergency use would benefit her in expectation, because of the chance it would be detrimental and so reinforce Bob's (incorrect) vaccine scepticism appears unjust to Alice: she is being obliged to make worse decisions for her own health to cater to Bob's mistaken health beliefs - beliefs she is not responsible for.

to non-communicable disease: among many examples, the risk reduction of anti-hypertensives for coronary heart disease and stroke is $\approx 20\%$ and $\approx 40\%$ respectively, statin medication on cardiovascular disease is $\approx 25\%$,[184] and aspirin $\approx 20\%$[185] for secondary prevention of vascular disease. All of these medications also have significant risks of adverse events: for example, $\approx 0.1\%$ of major gastrointestinal bleeds each year of aspirin use.[186]

COVID-19 will not be the last pandemic. The success of COVID-19 vaccine development demonstrates the potential for accelerated vaccine deployment to protect the global population from the next one. For this pandemic, the timelines for trials roughly matched those for manufacturing and logistics; the global vaccine shortage for vaccines has and will persist long after the clinical trials have concluded. Manufacturing and deployment will hopefully further improve between now and the next pandemic. If they do, data and decision-making may become the rate-limiting step to vaccine deployment.

There are a number of proposals to make this step faster, from adopting optimal adaptive trial design,[187] to 'pre-positioning' relevant pre-clinical work in advance of the emergence of a new infectious disease,[188] to the use of human challenge trials to rapidly find early signals of efficacy.[187, 189] Another significant advantage of human challenge trials is the rapid potential to detect vaccine enhancement of disease.

Our work suggests a complementary line of research is to improve decision-making where uncertainty remains - whether a given situation warrants hasty action or watchful waiting. Prediction platforms,[190] 'superforecasters' and markets all shifted in response to pre-clinical COVID-19 vaccine data, implying this information was being used to predict whether particular vaccine candidates would ultimately prove effective. Attempting these forecasts explicitly, and assessing their accuracy and reliability could provide an important decision aid for emergency use policy under uncertainty.

One key goal to aid this capability, still to be pioneered, would be approaches to find general 'base rates' for vaccines: e.g. how effective is a vaccine candidate likely to prove given particular results from phase 2 (or phase 1) studies; what is the

typical risk of a vaccine candidate provoking VDE; whether one vaccine modality tends to prove more or less effective than others, and so forth.

Ultimately, our modelling underlines that uncertainty may not always justify delay. 'Gambling on an unproven vaccine' may be safer bet for an individual than 'gambling on not being infected while waiting for the vaccine to be proven'. In COVID-19, the cost of the latter can be stark - at the extreme of risk, a 1-4% absolute risk of death. The underlying driver for these results is that vaccines, even experimental ones, are very safe; remaining susceptible to COVID-19, for some, is extremely dangerous. With the benefit of hindsight, delaying administration of vaccines subsequently shown to be safe and effective has cost lives. Our work suggests the same could have been predicted in advance.

4.5 Supplementary material

The modelling results for risk-benefit with an optimistic estimator for VE, but a conservative estimator for SAER (and vice-versa) are given in figure 4.4.

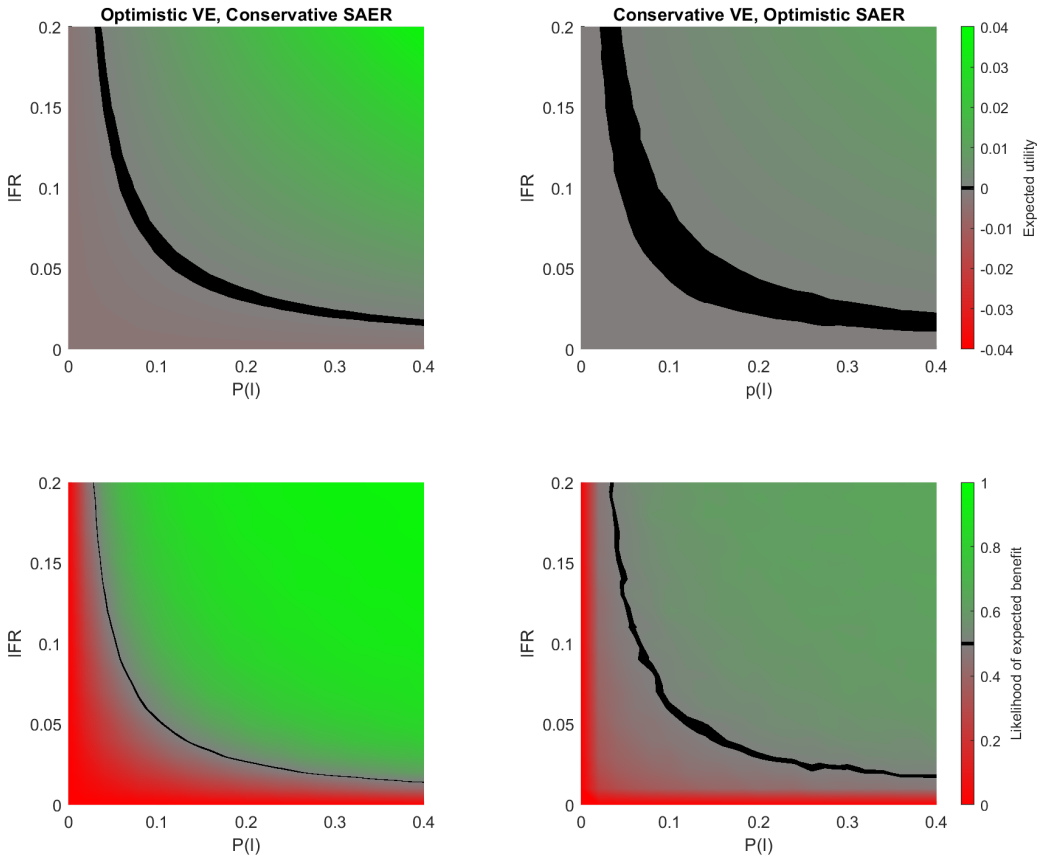


Figure 4.4: Expected utility (top row) and likelihood of expected benefit (bottom row), for the model of emergency COVID-19 vaccination with the optimistic estimator for VE and the conservative one for SAER (left column) and vice-versa (right column). Green denotes positive utility or likelihood of expected benefit > 0.5, and red the opposite. The black region corresponds to that of approximate equipoise between emergency vaccination or not: $-0.0005 <$ Expected Utility ≤ 0.0005 and $0.495 <$ Likelihood of expected benefit ≤ 0.505 respectively. These results are approximately intermediate between the modelling where conservative or optimistic estimators are used for both VE and SAER (see figure 4.3).

5

Modelling the public health trade-offs of vaccine dose scheduling policy in the COVID-19 pandemic

Many COVID-19 vaccines are provided across multiple doses, and provide some degree of protection after the first dose(s) are provided, but less than a completed course. As universal administration is not instant and timely vaccine protection key, how doses should be scheduled (and whether those who have yet to start a vaccination course should be prioritised for their first dose before others are provided later doses) is a public health dilemma. This chapter first distinguishes different types of vaccine efficacy (e.g. versus transmission, versus mortality) and introduces a mathematical framework of marginal vaccine efficacy. It then assesses different dose scheduling strategies in terms of a) protection of individual health; b) reduction of disease transmission; and c) early release of non-pharmaceutical interventions, using parameters modelled on the early COVID-19 pandemic. These models generally support the intuition that prioritising first doses is superior when one dose is more than half as good as two doses.

Contents

5.1 Introduction

The unprecedented speed of COVID-19 vaccine development has resulted in the novel situation of vaccine roll-out being (or having been) concurrent with epidemic spread in many populations.

Vaccine roll-out concurrent with epidemic spread poses a public health dilemma: earlier vaccination brings greater benefit to an individual, but not everyone can be vaccinated first. Even countries with abundant supplies of vaccine face limits in their rate of deployment: some will have to wait to receive a vaccine, and whilst they wait they remain at elevated risk of the epidemic disease.

This scarcity prompts strategies to prioritize and allocate vaccinations to bring the greatest benefit. Many countries adopted the policy of prioritizing older or medically vulnerable individuals, on the rationale these people benefit the most from earlier vaccination.[191–193] Alongside protecting the vulnerable, another rationale is to prioritise those at greatest risk of transmission to others if they become infected (e.g. carers, medical personnel), and so reduce overall disease spread.

A further complication to these strategies is many COVID-19 vaccines are given in two sequential doses. An individual who receives a single dose enjoys partial protection from infection compared to an individual who receives both doses. If this partial protection is substantial, the strategy of prioritising first doses at the expense of longer delays for those with first doses to receive their second dose ('First Doses First') may be beneficial: a greater number of partially vaccinated individuals bring more benefit than a smaller number of fully vaccinated ones.[194, 195]

Across the scales of this plausible benefit are a range of potential risks:

First dose efficacy and duration. None of the three major vaccines (Oxford/Astrazenica, Pfizer/BionTech, Moderna) had a single-dose arm to assess first dose efficacy, and all participants receiving a single dose were given a second shortly afterwards. Evidence on the efficacy of the first dose (and its duration of effect) were instead assessed opportunistically from subsets of the clinical trial data or observations from ongoing vaccine programs.[173–175, 196] This evidence base is weaker than that for the efficacy and duration after both doses.

Efficacy against emerging variants. Several variants of SARS-CoV-2 continue to be recognised, often with mutations in the spike protein, the antigen used in most vaccines.[197–199] Vaccination with the 'old' antigen appears to offer less protection. This may interact with first versus second dose efficacy non-linearly: vaccine efficacy with one dose may deteriorate more against an emerging variant than vaccine efficacy after both doses.

Transmission and sterilizing immunity: Vaccination may not only protect an individual from severe COVID-19, but prevent them transmitting SARS-CoV-2 to others. If the initial dose provides protective but non-sterilizing immunity, but sterilizing immunity is provided by a second dose, prioritising first doses may result in a greater epidemic size than completing vaccination courses.

Health behaviour and risk compensation: 'Risk compensation' is commonly observed in health behaviour: if the health risks of an activity are lowered, individuals may undertake more of this activity. In response to COVID-19 vaccination, individuals may resume activities that increase their risk of exposure.[200, 201]

Although risk compensation is often benign, it poses two risks. First, individuals may overestimate the degree vaccination de-risks COVID-19 exposure, thus leading to risk *over*-compensation. Second, if immunity is substantially non-sterilizing, vaccinated individuals may increase the risk to non-vaccinated individuals through heightened transmission, either through aforementioned risk over-compensation or an increased prevalence of asymptomatic carriers. With greater uncertainty around first dose efficacy, the greater the chance of these mistakes.

Vaccine escape and selection pressure: As the proportion of the population with immunity (either infection or vaccine derived) to SARS-CoV-2 increases, the greater the selection pressure for strains which can evade pre-existing immunity. The public health costs of vaccine escape could be extreme.

The immunological correlates of vaccine response are stronger after the second dose than the first. Prioritising first doses would leave a larger population with a lesser degree of protection, which may increase the risk of generating vaccine escape variants.

National practice varied in terms of 'dose schedule strategies'. Both the United Kingdom and Quebec relaxed the interval between doses of Pfizer and AstraZenica vaccines from 4 weeks to 12 to enable more initial doses to be provided.[202, 203] Other regions placed a higher priority on ensuring second doses were provided on the manufacturer recommended scheduling, including 'earmarking' stock to be

reserved for second doses.[193] The UK subsequently partially changed course in the wake of the Delta variant, bringing forward second doses for more vulnerable cohorts, in virtue of its higher infectiousness and reduced vaccine efficacy.[204]

Although many of these countries have now mostly completed their vaccination programs, the issues around how to decide between different dose strategies remain live. In the current global vaccine shortage, many countries remain at an early stage of their initial roll-out; many countries are starting 'booster programs' to give third or fourth doses to high risk groups: in both scenarios different strategies in dose allocation may achieve more or less of different public health outcomes.

The vaccine technologies pioneered for COVID-19 promise the potential for vaccination to be a response to the initial outbreak of an newly emerging infectious disease. Thus the public health dilemmas around varying dose schedules of vaccines in a concurrent epidemic are increasingly likely to repeat themselves.

5.1.1 Aims and Outline

This chapter develops mathematical models to evaluate different strategies of vaccine dose allocation. The exemplar for this modelling is COVID-19, although the emphasis is more towards understanding underlying principles, and developing useful heuristics, rather than maximal fidelity to a particular 'real-world' experience of the COVID-19 pandemic.

This work is in four parts. The first section outlines the potential objectives of an urgent vaccination program, and a mathematical framework for evaluating the costs and benefits of different allocation strategies. The next three sections assess optimal vaccine allocation with respect to three different objectives: reducing population vulnerability to disease, reducing risk of infection, and fastest substitution for non-pharmaceutical interventions.

5.2 A framework for 'wartime vaccinology'

Most vaccination programs are directed against a well-characterised and often endemic infectious disease. They are also typically administered before individuals

have accrued a significant risk of exposure, often in childhood or infancy. In long-established vaccination programs, annual demand is a given age-cohort of the wider population, which is relatively straightforward to forecast and meet. Very stringent safety demands are placed on vaccines intended for universal administration, as these tend to greatly reduce both the severity and prevalence of the infectious disease: the risks of vaccination should be lower than the now-reduced risk of exposure.

COVID-19 vaccination programs are exceptions to all of these trends. COVID-19 is incompletely characterised even now, and much less so when most vaccines now in use commenced development. Most individuals were at risk of COVID-19 long before they had access to an effective vaccine. Aggregate demand was difficult to forecast (e.g. dilemmas on whether to vaccinate teenagers or children, whether 'booster doses' should be anticipated) and remains substantially unmet worldwide. The urgent public health emergency prompted many nations to relax various aspects of vaccine licensing and regulation for the sake of speed: from emergency use authorization based on interim trial data, to early use without any clinical data, to changing dose schedules or starting booster programs in advance of clinical data.

All of these departures from the 'evidence base' were criticised for doing so. Many of them were subsequently vindicated. Better understanding of the current COVID-19 experience, and trying to infer underlying mathematical principles can better inform whether these departures were wise or lucky, and help determine how far optimal policy for vaccination in public health emergencies should diverge from vaccination in endemic disease

5.2.1 Health needs and priority-setting in vaccine schedules

Although COVID-19 vaccination is atypical, standard principles of Public Health priority-setting still apply. Everyone has a health need to be protected from COVID-19, although some are more vulnerable (and thus have a greater need) than others. Vaccinating an individual helps meet this need, but also provides a public good alongside this personal benefit: vaccinated individuals may pose less risk of transmitting the disease to others, or their continued health may both avoid them

burdening stretched medical services, and allow them to continue important work (e.g. healthcare, critical industries) during a global pandemic.

If universal vaccination was unaffordable, familiar concepts about allocation, prioritisation and rationing would apply to the scarce COVID-19 vaccines. Different allocations would have different results on public health, but which results are better than others - and thus which priorities should govern who receives a vaccine or not - are subject to both ethical controversy and empirical uncertainty.

Similar challenges remain for COVID-19 even if universal vaccination is expected to be ultimately achieved: in a surging pandemic, 'when' alongside 'whether' for vaccination is important. All else equal, individuals gain greater benefit from being vaccinated earlier, as this reduces their risk of being exposed prior to enjoying vaccine protection. In this context, 'early vaccination' is a scarce resource, as not everyone can be vaccinated immediately, and the health need of prompt vaccine protection is satisfied to a greater degree for some than for others. Similarly, different ordering of when individuals receive vaccine protection can alter the anticipated course of an epidemic in the population, and the best approach is uncertain.

5.2.2 Disentangling Vaccine Efficacy

Exposure to infectious diseases (like COVID-19) can result in a number of different outcomes: death, hospitalization, symptomatic disease, and asymptomatic transmission, among others. Vaccination may vary in its efficacy at preventing these different outcomes of exposure: a vaccine may be more effective at preventing severe disease or death than symptomatic disease, or more effective at preventing symptomatic disease than preventing an exposed individual from becoming infectious.

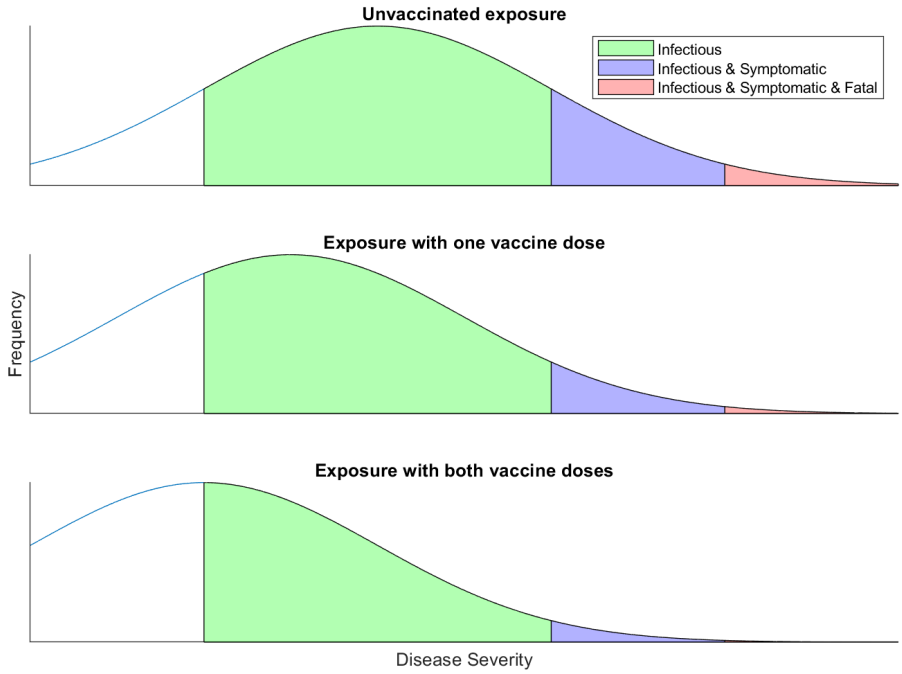
One plausible simplifying model is to propose an underlying latent variable which governs severity of disease subsequent to exposure (mechanistically, this might be reflected in 'duration of infection', 'viral load', or similar). Particular states are ordered sequentially, and are entered when this latent variable climbs above a certain threshold. Vaccination reduces this variable, and so shifts the population distribution towards zero, and thus less severe outcomes.

This suggests the efficacy of vaccination in reducing severe disease (hospitalization or death) may be greater than that reported for preventing cases generally: vaccination may not provide enough protection for some individuals not to develop symptoms, yet enough to prevent them becoming seriously unwell. Conversely, it also suggests vaccine efficacy at preventing an individual transmitting infection may be lower than the reported efficacy in terms of clinical cases ascertained. Vaccination immunity may be protective but incompletely sterilizing, thus some vaccinated individuals when exposed may still shed virus (albeit perhaps less and for a shorter duration than if they were not vaccinated).

To distinguish vaccine efficacy for preventing different outcomes, we use $e^{(t)}$, $e^{(d)}$, and $e^{(f)}$ to denote vaccine efficacy against **t**ransmission, (symptomatic) **d**isease, and **f**atality respectively. The model sketched above suggests $e^{(f)} \geq e^{(d)} \geq e^{(t)}$, given the progression in severity.

A further conjecture from this model is when vaccination comprises multiple doses, the relative efficacy of complete versus partial vaccination may not be proportionate to course completion: an individual who has one of their scheduled two doses may have more or less than half of their vaccine protection. This may also vary depending on the outcome of interest: a single dose may give 60% of the protection of two doses at preventing symptomatic infection, but greater than 60% of the protection of both doses in avoiding hospitalization or death, and less than 60% of the protection of both doses in terms of sterilizing immunity. These points are illustrated in figure 5.1.

These qualitative predictions appear to match the COVID-19 experience: although the primary outcome for most vaccine trials was whether individuals became detected cases, subsequent trial and empirical data suggested greater vaccine efficacy for more severe outcomes (e.g. hospitalization, mortality) and lower implied efficacies for reducing transmission.[205–207] Likewise, observations during roll-out, particularly in countries which prioritised first doses at the expense of a longer delay for vaccination to be completed, suggested that single doses preserved proportionally more of the benefit of complete vaccination for more severe



	Efficacy		
	Infectious ($e^{(t)}$)	Infectious & Symptomatic ($e^{(d)}$)	Infectious & Symptomatic & Fatal ($e^{(f)}$)
One dose (e_1)	0.18	0.58	0.72
Both doses (e_2)	0.41	0.86	0.94
Additional efficacy (e_a)	0.23	0.48	0.29
E_r	1.28	0.48	0.29

Figure 5.1: Schematic illustration of differential vaccine efficacy. Suppose there is a latent variable of disease severity, which when it exceeds a particular threshold results in a particular state (e.g. death, symptoms, infectiousness). For simplicity, let disease severity be normally distributed with standard deviation σ, and the thresholds corresponding developing infectiousness, symptoms, and fatality are -1σ, σ and 2σ respectively (upper panel). Thus subsequent to exposure, an individual has an 84% chance of becoming infectious, 16% chance of developing symptoms, and a 2% chance of death.
Suppose vaccination with a single dose reduces disease severity by 0.5σ (middle panel), and vaccination with both doses reduces it by σ (lower panel). These consecutive equal reductions in the latent variable have unequal effects on the probability of exposure resulting in a given state.
The vaccine efficacy of one or both doses in this illustration are given in the table. There are two features worth noting. First, efficacy is greater for states corresponding to greater disease severity: both doses are $> 90\%$ effective at preventing death, but $< 50\%$ effective at preventing infectiousness. Second, the additional benefit of the second dose relative to the benefit of the first dose also varies (E_r): the second dose more than doubles the reduction of those being infectious after one dose, but only reduces fatalities by an additional 30%.

outcomes.[208] Most recently, vaccines have proven less effective against emerging variants like Delta and Omicron, but this decay in efficacy is more pronounced for less severe outcomes.[209–211]

5.2.3 Marginal vaccine efficacy

Another consideration with vaccine dose scheduling where the vaccination course comprises multiple doses is to compare the benefits for individuals receiving their first or second (or nth) dose.

Consider a vaccine provided in two identical doses. Unvaccinated individuals receiving their first dose gain protection from disease corresponding to the efficacy of a single dose (e_1). On receiving their second dose, the additional efficacy (e_a) is the difference between the efficacy after both doses (e_2) and the efficacy after one dose:

$$e_a = e_2 - e_1 \tag{5.1}$$

Another useful variable is the ratio of the additional efficacy of a second dose divided by the efficacy of the first dose. Let this be E_r:

$$E_r = \frac{e_a}{e_1} = \frac{e_2 - e_1}{e_1} \tag{5.2}$$

If $E_r > 1$, vaccination doses have accelerating returns: an individual gains more protection moving from first dose $\rightarrow$ second dose than no doses $\rightarrow$ first dose. If $E_r < 1$, vaccination doses have diminishing returns, and the opposite is the case.

Two further results are worth noting. First, $E_r < 1$ when $e_1 > 0.5 \cdot e_2$: if the efficacy after one dose is more than half as good as efficacy after two doses, vaccination doses have diminishing returns (and vice versa). Second, $E_r < 1$ if $e_1 > 0.5$: as vaccination cannot be more than 100% effective, the second dose cannot bring more additional benefit than the first if it has efficacy greater than 50%.

Although we focus on two dose schedules for simplicity and relevance to COVID-19, this framework can be easily extended to n dose schedules. For example, with the stipulation e_0, the efficacy after zero vaccinations, is zero, $e_{a(n)}$ can represent the additional benefit of the nth dose after $(n-1)$ doses:

$$e_{a(n)} = e_n - e_{(n-1)} \tag{5.3}$$

And $E_{r(n)}$ the ratio of $e_{a(n)}$ to $e_{a(n-1)}$ for $n > 1$:

$$E_{r(n)} = \frac{e_{a(n)}}{e_{a(n-1)}} = \frac{e_n - e_{(n-1)}}{e_{(n-1)} - e_{(n-2)}} \tag{5.4}$$

This analysis can apply to the different vaccine efficacies distinguished above (e.g. $e_1^{(d)}$ and $e_2^{(d)}$ would be the efficacy in preventing disease after one or both doses, which may not be the same as the efficacies at preventing transmission $e_1^{(t)}$, $e_2^{(t)}$).

5.3 Population protection strategies

We first consider vaccine scheduling strategies with two simplifying assumptions. First, that vaccination offers no sterilizing immunity: $e_1^{(t)} = e_2^{(t)} = 0$. Second, the only outcome of interest is disease fatality, as opposed to hospitalization or non-fatal illness.

This renders vaccination strictly as a prophylactic, so all schedules have identical (zero) effect on disease transmission or final epidemic size. Although unrealistic, it may be a reasonable conservative assumption to make in the initial stages of vaccine deployment, as data on vaccine efficacy versus transmission usually arrives after large-scale administration has begun. It also serves as a useful limit case, to be contrasted with transmission modelling in the next section.

Given this, individual benefit from receiving vaccination can be approximated by this equation:

$$\text{Utility} = \text{p(I)} \cdot \text{IFR} \cdot e^{(f)} \tag{5.5}$$

Where p(I) is the probability of infection, IFR the infection fatality ratio (p(Death|infection) without vaccination), and $e^{(f)}$ the vaccine efficacy (against fatality).

Analogous to COVID-19, we consider a vaccine course that requires two identical doses. We start with an extremely simple 'base case', which is progressively

elaborated to incorporate factors both observed in the COVID-19 outbreak and likely to be generally applicable to future emerging infectious disease outbreaks.

5.3.1 Base case

The initial base case makes several simplifying assumptions. First, all individuals have identical risk to the disease (and thus receive identical benefits for vaccination). Second, there is no necessary delay between vaccine doses - a second dose can be given immediately after the first. Third, the additional benefit of a second dose remains the same no matter the delay between first and second doses.

With these assumptions, it is intuitive the optimal strategy will either be 'First doses first' (FDF), giving all individuals first doses, then giving all individuals second doses; or 'Both doses first' (BDF), giving all outstanding second doses to singly-vaccinated individuals before giving further individuals first doses. Either first or second doses bring the greater additional benefit: if the former, scheduling all first doses first is the best (and BDF the worst) for reducing 'population time at risk', and vice versa.

This can be shown mathematically. Let D be the fraction of required vaccine doses which have been administered (e.g. $D = 1$ where all individuals have received both doses, $D = 0.5$ where half of all doses have been given, such as everyone having received one dose or half the population receiving both doses). Let B be the fraction of achievable benefit from vaccination: $B = 1$ when all individuals have received both doses, $B = 0$ when none have been vaccinated, and in the general case:

$$B = \frac{p_1 \cdot e_1 + p_2 \cdot e_2}{e_2} \tag{5.6}$$

Where p_1 and p_2 are the proportion who have received only one and both vaccine doses respectively.

All strategies plot a curve between $D = 0, B = 0$ and $D = 1, B = 1$. Dose allocation strategies can be compared by their area under the curve (AUC), or $\int_0^1 B\mathrm{d}D$: higher values correspond to a strategy which achieves more of the benefit of population protection sooner, and so reduces population time at risk.

Consider a strategy which prioritises second doses. As we assume first and second doses can be given instantaneously, the proportional benefit equals the proportion of planned vaccines administered ($B = D$), thus the AUC is 0.5. For a strategy which prioritises 'first doses first' (i.e. allocating all individuals in a population to their first dose before any are given their second) B increases at rate $2 \cdot \frac{e_1}{e_2}$ when $D \leq 0.5$ then at $2 \cdot \frac{e_a}{e_2}$ for $0.5 < D \leq 1$ (the factor of 2 is owed to full vaccination requiring two doses). As B is strictly increasing with D, it intuitively follows that the AUC for this strategy will be greater than 0.5 whenever $2 \cdot \frac{e_1}{e_2} > 1$ - whenever a single dose is more than half as good as both doses. Precisely, the AUC for FDF is given by:

$$\begin{aligned} AUC &= \int_0^{0.5} 2 \cdot \frac{e_1}{e_2} \cdot D \, \mathrm{d}D + \int_{0.5}^{1} \frac{e_1}{e_2} + 2 \cdot \frac{e_a}{e_2} \cdot D \, \mathrm{d}D \\ &= 0.5 \cdot \frac{e_1}{e_2} + 0.25 \end{aligned} \tag{5.7}$$

This AUC is greater than 0.5 (thus FDF superior to BDF) when $\frac{e_1}{e_2} > 0.5$, confirming the intuitive finding. Figure 5.2 provides two illustrative examples, with $e_1 = 0.4, e_2 = 0.9$ (thus $\frac{e_1}{e_2} < 0.5$) and $e_1 = 0.7, e_2 = 0.9$ ($\frac{e_1}{e_2} > 0.5$).

5.3.2 Heterogeneous individual risk

In the base case outlined above, the only factor to prioritise was first versus second doses: thus when first doses give greater additional benefit, they should be prioritised over second doses.

An important complicating factor is individuals in a population often vary significantly in their risk: some subject to a greater likelihood of infection, and others more likely to die if infected. In COVID-19, both p(I) and IFR can vary by orders of magnitude between individuals. Thus even if a first dose provides more than half the the benefit of both doses in general, prioritising second doses for high risk individuals over first doses for low risk individuals could be superior.

One can extend equation 5.5 to evaluate this case. Consider two individuals, h and l, with higher and lower risks respectively (but identical responses to vaccination). The benefit of giving a second dose to h is:

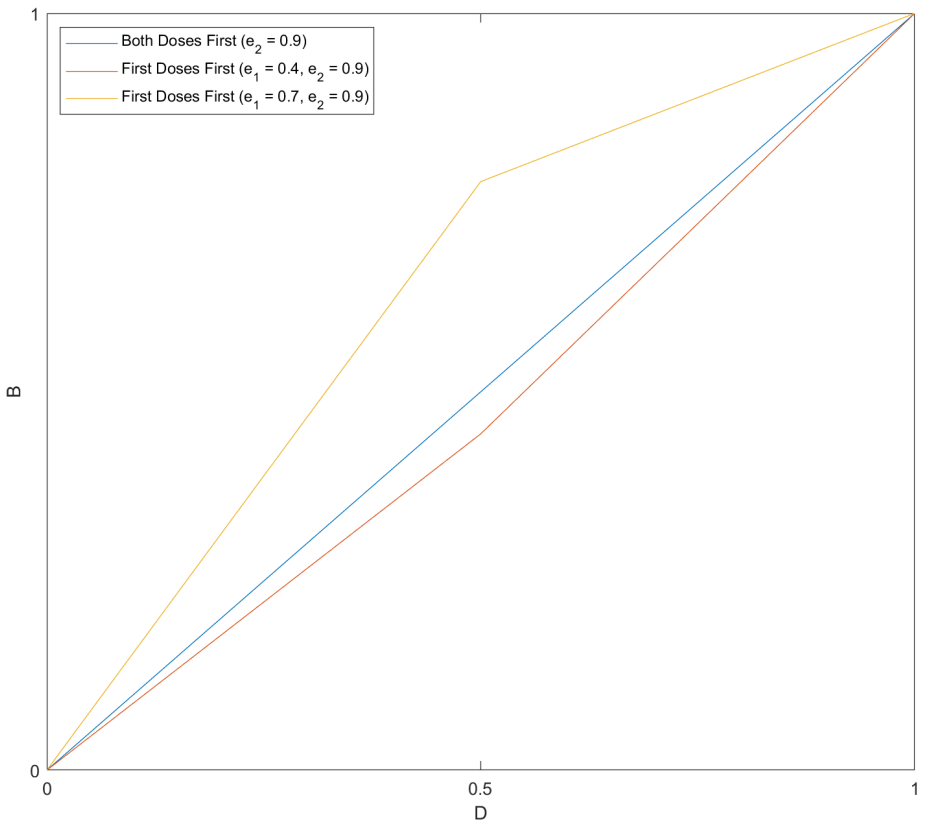


Figure 5.2: Illustration of different dose strategies with varying vaccine efficacy. With B and D the proportion of vaccines administered and then proportion of health benefit achieved for a population, one can compare how different dose schedules perform relative to one another with the AUC as vaccine efficacy is varied. 'First Doses First' is in equipoise with 'Both Doses First' (blue) when $e_1 = 0.5 \cdot e_2$: if a first dose provides equal benefit to a second dose, then all orderings of first and second doses have identical performance. When e_1 is less or more than this, first doses under- or over-performs second doses (red and yellow lines respectively). At $D = 0.5$, first doses first has achieved 78% of the total benefit if $e_1 = 0.7$, but 44% when $e_1 = 0.4$. The AUC in the first case is 0.64, and in the second 0.47.

$$\text{Utility}_{h(2)} = \text{p(I)}_h \cdot \text{IFR}_h \cdot e_a^{(f)} \tag{5.8}$$

For a first dose to l:

$$\text{Utility}_{l(1)} = \text{p(I)}_l \cdot \text{IFR}_l \cdot e_1^{(f)} \tag{5.9}$$

The difference in benefit between these cases is:

$$\text{Utility}_{h(2)} - \text{Utility}_{l(1)} = \text{p(I)}_h \cdot \text{IFR}_h \cdot e_a^{(f)} - \text{p(I)}_l \cdot \text{IFR}_l \cdot e_1^{(f)} \tag{5.10}$$

Rearranging, a second dose to h brings greater benefit to them than the benefit l receives from their first dose if:

$$\frac{\text{p(I)}_h \cdot \text{IFR}_h}{\text{p(I)}_l \cdot \text{IFR}_l} > \frac{1}{E_r} \tag{5.11}$$

Loosely, for a second dose to be prioritised, the ratio of risk from disease between h and l must be greater than the degree to which second doses have declining returns. For example if $e_1^{(f)} = 0.6$ and $e_2^{(f)} = 0.8$, h would need to have over four times the risk of COVID than l for their second vaccination to have greater benefit than l's first.

Optimal policy in this extended model is to rank individuals (or sub-populations) by their risk reduction from first or second doses, then schedule vaccination in descending order (alongside the constraint, only relevant with accelerating returns, that second doses for a sub-population cannot be scheduled before initial doses). To illustrate this, we consider a model scenario of COVID-19 vaccination using only age-specific IFR as a proxy for individual disease risk, using the age structure of the UK population and the age-specific IFRs reported by Brazeau and colleagues.[169]

Weighing age strata by their (unvaccinated) IFR reveals the risk from COVID is concentrated in a fraction of this population, e.g. those over 50 comprise $\approx 30\%$ of the population, yet incur $\approx 90\%$ of the risk burden (figure 5.3).

Consider a vaccination program for all individuals 20 years or older in this population, for a vaccine with $e_1 = 0.7$, $e_2 = 0.9$. We compare three schedules: (naive) FDF, where all age strata in descending order are given a first vaccine dose before any are given their second; (naive) BDF where first then second doses are administered to each age strata in descending order; and the optimal policy described previously.

We repeat the analysis in the previous section, with the elaboration cumulative B and D are calculated cohort by cohort in the sequence determined by a given vaccination schedule. Thus the line-segment corresponding to (e.g.) first doses for 90+ has a y-component (B) given by risk reduction first doses to 90+ year olds

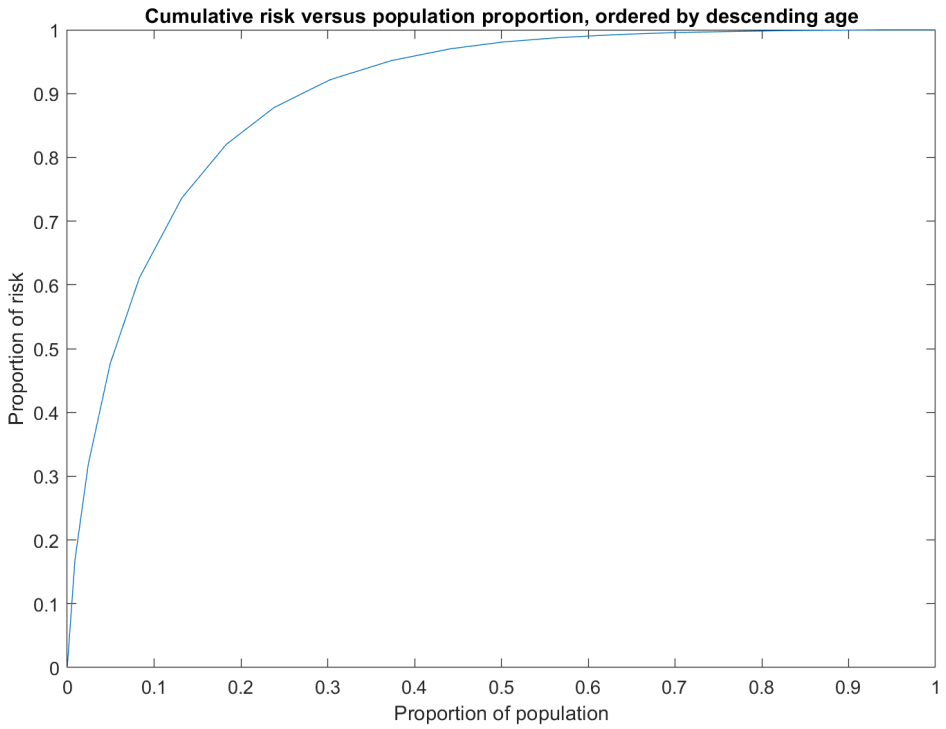


Figure 5.3: Cumulative risk curve of COVID-19 risk in the UK age structure. Cohorts are weighted by their observed IFR. The much greater IFR of older age cohorts results in the cumulative risk being concentrated in the oldest fraction of the population. If all ages had identical IFRs, the cumulative risk curve would be a straight line.

comprise as a fraction of the total benefit of full vaccination of the whole population and the x component (D) the proportion of doses required to give first doses to this cohort out of the vaccination program for the whole population.

The results are given in figure 5.4. 'Naive FDF' performs the worst, whilst optimal policy modestly outperforms BDF. The ordering of the first 10 strata is given in table 5.1. As risk increases log-linearly by age (roughly doubling every 6 years) the risk ratio between age strata is approximately a constant multiple. Thus optimal policy typically gives first doses to the first n strata, then interleaves first and second doses in descending order.

The degree of interleaving depends on E_r. If $E_r > 1$, optimal policy is BDF, as additional vaccination have accelerating returns. Optimal policy is also BDF if the risk ratio between strata is such that $\text{RR} \cdot E_r < 1$: adjusting our example with lower first dose efficacy (e.g. $e_1 = 0.5$) or coarser age brackets (e.g. 20-year

Priority	**FDF**	**BDF**	**Optimal** ($e_2^f = 0.9$) $e_1^f = 0.7$	$e_1^f = 0.5$	$e_1^f = 0.8$
1	90+	90+	90+	90+	90+
2	85-89	90+	85-89	90+	85-89
3	80-84	85-89	80-84	85-89	80-84
4	75-79	85-89	90+	85-89	75-79
5	70-74	80-84	75-79	80-84	70-74
6	65-69	80-84	85-89	80-84	90+
7	60-64	75-79	70-74	75-79	65-69
8	55-59	75-79	80-84	75-79	85-89
9	50-54	70-74	65-69	70-74	60-64
10	45-49	70-74	75-79	70-74	80-84

Table 5.1: First 10 priority groups for vaccination by varying strategy. First doses for a strata are highlighted in blue, and second doses highlighted in red. FDF and BDF are included for reference. With the baseline case of $e_1^f = 0.7$, $e_2^f = 0.9$ optimal policy gives first doses to all those over 80 then alternates second and first doses. The degree of interleaving is sensitive to A_r: with lower first dose efficacy, the optimal policy approximates BDF, with greater first dose efficacy, it approximates FDF.

strata) would have this effect.

At the extreme of $E_r = 0$, where additional doses have no additional benefit, optimal policy is identical to 'naive FDF'. Optimal policy increasingly approximates 'naive FDF' as E_r tends to zero. E_r is highly sensitive to facially small changes in vaccine efficacy: moving from $e_1 = 0.7$, $e_2 = 0.9$ to $e_1 = 0.8$, $e_2 = 0.9$ more than halves it. In the latter case optimal policy is first doses first for all individuals over 70.

The AUC calculated corresponds to the public health benefit (in terms of 'population time at risk reduction') when the vaccine is administered at a constant rate (i.e. $D = k \cdot \text{Time}$). Increases or decreases in the rate of vaccination over time will shrink or stretch (respectively) those regions of the curve along the x-axis, and different policies over and under-perform to different degrees in different regions of the curve. Although all possible variants are beyond the scope of this paper, we model a simple 'constant acceleration' model, by taking the square root of previously calculated values of D. This lessens both the relative and absolute performance gap between FDF and BDF (AUCs 0.667 and 0.707 respectively) and increases the relative and absolute gap between optimal policy and BDF (0.721 and 0.707).

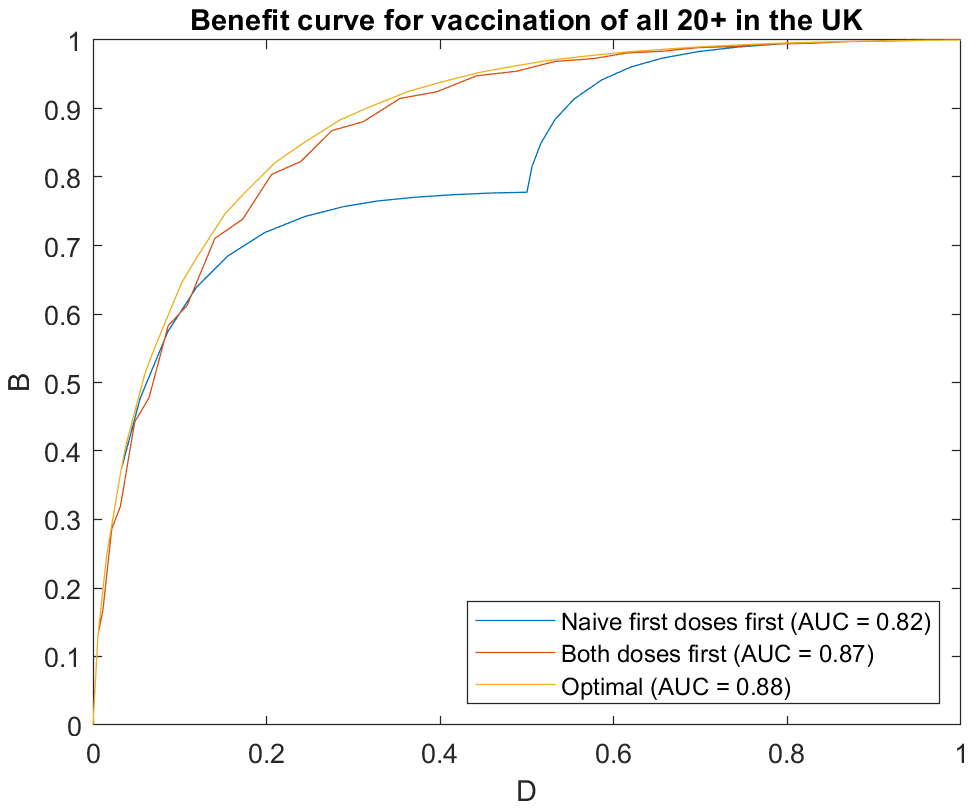


Figure 5.4: Protection curve for a vaccination program for all aged 20 or over in the UK, where $e_1 = 0.7$, $e_2 = 0.9$. By using age to prioritise, all policies outperform random allocation (AUC = 0.5). Naive FDF initially converges with optimal policy, ultimately performs the worst. Optimal policy modestly outperforms BDF.

5.4 Transmission reduction strategies

The prior section evaluated dose scheduling from the perspective of protecting individuals from disease. Yet vaccination programs may also produce sterilizing immunity which reduces transmission and final epidemic size. Similar to how different vaccination schedules between members of a population may be better or worse in terms of person-time at risk averted, different schedules may also be more or less effective in reducing transmission earlier.

To explore this, I construct a highly modified Susceptible-Infected-Recovered-Died model, again loosely modelled on the COVID-19 pandemic, and explore its behaviour with varying parameters and initial conditions to explore different scenarios of vaccine efficacy, transmission speed, and degree of sterilizing immunity.

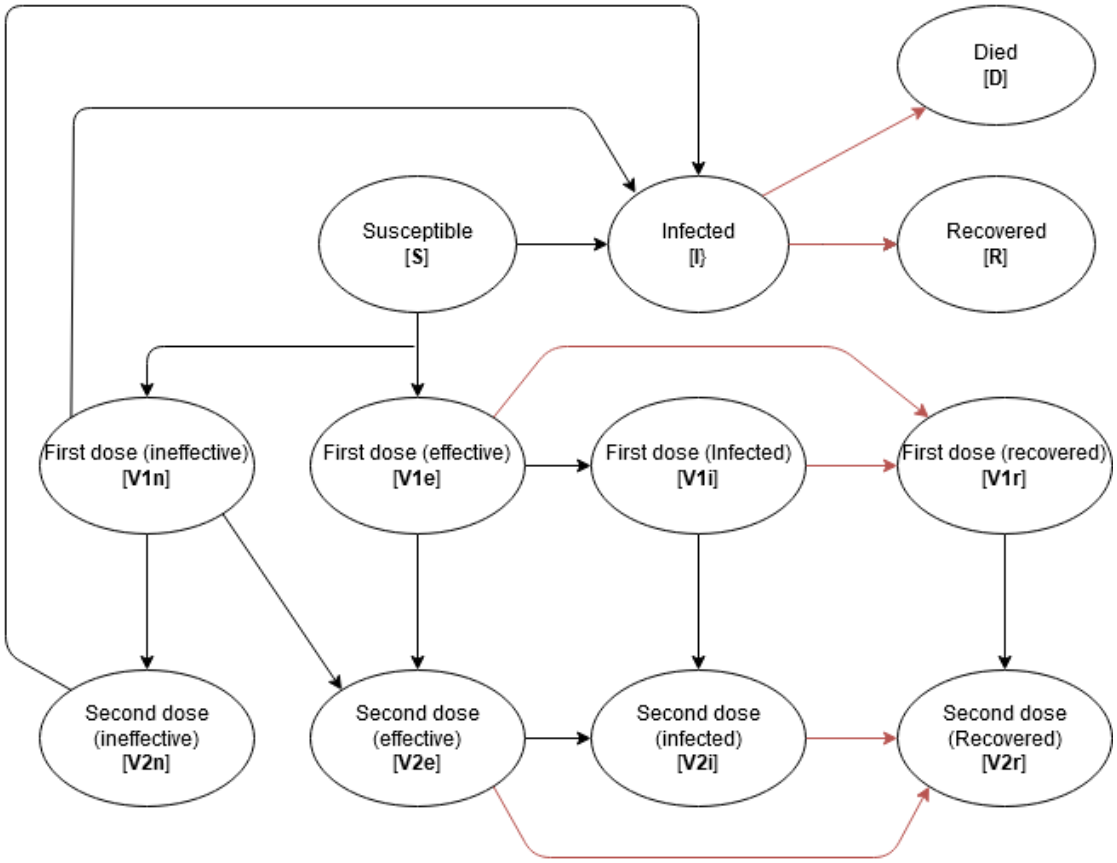


Figure 5.5: The compartments in the V^{2}SIRD model. This model extends a typical Susceptible-Infected-Recovered-Died model by introducing classes with one or two vaccine doses. 'Effective' vaccination protects individuals from death, but not necessarily infection: there are two routes from vaccination to recovery, one directly (representing sterilizing immunity) and one via infection. The red arrows represent delayed transitions between compartments for both infection and development of sterilizing immunity.

5.4.1 The V^{2}SIRD model

I extend a SIRD compartment model to include individuals receiving one or two doses of a vaccine, which may reduce their risk of infection, onward transmission, or death. The model is outlined in figure 5.5, and full details are provided in the supplementary material. The key additional features are:

Vaccination: Susceptible individuals can be vaccinated (and individuals vaccinated once can be vaccinated twice), with proportions moving from 'vaccine effective' or 'vaccine ineffective' in proportions determined by the vaccine efficacy (against fatality - e^f for first or second dose). Those in the vaccine ineffective compartments (**V1n**, **V2n**) are treated identically to susceptible individuals for infection.

Only susceptibles can receive a first vaccine dose, whilst second doses are provided across all compartments with a first dose, regardless of efficacy or infection status. Rate parameters govern the pace of overall vaccination, and the balance of first or second doses provided depending on the dose scheduling strategy.

Variably sterilizing immunity: Although 'effective' vaccination protects individuals from mortality, it may not prevent them becoming infected and transmitting the disease in turn. As such, both first and second vaccination doses have some chance of migrating individuals to an immune or recovered state (i.e. **V1e** $\rightarrow$ **V1r**; **V2e** $\rightarrow$ **V2r**), governed by parameters determining the degree of sterilizing immunity (i.e. $e_1^t,\ e_2^t$).

Delayed transitions: Two types of transition are delayed. The first is transition from infection to subsequent recovery or died (if unvaccinated). The second for the development of sterilizing immunity described above.

Implementation: The transitions between compartments and their updated proportions are calculated time-step by time-step. These models were produced in R v. 4.1.2 (R Core Team, Austria). Full details of the models (including equations for the transition rates and the underlying code) is provided in the supplementary material.

5.4.2 Baseline scenarios

I first consider the model's behaviour when vaccination is disabled, with parameters chosen to approximate the epidemiology of COVID-19 (i.e. infectious period of 7 days, a population-wide infection fatality rate of 0.5%). I initialize an epidemic at an early stage ($\mathbf{S} = 0.999$, $\mathbf{I} = 0.001$), and consider effective reproduction numbers (R_e) values of 1.1, 1.5 and 3.0. These could be considered analogous to highly effective, failing, and unconstrained control of transmission respectively.

In these cases, the model produces a typical epidemic curve, with greater final epidemic sizes with increasing R_e (figure 5.6). One notable feature across scenarios is significant 'overshoot' of the herd immunity threshold given by standard theory ($1 - \frac{1}{R_e}$). This is due to the threshold corresponding to the point where infected

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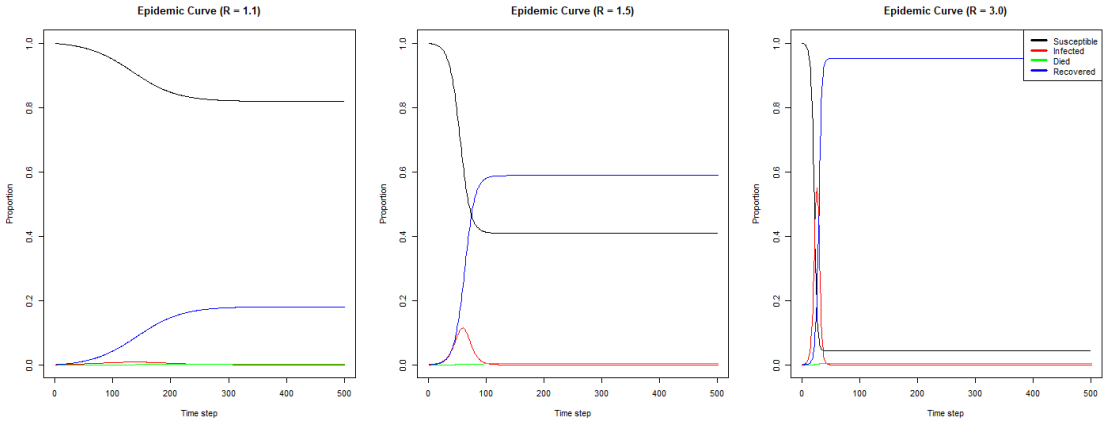

Figure 5.6: Epidemic curves in the underlying SIRD model with vaccination disabled for three values of R_e, giving typical epidemic curves.

individuals infect less than one infected individual in turn: it corresponds to the peak of the infected compartment but the inflection point for the trends in the susceptible and recovered compartments. The delayed transitions from infected compartments further accentuate this effect.

By setting very high vaccination rates, the model can also illustrate the impacts of effectively pre-existing vaccine coverage on transmission. Repeating the previous scenarios with Complete vaccination (of varying efficacy) results in either elimination or suppression of the outbreak, depending on whether the balance of R_e and e^t brings one above or below the effective herd immunity threshold $e^t > 1 - \frac{1}{R_e}$ (figure 5.7).

5.4.3 Dose scheduling strategies and transmission

I now use the model to explore scenarios where vaccination and infection are concurrent, to assess how different dose scheduling strategies perform in different contexts. For this, I initialize a wholly susceptible population (S = 0.999, **I** = 0.001). Reproduction numbers of 1.1, 1.5 and 3 are considered for transmission. I initially consider vaccination with efficacy against mortality of $e_1^f = 0.7$, $e_2^f = 0.9$, and half these respective efficacies against transmission (i.e. $e_1^f = 0.35$, $e_2^f = 0.45$). Vaccines are provided at a rate of 0.01 each time-step, with either first or second doses being prioritized.

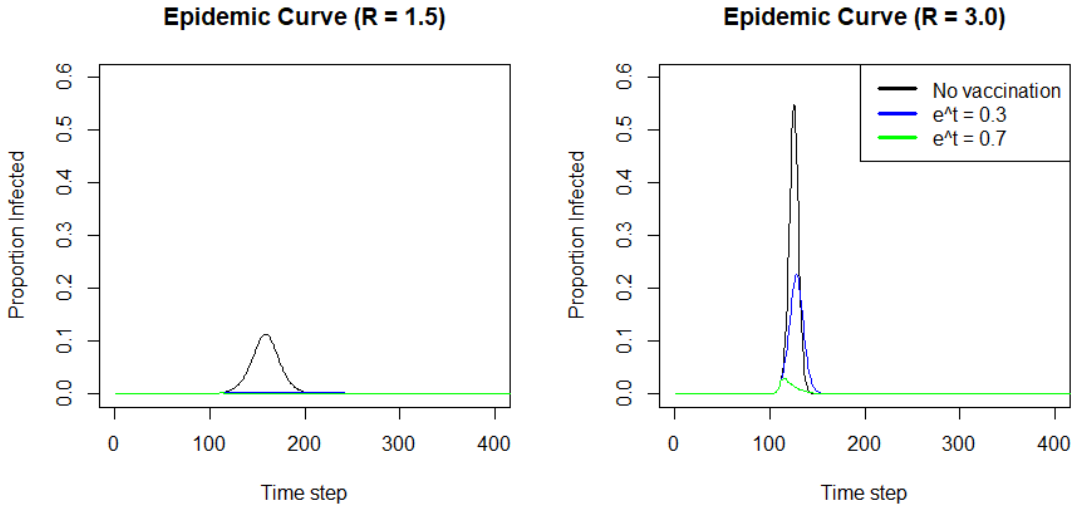

Figure 5.7: Effects of prior vaccination on transmission. Epidemics with $R_e = 1.5$ (left) and $R_e = 3$ (right) are initialized in a population either without vaccination (black), or fully vaccinated with an $e^t = 0.4$ (blue) or $e^t = 0.7$ (green) vaccine. The ordinate for both epidemic curves is the proportion of the population infected regardless of vaccine status (i.e. **I**, **V1i**, and **V2i**). Vaccination reduces cumulative proportion infected and reduces peak concurrent infections, with more effective vaccination having greater effect. Full vaccination with $e^t = 0.3$ is just below the herd immunity threshold for $R_e = 1.5$, and $e^t = 0.7$ just below the herd immunity threshold for $R_e = 1.5$, thus the outbreaks are almost eliminated in these cases (and $e^t = 0.7$ does eliminate an $R_e = 1.5$ outbreak). Either are sufficient to eliminate $R_e = 1.1$ (data not shown).

'First doses first' is the better strategy across these scenarios with lower peak incidence and final epidemic size (figure 5.8). The significance of this impact in absolute terms depends on the rate of transmission. Low transmission ($R_e = 1.1$) gives the greatest *relative* difference between vaccine scheduling strategies (and for vaccination at all versus no vaccination) with FDF resulting in roughly half the epidemic size of BDF, thus averting infection for an additional $\approx 5\%$ of the population. For outbreaks with greater transmission the impact of vaccination is smaller as is the difference between strategies: $\approx 3\%$ and 0.5% for R_e of 1.5 and 3 respectively (table 5.2). This is largely explained by infection-acquired immunity greatly outpacing vaccination-acquired immunity: for $R_e = 3$ the outbreak is at its height at approximately twenty days, where only one tenth of the vaccine program has been completed, thus vaccination (however scheduled) can at best fractionally flatten this curve.

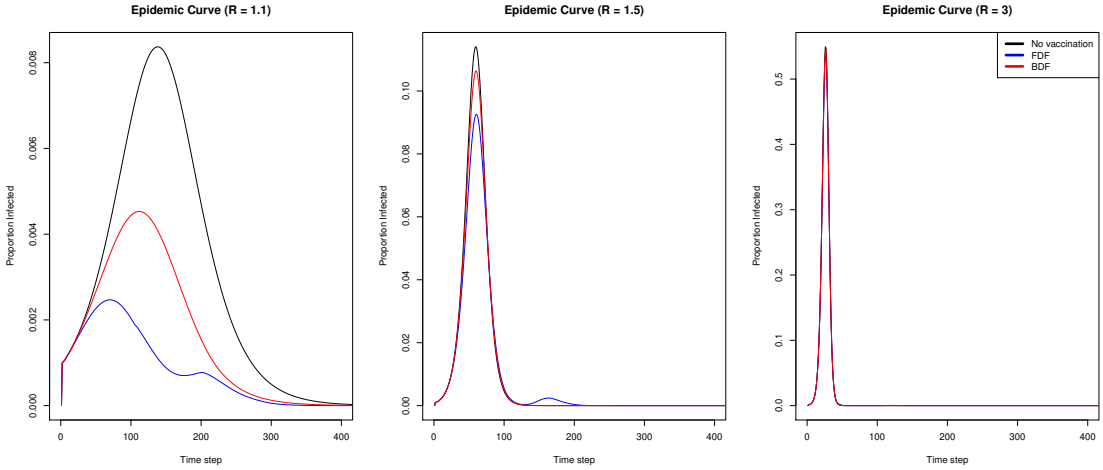

Figure 5.8: Effects of concurrent vaccination on transmission. Epidemics with $R_e = 1.1$ (left), $R_e = 1.5$ (center) and $R_e = 3$ (right) are initialized in a population either without vaccination (black) or vaccination at a rate of 0.01 per timestep prioritising first (blue) or second (red) doses. The ordinate for both epidemic curves is the proportion of the population infected regardless of vaccine status (i.e. **I**, **V1i**, and **V2i**). Note the panels are not given on a common y-axis scale: the left panel's is 80 times smaller than the right. Across all scenarios FDF has the greatest reduction of epidemic size, although it's significance varies with transmission (see text). FDF produces a bimodal distribution of infections, with a transient increase in infections following the switch from first to second doses at $t \approx 100$.

Proportion infected	$R_e = 1.1$	$R_e = 1.5$	$R_e = 3$
Baseline	0.181	0.591	0.956
First doses first	0.049	0.534	0.947
Both doses first	0.096	0.568	0.952

Table 5.2: Proportion who become infected with different dose scheduling strategies

5.4.4 Differential sterilizing immunity

This modelling of dose scheduling strategies assumed that sterilizing immunity was proportional to vaccine efficacy ($e^t \propto e^f$). With $e_1 = 0.7$, $e_2 = 0.9$, this meant vaccination had diminishing returns in terms of transmission reduction ($e_1^t > 0.5 \cdot e_2^t$), and is suggestive of a similar principle when considering vaccination from the perspective of population protection: if a single dose is more than half as good as both doses, prioritizing single doses first gives better results.

To assess this, we adjust the previous scenario to consider differential or non-proportionally sterilizing immunity, such that 20%, rather than 50% of 'first dose'

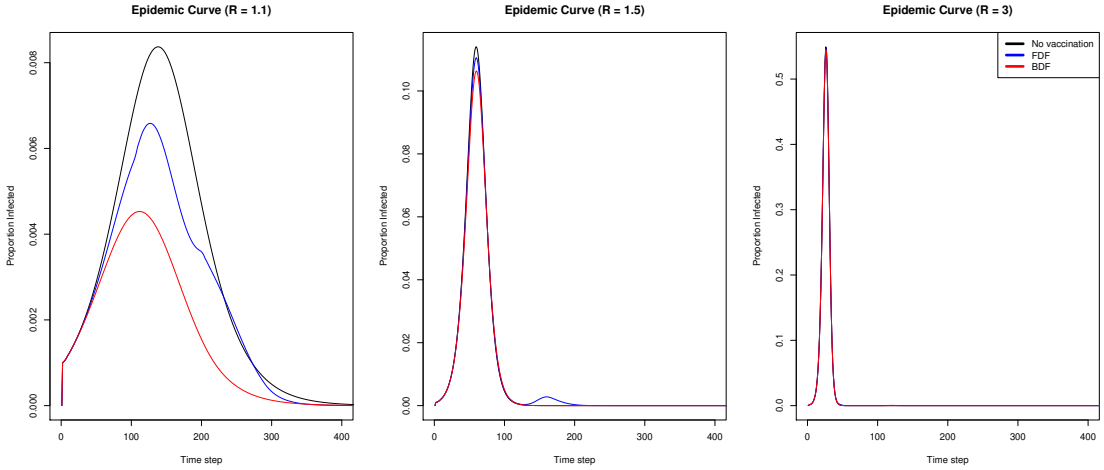

Figure 5.9: Effects of concurrent vaccination on transmission. Epidemics with $R_e = 1.1$ (left), $R_e = 1.5$ (center) and $R_e = 3$ (right) are initialized in a population either without vaccination (black) or vaccination at a rate of 0.01 per timestep prioritising first (blue) or second (red) doses. The ordinate for both epidemic curves is the proportion of the population infected regardless of vaccine status (i.e. **I**, **V1i**, and **V2i**). Note the panels are not given on a common y-axis scale: the left panel's is 80 times smaller than the right. Compared to figure 5.8, the vaccine efficacies have been changed such that $e_1^t = 0.14$, $e_2^t = 0.45$, thus $e_1^t < 0.5 \cdot e_2^t$. Thus prioritising both doses is superior to prioritizing first doses.

immunity is sterilizing. Thus $e_1^t = 0.14$, $e_2^t = 0.45$, and $e_1^t < 0.5 \cdot e_2^t$. In this case, prioritizing second doses has greater impact on reducing epidemic size (figure 5.9). Further analysis of different vaccine efficacies (and degree of sterilizing immunity) shows the 'cross-over threshold' for whether first or second dose prioritisation is superior corresponds to (but does not precisely match) $e_1^t = 0.5 \cdot e_2^t$ (data not shown).

The underlying explanation for this is fairly intuitive. The V^{2}SIRD model, like many other compartment models, permits arbitrarily fine divisions. Thus a rate of vaccination (whether comprised of first or second doses) amounts to a flow from unvaccinated (or singly vaccinated) to vaccinated (or doubly vaccinated) compartments. The degree of sterilizing immunity (e^t) amounts to a coefficient of these flows from infection-susceptible to infection-immune compartments (i.e **V1e** $\rightarrow$ **V1r**, **V2e** $\rightarrow$ **V2r**) without requiring transit through an infected state (i.e. **I**, **V1i**, **V2i**). Sterilizing vaccination thus competes with infection for susceptibles, and greater rates of sterilizing vaccination impede rates of transmission, as this is sensitive to the proportion of susceptible to non-susceptible individuals.

As 'rate of susceptible removal' is roughly $\propto e^t$, this benefit can be treated similarly to the 'base case' of individual health benefits and vaccine efficacy against fatality analysed in §5.3: achieving more of the final benefit of full vaccination (in terms of reduced susceptible population) earlier is better than later, and thus the same criteria and bounds determine when first doses are better prioritized before or after second doses (cf. equation 5.7).

5.5 Substitution of non-pharmaceutical interventions

Faster vaccination may allow faster relaxation for Non-Pharmaceutical Interventions (NPIs), either (if immunity is non-sterilizing) reducing the harms of epidemic spread so they are below those of NPI continuation, or (if sterilizing) substituting for infection to build up 'herd immunity'. Different dose schedules may allow this to happen earlier or later.

5.5.1 NPI and epidemic harms

Pricing the harms of different degrees of NPI, and when this should be traded-off against expected mortality from wider epidemic spread is beyond this work. However, it can be illustrated in general terms.

Stringent NPIs are costly on an individual and societal basis, thus there is some trade-off between these harms and the harms of the disease itself: few believe stringent NPIs would be justified to combat the annual seasonal influenza pandemic, despite a population fatality ratio (PFR) of 0.05 - 0.01% in wealthy northern hemisphere countries. Severe pandemics can be much more dangerous: the PFR from COVID-19 is already $\geq 0.1\%$ in many countries, and a naive model of an unmitigated epidemic with $R_0 \approx 3$ and IFR $\approx 1\%$ would result in a PFR $\approx 0.7\%$.

Suppose a country would be reconciled to prefer the costs of the epidemic to costs of maintaining stringent NPIs when PFR $\leq 0.2\%$: on an individual basis, on average this would amount to preferring a one in five-hundred risk of death to the

costs of continuing stringent NPIs. From the start of the COVID-19 epidemic this would require the reduction in population risk to be a factor of 3.5 - 73%.

For the UK with a vaccine with 90% efficacy against mortality after both doses, rolled out by age priority, this would be achieved after the highest-risk 18% of the population has been fully vaccinated. For example, if vaccination is prioritized by age and has a dosing rate of 1% of the population per day, this would amount to a release of lockdown 36 days after the vaccination program commences. Without any prioritisation, one would need to wait until 73% of the population are vaccinated, thus 146 days in the same scenario.

There are also scenarios where a more risk averse population cannot fully 'vaccinate their way out of lockdown' in the case of purely non-sterilizing immunity. Effecting a 90% reduction in PFR would require universal vaccination with a 90% effective vaccine. In cases where the desired risk reduction exceeds the multiple of vaccine efficacy and uptake, the social optimum would require some degree of NPIs included alongside vaccination.

Sterilizing immunity The second mechanism is reduction of epidemic spread when the vaccine makes people no longer susceptible to infection. On standard modelling, the observed $R_{(t)}$ can be approximated by the following:

$$R_{(t)} = R_0 \cdot k_{NPI} \cdot (1 - \frac{R}{N}) \tag{5.12}$$

Where R_0 the intrinsic reproduction rate, k_{NPI} a measure of the efficacy of non-pharmaceutical interventions (ranging from 0 with perfect efficacy to 1 where completely ineffective, and $\frac{R}{N}$ the proportion of the population already recovered.

From equation 5.12, if $R_{(t)} = 1$, and $k_{NPI} = 1$ (i.e. no social distancing) reproduces the standard bound for herd immunity ($\frac{R}{N} = 1 - \frac{1}{R_0}$). This also means NPIs and herd immunity can substitute for one another in epidemic control: an epidemic with $R_0 = 4$ is brought under control when $k_{NPI} \cdot (1 - \frac{R}{N}) \leq 0.25$. At either extreme this is NPIs which reduce transmission by a factor of 4 ($k_{NPI} \leq 0.25$ (which is sufficient to control the epidemic even with no pre-existing immunity),

or when 75% or more of the population has become immune (which prevents further spread even without NPIs).

A vaccine that contributes to sterilizing immunity can also substitute for NPIs. Equation 5.12 becomes:

$$R_{(t)} = R_0 \cdot k_{NPI} \cdot (1 - \frac{R}{N}) \cdot (1 - p_1 \cdot e_1^t) \cdot (1 - p_2 \cdot e_2^t) \tag{5.13}$$

Where p_1 and p_2 the fraction who have received the first or both doses respectively. Setting values for $R_{(t)}$, R_0, and $\frac{R}{N}$ gives a substitution curve of NPIs versus vaccination for a given outbreak. E.g. For $R_{(t)} = 1$, $R_0 = 3$, and $\frac{R}{N} = 0.1$:

$$\frac{1}{2.7 \cdot k_{NPI}} = (1 - p_1 \cdot e_1^t) \cdot (1 - p_2 \cdot e_2^t) \tag{5.14}$$

One can thus assess whether FDF or BDF allows social restrictions to be eased earlier whilst maintaining epidemic control ($R_{(t)} \leq 1$).

As with previous sections let D be the proportional completion of vaccination: $D = 0$ when none have been vaccinated, $D = 1$ when the entire population has been vaccinated twice, and intermediate values are given by $\frac{\text{Doses administered}}{2 \cdot \text{Total population}}$. Let $e_1^t = 0.7$ and $e_2^t = 0.9$. Again compare FDF (where everyone is administered their first dose before any are administered their second) to BDF (for simplicity, people are given their first and second doses at once).

For BDF, equation 5.14 becomes:

$$\frac{1}{2.7 \cdot k_{NPI}} = (1) \cdot (1 - (D \cdot e_1^t) \tag{5.15}$$

And for FDF:

$$\begin{cases} D \leq 0.5 & , \frac{1}{2.7 \cdot k_{NPI}} = (1 - (2 \cdot D \cdot e_1^t)) \\ 0.5 < D \leq 1 & , \frac{1}{2.7 \cdot k_{NPI}} = (1 - e_1^t - (2 \cdot (D - 0.5) \cdot (e_2^t - e_1^t)) \end{cases} \tag{5.16}$$

These are plotted in figure 5.10. FDF outpaces BDF in terms of minimum NPI stringency necessary to control the epidemic. $k_{NPI} = 1$, the point where the epidemic is controlled without any social distancing, at $D = 0.45$ for FDF, versus

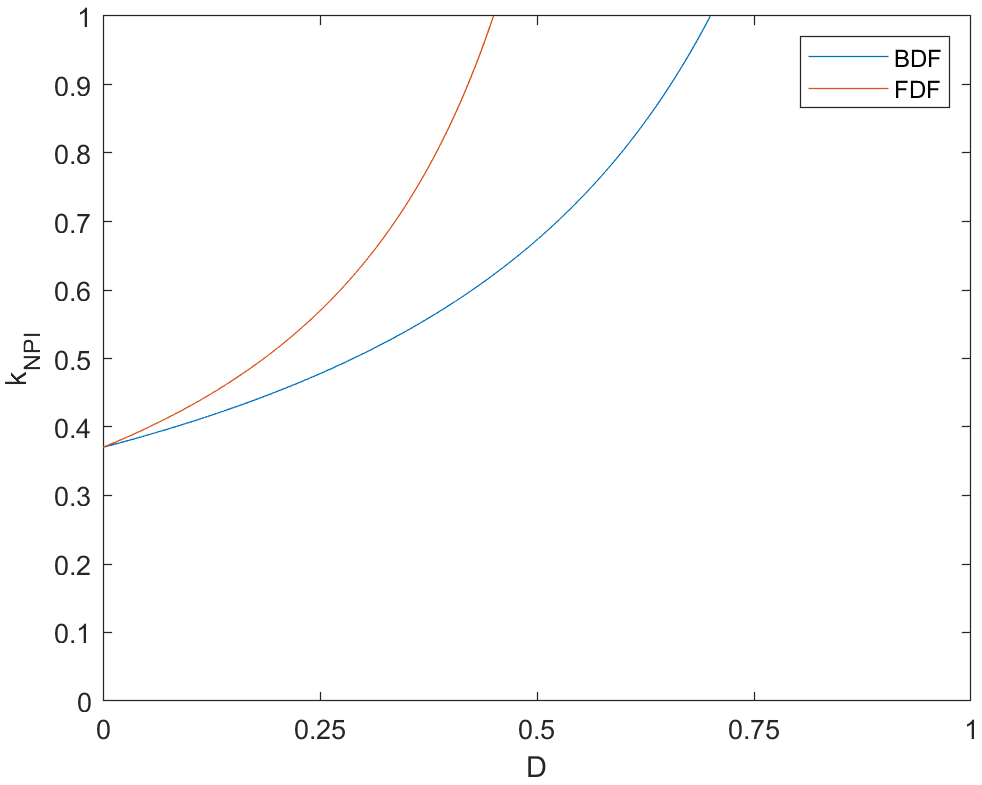

Figure 5.10: Necessary NPI stringency (lower is more severe) to maintain $R_(e) \leq 1$ with ongoing vaccination with either first or second doses prioritized.

$D = 0.7$ for BDF. At a rate of dosing of 0.5% per day (10000 doses administered per million people) FDF would allow all NPIs to be eased 50 days earlier than BDF.

This analysis can be extended to partial easing of NPIs. In the scenario above, suppose a country can only just achieve epidemic control ($k_{NPI} = \frac{1}{2.7}$) without vaccines with a suite of measures including school and university closure, which is the restriction it prioritises to ease first. Presuming restrictions are multiplicative, and taking the estimate of reproduction number reduction for school and university closure from Brauner et al.[212] (0.65), it can only open schools and universities once the threshold for epidemic control is $k_{NPI} \geq 0.56$. This is achieved at $D = 0.38$ for BDF, but $D = 0.24$ for FDF. Using the same constant rate as before, this means schools can be opened 28 days earlier under FDF than BDF.

5.6 Discussion

This work has explored how, with a vaccine provided in multiple doses, whether prioritising first doses or completing outstanding courses of vaccination performs better for a number of public health objectives. Our findings echo the results of other modelling studies on dose-scheduling in COVID-19, which are generally supportive of widening the interval between doses to prioritize providing an initial dose to as many as possible.[195, 213–215] There are some common themes across these analyses.

The modelling underlines the importance of precision over vaccine efficacy: both the efficacy achieved after a single dose versus both doses (e.g. e_1, e_2), but also efficacy versus a particular outcome of infection, whether it be mortality, ill health, or transmission (e.g e^f, versus e^t). Which dose scheduling strategy is superior depends on these precise values; a vaccine trial which reports a given efficacy after both doses against (for example) clinically detectable infection is insufficient to determine the best strategy alone.

The modelling also supports the commonsense intuition that prioritising first doses is superior when one dose provides more than half the benefit of two. In these cases earlier scheduled vaccination mirrors other scenarios of allocation of a scarce good among individuals where the returns to individuals diminish on the margin: giving 'some to all' brings greater aggregate benefit than 'all to some'.[1]

It also highlights a challenge for strategy and objective setting. A vaccine may show diminishing marginal returns with respect to one objective yet accelerating returns for another: if a second dose adds relatively little protection from severe

[1]The opposite is also true, although may be ethically complicated by matters of equity. Even when vaccination has accelerating returns such that prioritising dose completion brings greater social utility, this concentration of benefits is very unequal: some individuals receiving full vaccination benefit early whilst similarly deserving others have to endure continued risk of exposure for longer.

From here the ethical argument can ramify further. On one hand, lottery allocation of this benefit may still be considered fair: *ex ante* equal prospects among individuals to be benefited could vindicate *ex post* considerable inequality in outcomes. Concentration of benefit also seems more palatable when the benefits are steeply accelerating: even allocation of a scarce drug to provide doses to individuals too low to remain effective seems unwise. On the other, individuals may be risk averse, and collectively prefer allocation that guarantees them some benefit versus a gamble with higher expected value (and thus greater social utility overall). These recondite policy and ethical questions are outside the scope of this work.

disease but significantly greater reduction of transmission $e_1^f > 0.5 \cdot e_2^f$ yet $e_1^t < 0.5 \cdot e_2^t$. A similar dilemma may also apply with administration to individuals if (for example) individuals who tend to be more vulnerable to the disease nonetheless tend to transmit less if they become infected.

Thus the decision on the best dose scheduling strategy depends on the relative importance of these objectives, which themselves could vary on particular circumstances. Populations in the midst of a large poorly-controlled 'wave' of infections may prioritise protecting individuals from the consequences of infection rather than reducing transmission, and so elect to prioritise first doses: the impact of vaccination on a rapidly spreading epidemic is likely to be low even with optimal scheduling, whilst the benefits to providing substantial protection to those likely to be exposed is more significant. Conversely, populations subject to low and stable incidence may see greater benefit in achieving effective herd immunity as quickly as possible.

5.6.1 Limitations

The purpose of these mathematical models is to illustrate and highlight broader principles. Although they are based on COVID-19, they aim for similarity rather than maximal fidelity to a given population's experience of COVID-19: more elaborate and precise modelling of a given outbreak increases the risk the findings not generalizing beyond it. As such, these models are not the most appropriate to use for forecasting (or 'nowcasting') current COVID-19 outbreaks or their response to particular population's vaccine policies. One example of this would be using homogeneous compartments for transmission, whilst COVID-19 has demonstrated the value of heterogeneous transmission networks in capturing transmission dynamics.

More important limitations are those that apply to the intended generalization: overly elaborate models risk the results being dependent on the precise elaborations used, but overly simplistic ones may exclude considerations which are generally applicable and so should be taken into account when deciding strategy. The main challenge is the simplifying assumption of both vaccine efficacy being invariant to delay between doses, and that the minimal delay between doses can be arbitrarily low.

The second is less significant than the first. A given minimum delay between both doses can only act to reduce the performance of a strategy that prioritises second doses, by constraining the space of available strategies: if the ideal delay is greater than the minimum, the constraint is irrelevant; if it is less, this constraint removes the best performing strategy, and coerces BDF strategies to be more 'FDF-like'. At the limit where the necessary delay is long enough for the entire target population to be administered one dose, the question of optimal strategy is moot. Thus including a minimal delay between first and second doses would not alter the underlying mathematical principles which govern optimal strategy, but could restrict the range to optimise over.

The larger assumption is of 'delay invariance': an individual who receives a first dose enjoys protection of e_1 indefinitely, and a second dose gives them a further increment of protection to e_2 regardless of the delay between their two doses. The findings in this work rely on this assumption, but it is also an empirically dubious one. Although some vaccines provided in multiple doses show reasonable invariance past a given delay, the very practice of giving a vaccine in multiple doses and the use of boosters implies vaccine efficacy is sensitive to not only the number of doses provided but their relative timing. Concretely, with COVID-19 vaccination, 'waning immunity' is observed, although this may be differential between outcomes of interest (i.e. vaccines have lost more efficacy versus transmission or symptomatic infection than versus hospitalization or mortality),[216–219] heterogeneous across the population (e.g. greater loss of protection in older individuals),[219, 220] and also is owed to a complex interaction between immunology and virology (i.e. 'waning immunity' for the vaccine may be owed partly to reductions in antibody titres post-vaccination, but also the emergence of new variants).[221, 222]

In evaluating the relevance of our results, the question is less whether the null hypothesis of invariance with delay is always (or often) true, but whether it is a reasonable working assumption. Worries that postponing second doses in the initial UK vaccination rollout would reduce final protection proved unfounded - observations suggested that, if anything, a longer delay before a booster *enhanced*

final efficacy.[223, 224] Given both positive and negative non-linear effects of delay are both mechanistically plausible and observed in practice; and that pre-clinical data on the question is tentative and clinical information will typically arrive too late to inform strategy, modelling which is agnostic on this question can still usefully inform initial decision making. It may prove mistaken, and these mistakes may result in recommending an inferior strategy, but there is not a safe or conservative assumption which avoids this risk.

5.6.2 Conclusions and further work

Recent retrospective evaluation of the COVID pandemic in the UK supports the early modelling findings: prioritising first doses and delaying second ones likely saved lives and reduced transmission.[225] It also further underlines the 'epistemic challenge' of public health decision-making under profound uncertainty: this work was published more than two years after the initial UK decision to prioritise first doses.

Although the speed of COVID-19 vaccine development and deployment was unprecedented, it still took nearly a year from initial identification of the pathogen to clinical use of a vaccine. These months of experience informed both anticipatory modelling of vaccine dose scheduling and subsequent decision-making. The global ambition is to develop medical countermeasures to emerging pandemics still faster (e.g. the '100 days mission').[226] Successes here will compound the epistemic challenge, as decisions will need to be made (and options modelled) with less available information.

There are some approaches to better meet this forthcoming challenge. One is means of getting action-relevant information sooner. One relevant example is that COVID-19 vaccine trials did not have a 'single dose arm', leaving single dose efficacy to be inferred from subsets of the trial data (a similar issue applied to the proposal of dose stretching: lowering dosage to have a greater prevalence of somewhat-inferior protection).[227] Better anticipation of which strategies may be contemplated *in extremis* could prompt better expedient - if less rigorous - sources of evidence to inform early decision making, whether it is 'add ons' to

vaccine trials to assess departures from ideal clinical use, or independent studies like human challenge trials.[189]

Another is to quantitatively survey historical practice to gain better 'base rates' to reasonably extrapolate from. For example, if a vaccine strategy is sensitive to how much partial immunization would decay if subsequent doses are postponed, one could look to other vaccines for endemic or past pandemic outbreaks to make an estimate that is evidence informed, if not evidence based. Corralling or generating this data (e.g. trials of immunogenicity with incomplete vaccination courses for a range of pre-existing vaccines) has little relevance to peacetime vaccinology, but is an emerging need now.

5.7 Supplementary material: V²SIRD model specification

5.7.1 General features

The V²SIRD is a compartment model with discrete time-steps (with 1 step corresponding to 1 day in the model). The proportions in each compartment at $t + 1$ are calculated by calculating the flows to and from each compartment on t, then adding the balance of these transitions to each compartment.

This model was constructed in R v.4.1.2 (R Core Team 2021). Full model and analysis code is available at: `https://github.com/gjlewis37/DPhil/blob/main/Ch5`

5.7.2 Compartments

V²SIRD extends a SIRD model by adding compartments corresponding to proportions of the population who have received one or two doses of a two dose vaccine. These compartments are summarized in table 5.3, and described below.

As the model does not assume instantaneous and perfectly sterilizing immunity, there are also compartments corresponding to individuals who with one or more doses of the vaccine who are also susceptible, infected, or recovered from infection (e.g. **V1i** represents those who have received one dose of the vaccine and are also infected. Thus the model comprises two SIR models corresponding to infection among singly-vaccinated, and doubly-vaccinated individuals stacked above an SIRD model for infection in the unvaccinated (see figure 5.5).

The model captures imperfect efficacy (e.g. an individual who receives one or two doses has some risk of death due to infection) by splitting the susceptible compartment for singly or doubly vaccinated individuals into vaccine effective and vaccine ineffective compartments (i.e. **V1e, V1n, V2e, V2n**). Individuals with ineffective vaccination, if infected, move to **I**; those with effective vaccination, if infected, move to **V1i** or **V2i**: the died (**D**) compartment is only linked to **I**, entailing effective vaccination prevents proportions effectively vaccinated subsequently dying of infection.

Compartment		
Name	*Symbol*	*Notes*
Susceptible	**S**	Only susceptibles can receive a first vaccine dose
Infected	**I**	
Recovered	**R**	
Died	**D**	Only individuals in the infected compartment can transition to died. Effective vaccination results in non-fatal recovery from infection
First dose (ineffective)	**V1n**	Individuals who receive a dose yet are not protected from mortality, and thus infection leads to transition to **I** (and thus some onward flow to **D**).
First dose (effective)	**V1e**	Individuals who receive a dose and are protected from mortality, and thus infection results in transition not to **I** but **V1i**.
First dose (infected)	**V1i**	Individuals with effective (but non-sterilizing) immunity after the first dose who are infected.
First dose (recovered)	**V1r**	Individuals who, after the first dose, either recover from infection, or receive sterilizing immunity from the vaccination
Second dose (ineffective)	**V2n**	These compartments share the properties of corresponding compartments with a single vaccine dose, with the addition that all compartments with a first vaccine dose are eligible to receive a second regardless of infection status.
Second dose (effective)	**V2e**	
Second dose (infected)	**V2i**	
Second dose (recovered)	**V2r**	

Table 5.3: Compartments in the V^2SIRD model.

Variable sterilizing immunity is incorporated by with transitions directly from susceptible to recovered compartments after vaccination (e.g. **V1e** $\rightarrow$ **V1r**), thus eliminating some proportion of vaccinated individuals from the possibility of being subsequently infected.

Only susceptibles are eligible for a first vaccination out of the unvaccinated, whilst all those who have received one vaccine dose are equally eligible to receive a second. Thus there is both the possibility of second doses being 'wasted' (e.g. vaccinating those who already enjoy sterilizing immunity from the first dose or recovered from infection) but also providing another opportunity for susceptible individuals with ineffective or non-sterilizing immunity to gain these upon receiving their second dose.

Symbol	Parameter	Notes
R_0	Intrinsic rate of reproduction	
r_v	Rate of vaccination	Proportion of population which receive a vaccine dose per time-step (e.g. rv = 0.01 would mean 200 days to provide two doses to all members of a fully susceptible population.)
e_1^f	First dose vaccine efficacy (versus mortality)	
e_2^f	Second dose vaccine efficacy (versus mortality)	
e_1^t	First dose vaccine efficacy (versus transmission)	In the modelling code these variables are implied by two others: the first a constant multiple (between 0 and 1) of ef to provide proportional sterilizing
e_2^t	Second dose vaccine efficacy (versus transmission)	immunity (i.e. e1t/e1f = e2t/e2d), the second biasing variable which allows disproportionate sterilizing immunity (cf. section 5.4.4)

Table 5.4: Epidemiological and vaccination parameters

5.7.3 Modelling parameters

Beyond the initial distribution across compartments, the model also relies on parameters which govern vaccine performance and epidemic behaviour. These are given in table 5.4.

5.7.4 Vaccine program progression

The model includes logic to determine timestep by timestep allocation of available vaccine (r_v) between first and second doses depending on whether the vaccine program deploys a FDF or BDF strategy.

For FDF, the r_v allocation is provided at each timestep to susceptibles. If $r_v > \mathbf{S}$, the remainder is provided in to **V1n V1e V1i** and **V1r** *pro rata* to their relative proportions. For BDF these steps are performed in the opposite order: r_v in each timestep is first allocated to all who have received a single vaccine, and any remainder provided to provide initial vaccinations in **S**.

5.7.5 Transition equations

To update the proportions for the next timestep, the transitions between compartments are calculated for the current one. These are described in table 5.5.

Symbol	Transition	Equation	Notes
$\mathbf{S} \rightarrow \mathbf{I}$	Susceptibles being infected	$\frac{R_0}{7} \cdot \mathbf{S} \cdot \mathbf{I} \cdot \mathbf{V1i} \cdot \mathbf{V2i}$	Intrinsic rate of reproduction (amortised daily), from total infected.
$\mathbf{S} \rightarrow \mathbf{V1n}$	Individuals receiving an ineffective first dose	$r_{v1} \cdot (1 - e_1^f)$	
$\mathbf{S} \rightarrow \mathbf{V1e}$	Individuals receiving an effective (versus mortality) first dose	$r_{v1} \cdot e_1^f$	
$\mathbf{I} \rightarrow \mathbf{R}$	Recovery of infected individuals	$_{t-7}((\mathbf{S} \rightarrow \mathbf{I}) + (\mathbf{V1n} \rightarrow \mathbf{I}) + (\mathbf{V2n} \rightarrow \mathbf{I})) * (1 - \text{IFR})$	7 day pass through of influx of to infected compartment, proportioned by IFR
$\mathbf{I} \rightarrow \mathbf{D}$	Death of infected individuals	$_{t-7}((\mathbf{S} \rightarrow \mathbf{I}) + (\mathbf{V1n} \rightarrow \mathbf{I}) + (\mathbf{V2n} \rightarrow \mathbf{I})) \cdot \text{IFR}$	
$\mathbf{V1n} \rightarrow \mathbf{I}$	Infection of individuals with ineffective first dose	$\frac{R_0}{7} \cdot \mathbf{V1n} \cdot \mathbf{I} \cdot \mathbf{V1i} \cdot \mathbf{V2i}$	
$\mathbf{V1n} \rightarrow \mathbf{V2n}$	Second dose provided, but vaccination ineffective	$\frac{(1-e_2^f)}{(1-e_1^f)} \cdot r_{v2} \cdot \frac{\mathbf{V1n}}{(\mathbf{V1n}+\mathbf{V1e}+\mathbf{V1i}+\mathbf{V1r})}$	First term is the likelihood of 'rescue' to effective vaccine protection with a second vaccination if first ineffective. Second term is the rate of second doses provided proportionate to eligibe comparmtnets
$\mathbf{V1n} \rightarrow \mathbf{V2e}$	Second dose provided, vaccination now effective	$(1 - \frac{(1-e_2^f)}{(1-e_1^f)}) \cdot r_{v2} \cdot \frac{\mathbf{V1n}}{(\mathbf{V1n}+\mathbf{V1e}+\mathbf{V1i}+\mathbf{V1r})}$	

V1e → **V1r**	Sterilizing immunity after initial vaccination	${}_{t-7}(\mathbf{S} \rightarrow \mathbf{V1e}) \cdot e_1^t$ (Modulo attrition)	Delayed transition from initial vaccination to sterilizing immunity proportionate to et1. Attrition (e.g. some of this cohort being infected before sterilizing immunity has developed) is discussed in the text.
V1e to **V1i**	Infection of those with an effective (versus mortality) first vaccine dose	$\frac{R_0}{7} \cdot \mathbf{V1e} \cdot \mathbf{I} \cdot \mathbf{V1i} \cdot \mathbf{V2i}$	
V1e → **V2e**	Second vaccination to those who have recieved an effective (versus mortality) initial dose.	$r_{v2} \cdot \frac{\mathbf{V1e}}{(\text{textbfV1n}+\mathbf{V1e}+\mathbf{V1i}+\mathbf{V1r})}$	Proportional allocation of vaccine rate across all initially vaccinated compartments.
V1i → **V1r**	Recovery from infection of those with a first effective vaccination	${}_{t-7}(\mathbf{V1i} \rightarrow \mathbf{V1e})$, modulo attrition	Delayed transition of infections, modulo attrition due to vaccination (see text)
V1i → **V2i**	Second vaccination to infected individuals	$r_{v2} \cdot \frac{\mathbf{V1i}}{(\mathbf{V1n}+\mathbf{V1e}+\mathbf{V1i}+\mathbf{V1r})}$	
V1r → **V2r**	Second vaccinations to individuals who have received an effective first dose and recovered from infection	$r_{v2} \cdot \frac{\mathbf{V1r}}{(\mathbf{V1n}+\mathbf{V1e}+\mathbf{V1i}+\mathbf{V1r})}$	
V2n → **I**	Infection of those who have recieved both doses of vaccine, which has proved ineffective	$\frac{R_0}{7} \cdot \mathbf{V2n} \cdot \mathbf{I} \cdot \mathbf{V1i} \cdot \mathbf{V2i}$	
V2e → **V2r**	Sterilizing immunity produced after the second dose	${}_{t-7}((\mathbf{V1n} \rightarrow \mathbf{V2e}) + (\mathbf{V1e} \rightarrow \mathbf{V2e}))$, modulo attrition	See text for discussion of how attrition of cohorts is managed.

V2e → **V2i**	Infection of those with two doses and protection (versus mortality)	$\frac{R_0}{7} \cdot \mathbf{V2e} \cdot (\mathbf{I} + \mathbf{V1i} + \mathbf{V2i})$
V2i → **V2r**	Recovery of doubly vaccinated from infection	${}_{t-7}((\mathbf{V2e} \rightarrow \mathbf{V2i}) + (\mathbf{V1i} \rightarrow \mathbf{V2i}))$

Table 5.5: Transition equations

5.7.6 Delayed transitions with attrition

Several transitions between compartments are delayed. Naive use of 'carrying forward' inbound transitions n days previously does not work due to attrition of this cohort by flow to over compartments over the delay period. For example, without any infection the transition **V1e** → **V1r** on timestep n would be the transition $e_1^t \cdot (\mathbf{V1e} \rightarrow \mathbf{V1r})$ 7 days before, but with infection some of these individuals will become infected before they achieve sterilizing immunity.

This attrition is corrected by back-calculating the relative flow down these alternative transitions over the delay period, and calculating the impact on the delayed cohort (e.g. if 10% of **V1e** became infected each day, whilst the **V1e** → **V1r** cohort was waiting to develop sterilizing immunity, the correction is a multiple of $0.9^5 \approx 0.6$).

6 Discussion

Contents

Each chapter includes a discussion of its particular findings. This discussion thus focuses on broader themes and reflections which arise from these works as a whole.

6.1 Different species of uncertain judgement

One interesting contrast between chapters 2 and 3 and chapters 4 and 5 is the latter two make bolder conclusions in the face of remaining uncertainty. For example, chapter 3 suggests 'spiking' fever could be a consequence of optimal thermal restriction given an energy constraint; but is tentative on the relative plausibility of this hypothesis versus alternatives which attribute 'spiking' to an immunomodulatory signal, an exaptation, or a trait without functional value. In contrast, chapter 4 asserts more aggressive emergency use would have been *ex ante* beneficial in vaccine deployment in the COVID-19 pandemic, notwithstanding uncertainties around (for example) vaccine dependent enhancement and risk compensation.

Both are complex topics, and the simplicity of mathematical analysis for both does not address many sources of uncertainty. Why are the conclusions for one much stronger than the other?

One class of explanations would be that although these questions share some general features, their particular properties are very different: although both are complex questions, the scope of uncertainty around endotherm fever is much wider (and less tractable) than that surrounding an emerging infectious disease. Another is fever and immunity have been studied for much longer than COVID-19 vaccination, so for the former the straightforward discoveries are more likely to have already been made, making further advances harder and more tentative.

A more interesting one is these are different explanatory projects with different thresholds of evidence. For the role of fever and other questions in chapters 2 and 3, the objective is to determine the relative importance of different explanatory factors. As this is typically difficult, conclusions remain tentative: the modelling may show energy efficient thermal restriction is a *credible* explanation for spiking fever, but not that it is the primary or common explanation versus competing hypotheses. In contrast, when comparing interventions, a direction of effect which favours one over the other is a *pro tanto* recommendation. Even if many considerations are neglected in the simple model of individual benefits and risks from emergency vaccine use, unless one believes these uncertainties would point in the opposite direction, the better bet is the one which the modelling favours.

6.2 A mixed picture on evolutionary medicine

One common ambition is to use insights from evolutionary biology to better understand health and disease, and to inform medical management and public health interventions. This work provides little to temper the challenges illustrated in the introduction.

The evolutionary forces which sculpted present immunobiology, and the functional relevance of particular mechanisms are difficult to ascertain. Which mechanisms amount to maladaptive or adaptive selection (Chapter 2), or the precise

delineation of in virtue of what a given mechanism is adaptive (Chapter 3) remains challenging. Another example were speculations from optimal virulence theory to anticipate whether future variants of COVID-19 would be selected for greater or lesser virulence over time: theoretical predictions from optimal virulence were hard to apply (as a newly emergent pathogen, COVID-19 might be anticipated to lie very far from the efficient frontier of transmission/virulence trade-offs), hard to determine (given competing effects of vaccination and prior immunity, thus reduction in severity may be owed to human rather than viral biology) and the tentative suggestions have a mixed track record: common COVID-19 variants only show a tentative trend towards milder virulence, plausibly confounded by prevalent immunity acquired from infection with earlier variants.

In terms of guiding management, the steers from evolutionary theory would be tentative, and typically much inferior to direct assessment: rather than attempting to disentangle the functional import of pre-existing immunological mechanisms (to then determine whether one should intervene to enhance or limit them), one can test the intervention directly against the outcome of interest. This suggests evolutionary approaches may have more of an ancillary role in generating hypotheses for interventions, rather than direct value in clinical and public health decision-making.

6.3 Ceilings of performance in natural and artificial immunity

The modelling approaches in these chapters have touched upon not only current performance of particular immunological mechanisms but also their potential ceiling: whether certain arenas of co-evolutionary conflict between host and pathogen give one or the other an intrinsic advantage. One example is that, in the limit, heating is an efficient means of thermally excluding a pathogen. Although there are thermal limits which prevent this being achieved in the host body, this is commonly exploited in the environment in (e.g.) cooking and sterilization.

Better understanding of these determinants could enhance common approaches to 'optimal control'. Finding areas where pathogens, despite their often rapid

evolution, are unable to achieve parity could guide research, development, and deployment to more interventions more resilient to counter-adaptation. It may also indicate where natural immunity falls the furthest short from physical limits, and thus how artificial immunity can best complement and surpass it.

6.4 Coda: closing the book on infectious disease?

> It is time to close the book on infectious diseases, and declare the war against pestilence won.

This infamous quotation is attributed to William H. Stewart, US surgeon general (1965-1969). Its typical use is a cautionary tale: despite the optimism of the 1960s and 1970s, the subsequent 50 years have demonstrated pestilence remains a frightening adversary to humankind, and vigilance, rather than complacency, is called for. The quote is apocryphal: there is no evidence Stewart ever made this remark (and he made many others arguing precisely the opposite).[228]

Yet perhaps this commonly-maligned triumphalism is more right than wrong. The last 30 years alone has seen the global burden of communicable disease fall by 40%, a continuation of the trend observed over the last two centuries.[229] Even major pandemics have only interrupted this upward trend: the global health burden of HIV peaked in the early 2000s and has fallen by two thirds now;[229] the 1918 influenza pandemic reduced life expectancy that year by a decade, only to surpass pre-pandemic levels two years later (and for life expectancy to increase by another 30 years over the remainder of the century);[230] COVID-19 has reduced national life expectancies by at most 3 years, typically reversing 10 to 20 years of progress[231] - similar to 1918 Influenza, these setbacks are anticipated to reverse rapidly. None of this belittles these past humanitarian disasters, nor ongoing suffering, but a full accounting of the "war against pestilence" so far is a triumph of the human condition.

Could this trend culminate into a victory over infectious disease? Perhaps. There are various proposed threats to halting or reversing this long term trend: antimicrobial resistance may halt reductions in endemic infectious disease;[232] climate change and animal agriculture may mean major global pandemics like

COVID-19 occur with increasing frequency.[233, 234] Wise stewardship could avoid these pitfalls, but exuberant technological mastery could render them irrelevant. COVID-19 brought the unprecedented feat of deploying a vaccine at scale to an emerging infectious disease within a year of its first emergence. This remains too slow, and there are global efforts to shorten this timeline in future (for example, the '100 days mission').[226] There is no law of nature which prohibits a vaccine timeline of 10 days rather than 100, nor of generating novel antimicrobial agents at a rate which outpaces the evolution of antimicrobial resistance, nor for the successes of sanitation engineering to be extended to airborne alongside waterborne disease. In concert such capabilities offer the prospect of impenetrable public health defences from naturally emerging infectious disease.

Yet such capabilities raise the danger of *unnaturally* emerging infectious disease. It remains uncertain whether COVID-19 arose from zoonotic spillover or laboratory accident,[235] but scientific mishaps are the likely culprit for a host of outbreaks,[236] including the 1977 'Russian Flu' influenza pandemic.[237] Alongside misuse, there is a long history of attempts to use disease as a weapon;[238, 239] advancing and democratising biotechnology makes such attempts more accessible and more likely to succeed. Both well-intentioned scientists and bioweaponeers have seen success in engineering pathogens to make them more dangerous: greater lethality, easier means of transmission, evasion of vaccines and therapeutics, among others.[240–243] What such efforts could produce with next-generation biotechnology is harrowing, and an arms race between these and future biological defenses difficult to forecast.

The prospects for artificial immunity 'closing the book' on infectious diseases are good; further chapters on the conflict between it and artificial or engineered pestilence may not be so upbeat. Hopefully, nature is indeed the ultimate bioterrorist, and dangers which arise from evolutionary happenstance cannot be surpassed by deliberate design. Hopefully, even if biological threats unprecedented in natural history are possible, no one will possess both the ability and motivation together to unleash them. Hopefully, even if they do, humankind's collective capability would be equal to the task of defending themselves from it.

But not all hopes are expectations.

7

Appendix: Data and code availability

All data and code in thesis is available at the following repository, subdivided by chapter:

`https://github.com/gjlewis37/DPhil`

References

[1] Mark EJ Woolhouse et al. “Biological and biomedical implications of the co-evolution of pathogens and their hosts”. In: *Nature genetics* 32.4 (2002), pp. 569–577.

[2] Nadia Danilova. “The evolution of immune mechanisms”. In: *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution* 306.6 (2006), pp. 496–520.

[3] "Merriam-Webster". *Pathogen*. Online; accessed 20 April 2022. URL: `https://www.merriam-webster.com/dictionary/pathogen#medicalDictionary`.

[4] Liise-anne Pirofski and Arturo Casadevall. “Q&A: What is a pathogen? A question that begs the point”. In: *BMC biology* 10.1 (2012), pp. 1–3.

[5] Gilbert A. Castro and Leroy J. Olson. “Medical Microbiology”. In: ed. by S Baron. 4th ed. Galveston (TX): University of Texas, 1996. Chap. Introduction to Parasitology.

[6] "World Health Organisation". *West Nile Virus*. Online; accessed 14 April 2022. 2017. URL: `https://www.who.int/news-room/fact-sheets/detail/west-nile-virus`.

[7] "Centers for Disease Control and Prevention". *Parasites - Gnathostomiasis*. Online; accessed 14 April 2022. URL: `https://www.cdc.gov/parasites/gnathostoma/biology.html`.

[8] TM Cook, RT Protheroe, and JM Handel. “Tetanus: a review of the literature”. In: *British Journal of Anaesthesia* 87.3 (2001), pp. 477–487.

[9] Eddie Grace, Scott Asbill, and Kris Virga. “Naegleria fowleri: pathogenesis, diagnosis, and treatment options”. In: *Antimicrobial agents and chemotherapy* 59.11 (2015), pp. 6677–6681.

[10] Alan M O’Neill and Richard L Gallo. “Host-microbiome interactions and recent progress into understanding the biology of acne vulgaris”. In: *Microbiome* 6.1 (2018), pp. 1–16.

[11] Simon Carding et al. “Dysbiosis of the gut microbiota in disease”. In: *Microbial ecology in health and disease* 26.1 (2015), p. 26191.

[12] S. Alizon et al. “Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future”. In: *J. Evol. Biol.* 22.2 (Feb. 2009), pp. 245–259.

[13] Wikipedia contributors. *Immune system — Wikipedia, The Free Encyclopedia*. [Online; accessed 19-April-2022]. 2022. URL: `https://en.wikipedia.org/w/index.php?title=Immune_system&oldid=1080957927`.

[14] Val Curtis, Robert Aunger, and Tamer Rabie. “Evidence that disgust evolved to protect from risk of disease”. In: *Proceedings of the Royal Society of London. Series B: Biological Sciences* 271.suppl_4 (2004), S131–S133.

[15] Himanshu Kumar, Taro Kawai, and Shizuo Akira. “Pathogen recognition by the innate immune system”. In: *International reviews of immunology* 30.1 (2011), pp. 16–34.

[16] Tao Gong et al. “DAMP-sensing receptors in sterile inflammation and inflammatory diseases”. In: *Nature Reviews Immunology* 20.2 (2020), pp. 95–112.

[17] I Sabroe et al. “The role of TLR activation in inflammation”. In: *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland* 214.2 (2008), pp. 126–135.

[18] Katherine A Fitzgerald and Jonathan C Kagan. “Toll-like receptors and the control of immunity”. In: *Cell* 180.6 (2020), pp. 1044–1066.

[19] Jonathan W Yewdell, Devin Dersh, and Robin Fåhraeus. “Peptide channeling: the key to MHC class I immunosurveillance?” In: *Trends in cell biology* 29.12 (2019), pp. 929–939.

[20] Paul J Lehner and Peter Cresswell. “Processing and delivery of peptides presented by MHC class I molecules”. In: *Current opinion in immunology* 8.1 (1996), pp. 59–67.

[21] Peter Cresswell. “Assembly, transport, and function of MHC class II molecules”. In: *Annual review of immunology* 12.1 (1994), pp. 259–291.

[22] Paul A Roche and Kazuyuki Furuta. “The ins and outs of MHC class II-mediated antigen processing and presentation”. In: *Nature Reviews Immunology* 15.4 (2015), pp. 203–216.

[23] Michael S Krangel. “Mechanics of T cell receptor gene rearrangement”. In: *Current opinion in immunology* 21.2 (2009), pp. 133–139.

[24] Mark M Davis. “T cell receptor gene diversity and selection”. In: *Annual review of biochemistry* 59.1 (1990), pp. 475–496.

[25] Hiroyuki Takaba and Hiroshi Takayanagi. “The mechanisms of T cell selection in the thymus”. In: *Trends in immunology* 38.11 (2017), pp. 805–816.

[26] Alan G Baxter and Philip D Hodgkin. “Activation rules: the two-signal theories of immune activation”. In: *Nature Reviews Immunology* 2.6 (2002), pp. 439–446.

[27] Yang Liu and Peter S Linsley. “Costimulation of T-cell growth”. In: *Current opinion in immunology* 4.3 (1992), pp. 265–270.

[28] Leonard J Appleman and Vassiliki A Boussiotis. “T cell anergy and costimulation”. In: *Immunological reviews* 192.1 (2003), pp. 161–180.

[29] Timothy E O’Sullivan, Joseph C Sun, and Lewis L Lanier. “Natural killer cell memory”. In: *Immunity* 43.4 (2015), pp. 634–645.

[30] Tanja Stögerer and Simona Stäger. “Innate immune sensing by cells of the adaptive immune system”. In: *Frontiers in Immunology* 11 (2020), p. 1081.

[31] Geert W Schmid-Schönbein. “Analysis of inflammation”. In: *Annu. Rev. Biomed. Eng.* 8 (2006), pp. 93–151.

[32] Anders Blomqvist and David Engblom. “Neural mechanisms of inflammation-induced fever”. In: *The Neuroscientist* 24.4 (2018), pp. 381–399.

[33] Marianne Wessling-Resnick. “Iron homeostasis and the inflammatory response”. In: *Annual review of nutrition* 30 (2010), pp. 105–122.

[34] John T Harty, Amy R Tvinnereim, and Douglas W White. “CD8+ T cell effector mechanisms in resistance to infection”. In: *Annual review of immunology* 18.1 (2000), pp. 275–308.

[35] Thomas Dörner and Andreas Radbruch. “Antibodies and B cell memory in viral immunity”. In: *Immunity* 27.3 (2007), pp. 384–392.

[36] Rishi Vishal Luckheeram et al. “CD4+ T cells: differentiation and functions”. In: *Clinical and developmental immunology* 2012 (2012).

[37] Carmen Infante-Duarte and Thomas Kamradt. “Th1/Th2 balance in infection”. In: *Springer seminars in immunopathology*. Vol. 21. 3. Springer. 1999, pp. 317–338.

[38] Shane Crotty and Rafi Ahmed. “Immunological memory in humans”. In: *Seminars in immunology*. Vol. 16. 3. Elsevier. 2004, pp. 197–203.

[39] Peng Guo et al. “Dual nature of the adaptive immune system in lampreys”. In: *Nature* 459.7248 (2009), pp. 796–801.

[40] Zeev Pancer et al. “Somatic diversification of variable lymphocyte receptors in the agnathan sea lamprey”. In: *Nature* 430.6996 (2004), pp. 174–180.

[41] Dustin Cooper and Ioannis Eleftherianos. “Memory and specificity in the insect immune system: current perspectives and future challenges”. In: *Frontiers in immunology* 8 (2017), p. 539.

[42] Michael P Terns and Rebecca M Terns. “CRISPR-based adaptive immune systems”. In: *Current opinion in microbiology* 14.3 (2011), pp. 321–327.

[43] Arno Wouters. “The function debate in philosophy”. In: *Acta Biotheoretica* 53.2 (2005), pp. 123–151.

[44] Paul E Griffiths. “Functional analysis and proper functions”. In: *The British Journal for the Philosophy of Science* 44.3 (1993), pp. 409–422.

[45] Karen Neander. “Functions as selected effects: The conceptual analyst’s defense”. In: *Philosophy of science* 58.2 (1991), pp. 168–184.

[46] Andrea Orús-Alcalde et al. “The evolution of the metazoan Toll receptor family and its expression during protostome development”. In: *BMC ecology and evolution* 21.1 (2021), pp. 1–21.

[47] Se Jin Park et al. “Toll-like receptor-2 deficiency induces schizophrenia-like behaviors in mice”. In: *Scientific reports* 5.1 (2015), pp. 1–13.

[48] Agustina Noailles et al. “The absence of toll-like receptor 4 mildly affects the structure and function in the adult mouse retina”. In: *Frontiers in Cellular Neuroscience* 13 (2019), p. 59.

[49] Li Nie et al. “Toll-like receptors, associated biological roles, and signaling networks in non-mammals”. In: *Frontiers in immunology* 9 (2018), p. 1523.

[50] Paul J Maglione, Noa Simchoni, and Charlotte Cunningham-Rundles. “Toll-like receptor signaling in primary immune deficiencies”. In: *Annals of the New York Academy of Sciences* 1356.1 (2015), pp. 1–21.

[51] Mark S Bulmer and Alanna M Stefano. “Termite eusociality and contrasting selective pressure on social and innate immunity”. In: *Behavioral Ecology and Sociobiology* 76.1 (2022), pp. 1–12.

[52] Joël Meunier. “Social immunity and the evolution of group living in insects”. In: *Philosophical Transactions of the Royal Society B: Biological Sciences* 370.1669 (2015), p. 20140102.

[53] Sharon S Evans, Elizabeth A Repasky, and Daniel T Fisher. “Fever and the thermal regulation of immunity: the immune system feels the heat”. In: *Nature Reviews Immunology* 15.6 (2015), pp. 335–349.

[54] Jeffrey D Hasday, Christopher Thompson, and Ishwar S Singh. “Fever, immunity, and molecular adaptations”. In: *Comprehensive Physiology* 4.1 (2011), pp. 109–148.

[55] Marsha Wills-Karp, Joanna Santeliz, and Christopher L Karp. “The germless theory of allergic disease: revisiting the hygiene hypothesis”. In: *Nature Reviews Immunology* 1.1 (2001), pp. 69–75.

[56] Marc Lipsitch and E Richard Moxon. “Virulence and transmissibility of pathogens: what is the relationship?” In: *Trends in microbiology* 5.1 (1997), pp. 31–37.

[57] Richard E Lenski and Robert M May. “The evolution of virulence in parasites and pathogens: reconciliation between two competing hypotheses”. In: *Journal of theoretical biology* 169.3 (1994), pp. 253–265.

[58] R. Poulin and C. Combes. “The concept of virulence: interpretations and implications”. In: *Parasitol. Today (Regul. Ed.)* 15.12 (Dec. 1999), pp. 474–475.

[59] Theobald Smith. “Some Problems in the Life History of Pathogenic Microorganisms”. In: *Science* 20.520 (1904), pp. 817–832. URL: http://www.jstor.org/stable/1630323.

[60] R. M. May and R. M. Anderson. “Epidemiology and genetics in the coevolution of parasites and hosts”. In: *Proc. R. Soc. Lond., B, Biol. Sci.* 219.1216 (Oct. 1983), pp. 281–313.

[61] P W Ewald. “Host-Parasite Relations, Vectors, and the Evolution of Disease Severity”. In: *Annual Review of Ecology and Systematics* 14.1 (1983), pp. 465–485.

[62] Sharon L. Messenger, Ian J. Molineux, and J. J. Bull. “Virulence evolution in a virus obeys a trade off”. In: *Proceedings of the Royal Society of London B: Biological Sciences* 266.1417 (1999), pp. 397–404. eprint: http://rspb.royalsocietypublishing.org/content/266/1417/397.full.pdf. URL: http://rspb.royalsocietypublishing.org/content/266/1417/397.

[63] Israel Pagán et al. “Vertical Transmission Selects for Reduced Virulence in a Plant Virus and for Increased Resistance in the Host”. In: *PLOS Pathogens* 10.7 (July 2014), pp. 1–12. URL: https://doi.org/10.1371/journal.ppat.1004293.

[64] Paul W. Ewald. “The Evolution of Virulence”. In: *Scientific American* 268.4 (1993), pp. 86–93. URL: http://www.jstor.org/stable/24941444.

[65] T. Day. “The evolution of virulence in vector-borne and directly transmitted parasites”. In: *Theor Popul Biol* 62.2 (Sept. 2002), pp. 199–213.

[66] D. Ebert and J. J. Bull. "Challenging the trade-off model for the evolution of virulence: is virulence management feasible?" In: *Trends Microbiol.* 11.1 (Jan. 2003), pp. 15–20.

[67] J. J. Bull and A. S. Lauring. "Theory and empiricism in virulence evolution". In: *PLoS Pathog.* 10.10 (Oct. 2014), e1004387.

[68] C. E. Cressler et al. "The adaptive evolution of virulence: a review of theoretical predictions and empirical tests". In: *Parasitology* 143.7 (June 2016), pp. 915–930.

[69] Brigitte Lamy et al. "How to Optimize the Use of Blood Cultures for the Diagnosis of Bloodstream Infections? A State-of-the Art". In: *Frontiers in Microbiology* 7 (2016), p. 697. URL: https://www.frontiersin.org/article/10.3389/fmicb.2016.00697.

[70] M. Stone et al. "Comparison of Detection Limits of Fourth- and Fifth-Generation Combination HIV Antigen-Antibody, p24 Antigen, and Viral Load Assays on Diverse HIV Isolates". In: *J. Clin. Microbiol.* 56.8 (Aug. 2018).

[71] S Zeuzem, B Rüster, and WK Roth. "Clinical evaluation of a new polymerase chain reaction assay (Amplicor HCV) for detection of hepatitis C virus". In: *Zeitschrift fur Gastroenterologie* 32.6 (June 1994), pp. 342–347. URL: http://europepmc.org/abstract/MED/7526563.

[72] Helen C Leggett et al. "Growth rate, transmission mode and virulence in human pathogens". In: *Philosophical Transactions of the Royal Society B: Biological Sciences* 372.1719 (2017), p. 20160094.

[73] A. Scally. "The mutation rate in human evolution and demographic inference". In: *Curr. Opin. Genet. Dev.* 41 (Dec. 2016), pp. 36–43.

[74] M. W. Nachman and S. L. Crowell. "Estimate of the mutation rate per nucleotide in humans". In: *Genetics* 156.1 (Sept. 2000), pp. 297–304.

[75] John W. Drake et al. "Rates of Spontaneous Mutation". In: *Genetics* 148.4 (1998), pp. 1667–1686. eprint: http://www.genetics.org/content/148/4/1667.full.pdf. URL: http://www.genetics.org/content/148/4/1667.

[76] B. D. Preston, B. J. Poiesz, and L. A. Loeb. "Fidelity of HIV-1 reverse transcriptase". In: *Science* 242.4882 (Nov. 1988), pp. 1168–1171.

[77] Anita Huovilainen et al. "Evolution of Poliovirus During an Outbreak: Sequential Type 3 Poliovirus Isolates from Several Persons Show Shifts of Neutralization Determinants". In: *Journal of General Virology* 68.5 (1987), pp. 1373–1378. URL: https://www.microbiologyresearch.org/content/journal/jgv/10.1099/0022-1317-68-5-1373.

[78] Elena López-Camacho et al. "Genomic analysis of the emergence and evolution of multidrug resistance during a Klebsiella pneumoniae outbreak including carbapenem and colistin resistance". In: *Journal of Antimicrobial Chemotherapy* 69.3 (Oct. 2013), pp. 632–636. eprint: http://oup.prod.sis.lan/jac/article-pdf/69/3/632/2353923/dkt419.pdf. URL: https://doi.org/10.1093/jac/dkt419.

[79] Daniel J. Park et al. “Ebola Virus Epidemiology, Transmission, and Evolution during Seven Months in Sierra Leone”. In: *Cell* 161.7 (2015), pp. 1516–1526. URL: http://www.sciencedirect.com/science/article/pii/S009286741500690X.

[80] World Health Organization et al. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. World Health Organization, 2016.

[81] A. F. Read. “The evolution of virulence”. In: *Trends Microbiol.* 2.3 (Mar. 1994), pp. 73–76.

[82] J. T. Herbeck et al. “Is the virulence of HIV changing? A meta-analysis of trends in prognostic markers of HIV disease progression and transmission”. In: *AIDS* 26.2 (Jan. 2012), pp. 193–205.

[83] M. T. Sofonea et al. “Can Ebola virus evolve to be less virulent in humans?” In: *Journal of Evolutionary Biology* 31.3 (), pp. 382–392. eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1111/jeb.13229. URL: https://onlinelibrary.wiley.com/doi/abs/10.1111/jeb.13229.

[84] S. C. Segerstrom. “Stress, Energy, and Immunity: An Ecological View”. In: *Curr Dir Psychol Sci* 16.6 (2007), pp. 326–330.

[85] JR Ward et al. “Translational Mini-Review Series on Immunology of Vascular Disease: Inflammation, infections and Toll-like receptors in cardiovascular disease”. In: *Clinical & Experimental Immunology* 156.3 (2009), pp. 386–394.

[86] D. J. Stearns-Kurosawa et al. “The pathogenesis of sepsis”. In: *Annu Rev Pathol* 6 (2011), pp. 19–48.

[87] M Van Baalen. “Coevolution of recovery ability and virulence”. In: *Proceedings of the Royal Society of London. Series B: Biological Sciences* 265.1393 (1998), pp. 317–325.

[88] N. Mideo, S. Alizon, and T. Day. “Linking within- and between-host dynamics in the evolutionary epidemiology of infectious diseases”. In: *Trends Ecol. Evol. (Amst.)* 23.9 (Sept. 2008), pp. 511–517.

[89] Jacob C. Koella, C. Boëte, and Associate Editor: Curt Lively. “A Model for the Coevolution of Immunity and Immune Evasion in Vector-Borne Diseases with Implications for the Epidemiology of Malaria”. In: *The American Naturalist* 161.5 (2003), pp. 698–707. URL: http://www.jstor.org/stable/10.1086/374202.

[90] Jukka Jokela, Paul Schmid-Hempel, and Mark C. Rigby. “Dr. Pangloss restrained by the Red Queen – steps towards a unified defence theory”. In: *Oikos* 89.2 (2000), pp. 267–274. eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1034/j.1600-0706.2000.890207.x. URL: https://onlinelibrary.wiley.com/doi/abs/10.1034/j.1600-0706.2000.890207.x.

[91] Sylvain Gandon, Philip Agnew, and Yannis Michalakis. “Coevolution between Parasite Virulence and Host Life-History Traits.” In: *The American Naturalist* 160.3 (2002). PMID: 18707446, pp. 374–388. eprint: https://doi.org/10.1086/341525. URL: https://doi.org/10.1086/341525.

[92] R. Dawkins and J. R. Krebs. “Arms races between and within species”. In: *Proc. R. Soc. Lond., B, Biol. Sci.* 205.1161 (Sept. 1979), pp. 489–511.

[93] A Sasaki and HCJ Godfray. “A model for the coevolution of resistance and virulence in coupled host–parasitoid interactions”. In: *Proceedings of the Royal Society of London. Series B: Biological Sciences* 266.1418 (1999), pp. 455–463.

[94] Maia Martcheva, Necibe Tuncer, and Yena Kim. “On the principle of host evolution in host–pathogen interactions”. In: *Journal of biological dynamics* 11.sup1 (2017), pp. 102–119.

[95] S. M. Candeias and U. S. Gaipl. “The Immune System in Cancer Prevention, Development and Therapy”. In: *Anticancer Agents Med Chem* 16.1 (2016), pp. 101–107.

[96] A. M. Cuervo et al. “Autophagy and aging: the importance of maintaining "clean" cells”. In: *Autophagy* 1.3 (2005), pp. 131–140.

[97] HH Flor. “The complementary genic systems in flax and flax rust”. In: *Advances in genetics*. Vol. 8. Elsevier, 1956, pp. 29–54.

[98] Erik A Van Der Biezen and Jonathan DG Jones. “Plant disease-resistance proteins and the gene-for-gene concept”. In: *Trends in biochemical sciences* 23.12 (1998), pp. 454–456.

[99] Richard Levins. “The strategy of model building in population biology”. In: *American scientist* 54.4 (1966), pp. 421–431.

[100] T. J. Little et al. “The coevolution of virulence: tolerance in perspective”. In: *PLoS Pathog.* 6.9 (Sept. 2010), e1001006.

[101] M. Boots and A. Best. “The evolution of constitutive and induced defences to infectious disease”. In: *Proc. Biol. Sci.* 285.1883 (July 2018).

[102] P. A. zur Wiesch et al. “Population biological principles of drug-resistance evolution in infectious diseases”. In: *Lancet Infect Dis* 11.3 (Mar. 2011), pp. 236–247.

[103] S. Alizon and P. O. Methot. “Reconciling Pasteur and Darwin to control infectious diseases”. In: *PLoS Biol.* 16.1 (Jan. 2018), e2003815.

[104] Randolph M Nesse, George C Williams, and Iver Mysterud. “Why we get sick”. In: *Trends in Ecology and Evolution* 10.7 (1995), pp. 300–301.

[105] Ben Garfinkel and Allan Dafoe. “How does the offense-defense balance scale?” In: *Journal of Strategic Studies* 42.6 (2019), pp. 736–763.

[106] Arturo Casadevall. “Thermal restriction as an antimicrobial function of fever”. In: *PLoS pathogens* 12.5 (2016).

[107] Matthew B Thomas and Simon Blanford. “Thermal biology in insect-parasite interactions”. In: *Trends in Ecology & Evolution* 18.7 (2003), pp. 344–350.

[108] Corinne L Richards-Zawacki. “Thermoregulatory behaviour affects prevalence of chytrid fungal infection in a wild population of Panamanian golden frogs”. In: *Proceedings of the Royal Society B: Biological Sciences* 277.1681 (2010), pp. 519–528.

[109] Ryan S Mohammed et al. “Getting into hot water: sick guppies frequent warmer thermal conditions”. In: *Oecologia* 181.3 (2016), pp. 911–917.

[110] Krzysztof Rakus, Maygane Ronsmans, and Alain Vanderplasschen. “Behavioral fever in ectothermic vertebrates”. In: *Developmental & Comparative Immunology* 66 (2017), pp. 84–91.

[111] Vincent A Robert and Arturo Casadevall. “Vertebrate endothermy restricts most fungi as potential pathogens”. In: *The Journal of infectious diseases* 200.10 (2009), pp. 1623–1626.

[112] Douglas C Woodhams, Ross A Alford, and Gerry Marantelli. “Emerging disease of amphibians cured by elevated body temperature”. In: *Diseases of aquatic organisms* 55.1 (2003), pp. 65–67.

[113] Carol Uphoff Meteyer et al. “Recovery of little brown bats (Myotis lucifugus) from natural infection with Geomyces destructans, white-nose syndrome”. In: *Journal of Wildlife Diseases* 47.3 (2011), pp. 618–626.

[114] M Benhariz et al. “Energy cost of fever in children on total parenteral nutrition”. In: *Clinical Nutrition* 16.5 (1997), pp. 251–255.

[115] Vickie E Baracos, WT Whitmore, and R Gale. “The metabolic cost of fever”. In: *Canadian journal of physiology and pharmacology* 65.6 (1987), pp. 1248–1254.

[116] Eugene F Du Bois et al. “The basal metabolism in fever”. In: *Jama* 77.5 (1921), pp. 352–357.

[117] ER Buskirk et al. “Heat exchange in men and women following intravenous injection of endotoxin”. In: *Journal of applied physiology* 19.5 (1964), pp. 907–913.

[118] MANUEL Banet. “Fever in mammals: is it beneficial?” In: *The Yale journal of biology and medicine* 59.2 (1986), p. 117.

[119] PM Small et al. “Influence of body temperature on bacterial growth rates in experimental pneumococcal meningitis in rabbits.” In: *Infection and immunity* 52.2 (1986), pp. 484–487.

[120] Sally Eyers et al. “The effect on mortality of antipyretics in the treatment of influenza infection: systematic review and meta-analyis”. In: *Journal of the Royal Society of Medicine* 103.10 (2010), pp. 403–411.

[121] Jean Klastersky. “Etude experimentale et clinique des effets favorables et defavorables de la fievre et de l’administration de corticoides au cours d’infections bacteriennes”. In: *Acta Clinica Belgica* 27.sup6 (1972), pp. 8–84.

[122] Jeffrey D Hasday and Allen Garrison. “Antipyretic therapy in patients with sepsis”. In: *Clinical infectious diseases* 31.Supplement_5 (2000), S234–S241.

[123] S Haahr and S Mogensen. “Function of fever in infectious disease.” In: *Biomedicine/[publiee pour l’AAICIG]* 28.6 (1978), pp. 305–307.

[124] Philip A Mackowiak. “Physiological rationale for suppression of fever”. In: *Clinical infectious diseases* 31.Supplement_5 (2000), S185–S189.

[125] Matthew J Kluger et al. “Role of fever in disease”. In: *Annals of the new York Academy of Sciences* 856.1 (1998), pp. 224–233.

[126] Clark M Blatteis. “Fever: pathological or physiological, injurious or beneficial?” In: *Journal of thermal biology* 28.1 (2003), pp. 1–13.

[127] Panagiotis Kiekkas et al. “Nursing personnel’s attitudes towards fever and antipyresis of adult patients: cross-sectional survey”. In: *Journal of clinical nursing* 23.19-20 (2014), pp. 2949–2957.

[128] Anne Walsh, Helen Edwards, and Jenny Fraser. “Over-the-counter medication use for childhood fever: a cross-sectional study of Australian parents”. In: *Journal of paediatrics and child health* 43.9 (2007), pp. 601–606.

[129] Walter M Simpson. “Artificial fever therapy of syphilis and gonococcic infections”. In: *British Journal of Venereal Diseases* 12.3 (1936), p. 133.

[130] Kristijan Skok et al. “Thermoregulation: A journey from physiology to computational models and the intensive care unit”. In: *WIREs Mechanisms of Disease* 13.4 (2021), e1513.

[131] Deniz Gazel and Mehmet Yılmaz. “Are infectious diseases and microbiology new fields for thermal therapy research?” In: *International Journal of Hyperthermia* 34.7 (2018), pp. 918–924.

[132] Sylwia Wrotek et al. “Let fever do its job: The meaning of fever in the pandemic era”. In: *Evolution, medicine, and public health* 9.1 (2021), pp. 26–35.

[133] Ghjuvan Micaelu Grimaud et al. “Modeling the temperature effect on the specific growth rate of phytoplankton: a review”. In: *Reviews in Environmental Science and Bio/Technology* 16.4 (2017), pp. 625–645.

[134] Daniel Padfield, Meaghan Castledine, and Angus Buckling. “Temperature-dependent changes to host–parasite interactions alter the thermal performance of a bacterial host”. In: *The ISME journal* 14.2 (2020), pp. 389–398.

[135] Nathalie Smits, Jean-François BriÈRe, and Jacques Fargues. “Comparison of non-linear temperature-dependent development rate models applied to in vitro growth of entomopathogenic fungi”. In: *Mycological research* 107.12 (2003), pp. 1476–1484.

[136] Maria M Gil et al. “Mathematical models for prediction of temperature effects on kinetic parameters of microorganisms’ inactivation: Tools for model comparison and adequacy in data fitting”. In: *Food and Bioprocess Technology* 10.12 (2017), pp. 2208–2225.

[137] DA Ratkowsky et al. “Model for bacterial culture growth rate throughout the entire biokinetic temperature range.” In: *Journal of bacteriology* 154.3 (1983), pp. 1222–1226.

[138] Philip L Altman, Dorothy S Dittmer, et al. “Biology data book”. In: Federation of American Societies for Experimental Biology Bethesda, MD. 1972.

[139] Eleanore D Sternberg and Matthew B Thomas. “Local adaptation to temperature and the implications for vector-borne diseases”. In: *Trends in Parasitology* 30.3 (2014), pp. 115–122.

[140] Burke A Cunha. “The clinical significance of fever patterns”. In: *Infectious Disease Clinics* 10.1 (1996), pp. 33–44.

[141] Sarah Jefferies et al. “The effect of antipyretic medications on mortality in critically ill patients with infection: a systematic review and meta-analysis”. In: *Critical Care and Resuscitation* 13.2 (2011), p. 125.

[142] Daniel J Niven, H Tom Stelfox, and Kevin B Laupland. "Antipyretic therapy in febrile critically ill adults: a systematic review and meta-analysis". In: *Journal of critical care* 28.3 (2013), pp. 303–310.

[143] Anne M Drewry et al. "Antipyretic therapy in critically ill septic patients: a systematic review and meta-analysis". In: *Critical care medicine* 45.5 (2017), p. 806.

[144] HY Long et al. "Plasmodium falciparum: in vitro growth inhibition by febrile temperatures". In: *Parasitology research* 87.7 (2001), pp. 553–555.

[145] Bertrand Lell et al. "Effect of antipyretic drugs in children with malaria". In: *Clinical infectious diseases* 32.5 (2001), pp. 838–841.

[146] Martin M Meremikwu et al. "Antipyretic measures for treating fever in malaria". In: *Cochrane Database of Systematic Reviews* 9 (2012).

[147] Michael Logan. "Did pathogens facilitate the rise of endothermy?" In: *Ideas in Ecology and Evolution* 12 (2019).

[148] Thomas J. Lee et al. "Honest Signaling and the Uses of Prey Coloration". In: *The American Naturalist* 178.1 (2011), E1–E9. URL: http://www.jstor.org/stable/10.1086/660197.

[149] Shigeo Yachi. "How can honest signalling evolve? The role of handicap principle". In: *Proceedings of the Royal Society of London. Series B: Biological Sciences* 262.1365 (1995), pp. 283–288.

[150] Pierre-Stéphane Gsell et al. "Ring vaccination with rVSV-ZEBOV under expanded access in response to an outbreak of Ebola virus disease in Guinea, 2016: an operational and vaccine safety report". In: *The Lancet infectious diseases* 17.12 (2017), pp. 1276–1284.

[151] Amy Maxmen. "Ebola vaccine approved for use in ongoing outbreak". In: *Nature News* (2017).

[152] Maxwell J Smith et al. "Emergency use authorisation for COVID-19 vaccines: lessons from Ebola". In: *The Lancet* 396.10264 (2020), pp. 1707–1709.

[153] World Health Organization. *New emergency use listing procedure (EUL)*. Geneva, Switzerland, 2020. URL: https://www.who.int/publications/m/item/emergency-use-listing-procedure.

[154] Louise Cummings. "Emerging infectious diseases: Coping with uncertainty". In: *Argumentation* 23.2 (2009), pp. 171–188.

[155] C Degeling et al. "One Health and Zoonotic Uncertainty in Singapore and Australia: Examining Different Regimes of Precaution in Outbreak Decision-Making". In: *Public Health Ethics* 13.1 (2020), pp. 69–81.

[156] Sam Moore et al. "Modelling optimal vaccination strategy for SARS-CoV-2 in the UK." In: *medRxiv* (2020).

[157] H. Holden Thorp. "A dangerous rush for vaccines". In: *Science* 369.6506 (2020), pp. 885–885. eprint: https://science.sciencemag.org/content/369/6506/885.full.pdf. URL: https://science.sciencemag.org/content/369/6506/885.

[158] Jesse L. Goodman and Luciana Borio. "Finding Effective Treatments for COVID-19: Scientific Integrity and Public Confidence in a Time of Crisis". In: *JAMA* 323.19 (May 2020), pp. 1899–1900. eprint: https://jamanetwork.com/journals/jama/articlepdf/2764823/jama_goodman_2020_vp_200077.pdf. URL: https://doi.org/10.1001/jama.2020.6434.

[159] Boris Johnson. "Prime Minister's speech to the United Nations General Assembly: 26 September 2020". In: (2020). URL: https://www.gov.uk/government/speeches/prime-ministers-speech-to-un-general-assembly-26-september-2020.

[160] David Cyranoski. "What China's speedy COVID vaccine deployment means for the pandemic." In: *Nature* (2020), pp. 343–344.

[161] Talha Khan Burki. "The Russian vaccine for COVID-19". In: *The Lancet Respiratory Medicine* 8.11 (2020), e85–e86.

[162] Institute of Medicine. *Environmental Decisions in the Face of Uncertainty*. Washington, D.C.: National Academies Press, 2013.

[163] Loıc Berger et al. "Uncertainty and decision-making during a crisis: How to make policy decisions in the COVID-19 context?" In: *University of Chicago, Becker Friedman Institute for Economics Working Paper* 2020-95 (2020).

[164] Marieka A Helou et al. "Uncertainty in decision-making in medicine: A scoping review and thematic analysis of conceptual models". In: *Academic medicine: journal of the Association of American Medical Colleges* 95.1 (2020), p. 157.

[165] Elisabeth Fenwick et al. "Value of information analysis for research decisions—an introduction: report 1 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force". In: *Value in Health* 23.2 (2020), pp. 139–150.

[166] Jan B Oostenbrink et al. "Expected value of perfect information: an empirical example of reducing decision uncertainty by conducting additional research". In: *Value in Health* 11.7 (2008), pp. 1070–1080.

[167] World Health Organisation. "WHO Health Emergency Dashboard: New Zealand". In: (2021). URL: https://covid19.who.int/region/wpro/country/nz.

[168] Komal Shah, Deepak Saxena, and Dileep Mavalankar. "Secondary Attack Rate of COVID-19 in household contacts: Systematic review". In: *QJM: An International Journal of Medicine* (2020).

[169] N Brazeau et al. "Report 34: COVID-19 infection fatality ratio: estimates from seroprevalence". In: (2020).

[170] Rebecca A Johnson et al. "Risks of phase I research with healthy participants: a systematic review". In: *Clinical Trials* 13.2 (2016), pp. 149–160.

[171] Rajesh Kumar and Edith A Burns. "Age-related decline in immunity: implications for vaccine responsiveness". In: *Expert review of vaccines* 7.4 (2008), pp. 467–479.

[172] Derek J Smith et al. "Variable efficacy of repeated annual influenza vaccination". In: *Proceedings of the National Academy of Sciences* 96.24 (1999), pp. 14001–14006.

[173] Fernando P. Polack et al. “Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine”. In: *New England Journal of Medicine* 0.0 (0), null. eprint: https://doi.org/10.1056/NEJMoa2034577. URL: https://doi.org/10.1056/NEJMoa2034577.

[174] Moderna. “Moderna’s COVID-19 Vaccine Candidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study”. In: (2020). URL: https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy.

[175] Merryn Voysey et al. “Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK”. In: *The Lancet* (2020).

[176] MHRA. “Coronavirus vaccine - weekly summary of Yellow Card reporting: updated 24 June 2021”. In: (2021). URL: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting#analysis-of-data.

[177] Tom Shimabukuro. “COVID-19 Vaccine safety updates. Advisory Committee on Immunization Practices (ACIP), June 23, 2021”. In: (2021). URL: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/03-COVID-Shimabukuro-508.pdf.

[178] Chi Heem Wong, Kien Wei Siah, and Andrew W Lo. “Estimation of clinical trial success rates and related parameters”. In: *Biostatistics* 20.2 (Jan. 2018), pp. 273–286. eprint: https://academic.oup.com/biostatistics/article-pdf/20/2/273/32914001/kxx069.pdf. URL: https://doi.org/10.1093/biostatistics/kxx069.

[179] Willem Huisman et al. “Vaccine-induced enhancement of viral infections”. In: *Vaccine* 27.4 (2009), pp. 505–512.

[180] Wen Shi Lee et al. “Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies”. In: *Nature microbiology* 5.10 (2020), pp. 1185–1191.

[181] Sunil S Bhopal and Raj Bhopal. “Sex differential in COVID-19 mortality varies markedly by age”. In: *Lancet (London, England)* (2020).

[182] Ladan Golestaneh et al. “The association of race and COVID-19 mortality”. In: *EClinicalMedicine* 25 (2020), p. 100455.

[183] Paddy Ssentongo et al. “Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis”. In: *PloS one* 15.8 (2020), e0238215.

[184] Henock G Yebyo et al. “Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: a systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants”. In: *American heart journal* 210 (2019), pp. 18–28.

[185] Colin Baigent et al. “Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials.” In: *Lancet* 373.9678 (2009), pp. 1849–1860.

[186] Kenneth R McQuaid and Loren Laine. "Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials". In: *The American journal of medicine* 119.8 (2006), pp. 624–638.

[187] Donald A Berry et al. *A cost/benefit analysis of clinical trial designs for COVID-19 vaccine candidates*. Tech. rep. National Bureau of Economic Research, 2020.

[188] David Wallace-Wells. "We Had the Vaccine the Whole Time". In: (2020). URL: https://nymag.com/intelligencer/2020/12/moderna-covid-19-vaccine-design.html.

[189] Nir Eyal, Marc Lipsitch, and Peter G Smith. "Human challenge studies to accelerate coronavirus vaccine licensure". In: *The Journal of infectious diseases* 221.11 (2020), pp. 1752–1756.

[190] Metaculus. "COVID-19 vaccine administered to 10K people in 2020?" In: (2020). URL: https://www.metaculus.com/questions/3655/will-a-vaccine-targeted-at-the-2019-novel-coronavirus-covid-19-be-administered-to-at-least-10000-people-in-2020/.

[191] Public Health England. *COVID-19 vaccination first phase priority groups*. [Online; accessed 19-May-2022]. 2021. URL: https://www.gov.uk/government/publications/covid-19-vaccination-care-home-and-healthcare-settings-posters/covid-19-vaccination-first-phase-priority-groups.

[192] World Health Organisation. *WHO SAGE Roadmap for prioritising uses of COVID-19 vaccines in the context of limited supply*. [Online; accessed 19-May-2022]. 2020. URL: https://www.who.int/docs/default-source/immunization/sage/covid/sage-prioritization-roadmap-covid19-vaccines.pdf?Status=Temp&sfvrsn=bf227443_2&ua=1.

[193] Kathleen Dooling. "The Advisory Committee on Immunization Practices' updated interim recommendation for allocation of COVID-19 vaccine—United States, December 2020". In: *MMWR. Morbidity and mortality weekly report* 69 (2021).

[194] Ashleigh R Tuite et al. "Alternative dose allocation strategies to increase benefits from constrained COVID-19 vaccine supply". In: *Annals of internal medicine* 174.4 (2021), pp. 570–572.

[195] Seyed M Moghadas et al. "Evaluation of COVID-19 vaccination strategies with a delayed second dose". In: *PLoS biology* 19.4 (2021), e3001211.

[196] Ingrid Torjesen. *Covid-19: First doses of vaccines in Scotland led to a substantial fall in hospital admissions*. 2021.

[197] S Alexandar et al. "A comprehensive review on Covid-19 Delta variant". In: *International Journal of Pharmacology and Clinical Research (IJPCR)* 5.83-85 (2021), p. 7.

[198] Sophie M-C Gobeil et al. "Structural diversity of the SARS-CoV-2 Omicron spike". In: *Molecular cell* (2022).

[199] Houriiyah Tegally et al. "Continued Emergence and Evolution of Omicron in South Africa: New BA. 4 and BA. 5 lineages". In: *medRxiv* (2022).

[200] Brit Trogen and Arthur Caplan. *Risk compensation and COVID-19 vaccines*. 2021.

[201] Eleni Mantzari, G James Rubin, and Theresa M Marteau. "Is risk compensation threatening public health in the covid-19 pandemic?" In: *Bmj* 370 (2020).

[202] "Department of Health and Social Care". *UK COVID-19 vaccines delivery plan*. Tech. rep. [Online; accessed 19-May-2022]. HM Government, 2021. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/951928/uk-covid-19-vaccines-delivery-plan-final.pdf.

[203] Quebec.ca. *COVID-19 vaccination*. [Online; accessed 19-May-2022]. 2022. URL: https://www.quebec.ca/en/health/advice-and-prevention/vaccination/covid-19-vaccine/.

[204] NHS England. *COVID-19 vaccination programme: FAQs on second doses*. [Online; accessed 19-May-2022]. 2021. URL: https://www.england.nhs.uk/coronavirus/documents/covid-19-vaccination-programme-faqs-on-second-doses/.

[205] Noa Dagan et al. "BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting". In: *New England Journal of Medicine* (2021).

[206] David A Henry et al. "Effectiveness of COVID-19 vaccines: findings from real world studies". In: *The Medical Journal of Australia* 215.4 (2021), p. 149.

[207] Julia Shapiro et al. "Efficacy estimates for various COVID-19 vaccines: what we know from the literature and reports". In: *medRxiv* (2021).

[208] Eleftheria Vasileiou et al. "Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study". In: *The Lancet* 397.10285 (2021), pp. 1646–1657.

[209] Lianlian Bian et al. "Impact of the Delta variant on vaccine efficacy and response strategies". In: *Expert review of vaccines* 20.10 (2021), pp. 1201–1209.

[210] Shirley Collie et al. "Effectiveness of BNT162b2 vaccine against omicron variant in South Africa". In: *New England Journal of Medicine* 386.5 (2022), pp. 494–496.

[211] SO Minka and FH Minka. "A tabulated summary of the evidence on humoral and cellular responses to the SARS-CoV-2 Omicron VOC, as well as vaccine efficacy against this variant." In: *Immunology Letters* 243 (2022), pp. 38–43.

[212] Jan M Brauner et al. "Inferring the effectiveness of government interventions against COVID-19". In: *Science* 371.6531 (2021), eabd9338.

[213] Santiago Romero-Brufau et al. "Public health impact of delaying second dose of BNT162b2 or mRNA-1273 covid-19 vaccine: simulation agent based modeling study". In: *bmj* 373 (2021).

[214] Edward M Hill and Matt J Keeling. "Comparison between one and two dose SARS-CoV-2 vaccine prioritization for a fixed number of vaccine doses". In: *Journal of the Royal Society Interface* 18.182 (2021), p. 20210214.

[215] Paulo JS Silva et al. "Optimized delay of the second COVID-19 vaccine dose reduces ICU admissions". In: *Proceedings of the National Academy of Sciences* 118.35 (2021), e2104640118.

[216] Sara Y Tartof et al. “Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study”. In: *The Lancet* 398.10309 (2021), pp. 1407–1416.

[217] Theodore Lytras et al. “Comparative effectiveness and durability of COVID-19 vaccination against death and severe disease in an ongoing nationwide mass vaccination campaign”. In: *Journal of Medical Virology* 94.10 (2022), pp. 5044–5050.

[218] Jing Lian Suah et al. “Waning COVID-19 vaccine effectiveness for BNT162b2 and CoronaVac in Malaysia: an observational study”. In: *International Journal of Infectious Diseases* 119 (2022), pp. 69–76.

[219] Daniel R Feikin et al. “Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression”. In: *The Lancet* (2022).

[220] Cristina Menni et al. “COVID-19 vaccine waning and effectiveness and side-effects of boosters: A prospective community study from the ZOE COVID Study”. In: *The Lancet Infectious Diseases* 22.7 (2022), pp. 1002–1010.

[221] Yair Goldberg et al. “Protection and waning of natural and hybrid immunity to SARS-CoV-2”. In: *New England Journal of Medicine* 386.23 (2022), pp. 2201–2212.

[222] Anyin Feng et al. “Modelling COVID-19 vaccine breakthrough infections in highly vaccinated Israel—the effects of waning immunity and third vaccination dose”. In: *PLOS Global Public Health* 2.11 (2022), e0001211.

[223] Amy Flaxman et al. “Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002)”. In: *The Lancet* 398.10304 (2021), pp. 981–990.

[224] Alexandra Tauzin et al. “Strong humoral immune responses against SARS-CoV-2 Spike after BNT162b2 mRNA vaccination with a 16-week interval between doses”. In: *Cell host & microbe* 30.1 (2022), pp. 97–109.

[225] Natsuko Imai et al. “Quantifying the effect of delaying the second COVID-19 vaccine dose in England: a mathematical modelling study”. In: *The Lancet Public Health* 8.3 (2023), e174–e183.

[226] "Pandemic Preparedness Partnership". *100 Days Mission to respond to future pandemic threats*. Tech. rep. [Online; accessed 19-May-2022]. HM Government, 2022. URL: `https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/992762/100_Days_Mission_to_respond_to_future_pandemic_threats__3_.pdf`.

[227] Witold Więcek et al. “Testing fractional doses of COVID-19 vaccines”. In: *Proceedings of the National Academy of Sciences* 119.8 (2022), e2116932119.

[228] Brad Spellberg and Bonnie Taylor-Blake. “On the exoneration of Dr. William H. Stewart: debunking an urban legend”. In: *Infectious Diseases of Poverty* 2.1 (2013), pp. 1–5.

[229] Institute of Health Metrics and Evaluation (IHME). *GBD Results*. [Online; accessed 19-May-2022]. 2022. URL: https://vizhub.healthdata.org/gbd-results/.

[230] Andrew Noymer and Michel Garenne. "The 1918 influenza epidemic's effects on sex differentials in mortality in the United States". In: *Population and development review* 26.3 (2000), pp. 565–581.

[231] Nazrul Islam et al. "Effects of covid-19 pandemic on life expectancy and premature mortality in 2020: time series analysis in 37 countries". In: *bmj* 375 (2021).

[232] Ursula Hofer. "The cost of antimicrobial resistance". In: *Nature Reviews Microbiology* 17.1 (2019), pp. 3–3.

[233] Nita Madhav et al. "Pandemics: risks, impacts, and mitigation". In: (2018).

[234] David M Morens and Anthony S Fauci. "Emerging pandemic diseases: how we got to COVID-19". In: *Cell* 182.5 (2020), pp. 1077–1092.

[235] "National Intelligence Council". *Updated Assessment on COVID-19 Origins*. Tech. rep. [Online; accessed 19-May-2022]. US Government, 2021. URL: https://www.dni.gov/files/ODNI/documents/assessments/Declassified-Assessment-on-COVID-19-Origins.pdf.

[236] David Manheim and Gregory Lewis. "High-risk human-caused pathogen exposure events from 1975-2016". In: *F1000Research* 10.752 (2021), p. 752.

[237] Michelle Rozo and Gigi Kwik Gronvall. "The reemergent 1977 H1N1 strain and the gain-of-function debate". In: *MBio* 6.4 (2015), e01013–15.

[238] W Seth Carus. *Bioterrorism and biocrimes: the illicit use of biological agents since 1900*. The Minerva Group, Inc., 2002.

[239] W Seth Carus. "A century of biological-weapons programs (1915–2015): reviewing the evidence". In: *The Nonproliferation Review* 24.1-2 (2017), pp. 129–153.

[240] Milton Leitenberg, Raymond A Zilinskas, and Jens H Kuhn. "The Soviet biological weapons program". In: *The Soviet Biological Weapons Program*. Harvard University Press, 2012.

[241] Sander Herfst et al. "Airborne transmission of influenza A/H5N1 virus between ferrets". In: *science* 336.6088 (2012), pp. 1534–1541.

[242] Xuping Xie et al. "Engineering SARS-CoV-2 using a reverse genetic system". In: *Nature protocols* 16.3 (2021), pp. 1761–1784.

[243] Tanner S Miest et al. "Envelope-chimeric entry-targeted measles virus escapes neutralization and achieves oncolysis". In: *Molecular Therapy* 19.10 (2011), pp. 1813–1820.