A pragmatic approach to account for individual risks to optimise health policy

M. Gabriela M. Gomes,1,2*

1 University of Strathclyde, Glasgow, United Kingdom.
2 Centro de Matemática da Universidade do Porto, Porto, Portugal.
* Correspondence to: gabriela.gomes@strath.ac.uk.

Developing feasible strategies and setting realistic targets for disease prevention and control depends on representative models, whether conceptual, experimental, logistical or mathematical. Mathematical modelling was established in infectious diseases over a century ago, with the seminal works of Ross1 and others. Propelled by the discovery of aetiological agents for infectious diseases, and Koch’s postulates, models have focused on the complexities of pathogen transmission and evolution to understand and predict disease trends in greater depth. This has led to their adoption by policy makers; however, as model-informed policies are being implemented, the inaccuracies of some predictions are increasingly apparent, most notably their tendency to overestimate the impact of control interventions3-6. Here, we discuss how these discrepancies could be explained by methodological limitations in capturing the effects of heterogeneity in real-world systems. We suggest that improvements could derive from theory developed in demography to study variation in life-expectancy and ageing7. Using simulations, we illustrate the problem and its impact, and formulate a pragmatic way forward.

HETEROGENEITY AFFECTS ACCURACY OF PREDICTIVE MODELS FOR DISEASE CONTROL

We use the examples of acquired immunodeficiency syndrome (AIDS) and coronavirus disease 2019 (COVID-19) to illustrate the effects that individual variation can have on the performance of mathematical models for the dynamics of endemic and epidemic diseases.

Endemic infectious diseases

Since the detection of AIDS in the early 1980s, it has been evident that heterogeneity in individual sexual behaviours needed to be considered in mathematical models for the transmission of the causative agent – the Human Immunodeficiency Virus (HIV)8. Much research has been devoted to measuring contact networks in diverse settings and by different methods, to attempt to reproduce transmission dynamics accurately9-11. Meanwhile other equally important sources of inter-individual variation were overlooked. For example, unmodelled heterogeneity in infectiousness and susceptibility led to over-attribution of HIV infectivity to the acute phase12 and, consequently, to concerns that interventions relying on treatment as prevention might be compromised.

The problem of unaccounted heterogeneity in predictive models can be illustrated with the simplest mathematical description of infectious disease transmission in a host population. Figure 1 shows the prevalence of infection over time under three alternative scenarios: all individuals are at equal risk of acquiring infection (black trajectories [notice unrealistic time scale]); individual risk is affected by a factor that modifies either their susceptibility to infection (blue) or exposure through connectivity with other individuals (green). Risk modifying factors are drawn from a distribution with mean one (blue and green density plots on the left) while the
homogeneous scenario is sketched by assigning a factor one to all individuals (black frequency plot). As the virus spreads in the human population, individuals at higher risk are predominantly infected as indicated at endemic equilibrium (Figure 1 A, B, C, density plots on the right, coloured red) and after 100 years of control (Figure 1 D, E, F). The control strategy applied to endemic equilibrium in the figure is the 90-90-90 treatment as prevention target advocated by the Joint United Nations Programme on HIV/AIDS whereby 90% of infected individuals should be detected, with 90% of these receiving antiretroviral therapy, and 90% of these should achieve viral suppression (becoming effectively non-infectious).

Figure 1: Prevalence trajectories under homogeneous and heterogeneous models. Risk distributions are simulated in three scenarios: homogeneous (A, D); distributed susceptibility to infection with variance 10 (B, E); distributed connectivity with variance 10 (C, F). In disease-free equilibrium, individuals differ in potential risk in scenarios B and C, but not in scenario A (risk panels on the left). The vertical lines mark the mean risk values (1 in all cases). At endemic equilibrium, individuals with higher risk are predominantly infected (risk panels on the right, where red vertical lines mark mean baseline risk among individuals who eventually became infected), resulting in reduced mean risk among those who remain uninfected (black vertical lines). To compensate for this selection effect, heterogeneous models require a higher $R_0$ to attain the same endemic prevalence (A, B, C). Interventions that reduce infection also reduce selection pressure, which unintendedly increases mean risk in the uninfected poll and undesirably reduces intervention impact (D, E, F). Models: homogeneous (A, D) $dS/dt = \mu - \beta IS - \mu S$, $dI/dt = \beta IS - \mu I$, and $R_0 = \beta/\mu$; heterogeneous susceptibility (B, E) $dS(x)/dt = q(x)\mu - \beta \int I(u)du xS(x) - \mu S(x)$, $dI(x)/dt = \beta \int I(u)du xS(x) - \mu I(x)$, and $R_0 = \langle x \rangle \beta/\mu$; heterogeneous connectivity (C, F) $dS(x)/dt = q(x)\mu - \beta \int uI(u)du / \int uq(u)du xS(x) - \mu S(x)$, $dI(x)/dt = \beta \int uI(u)du / \int uq(u)du xS(x) - \mu I(x)$, and $R_0 = \langle x^2 \rangle \beta/\mu \mu$. In heterogeneous models, $q(x)$ is a probability density function with mean 1 and variance 10, and $\langle x^i \rangle$ denotes the $i^{th}$-moment of the distribution. Gamma distributions were used for concreteness.
Figure 1 shows that heterogeneous models that account for wide biological and social variation require higher basic reproduction numbers ($R_0$) to reach a given endemic level and predict less impact for control efforts when compared with the homogeneous counterpart model. This holds true regardless of whether heterogeneity affects susceptibility or connectivity. At endemic equilibrium, individuals at higher risk are predominantly infected (red distributions have mean greater than one as marked by the red vertical lines), and hence those who remain uninfected are individuals with lower risk (blue and green distributions have mean lower than one as marked by the black vertical lines). Thus, the mean risk in the uninfected but susceptible subpopulation decreases, and the epidemic decelerates (thin blue and green curves); higher values of $R_0$ are consequently required if the heterogeneous models are to attain the same endemic level as the homogeneous formulation (heavy blue and green curves). Finally, interventions are less impactful under heterogeneity because $R_0$ is implicitly higher. Indeed, these biases could help explain trends in HIV incidence data which lag substantially behind targets informed by model predictions, even in settings that have reached the 90-90-90 implementation targets $^{3,4}$.

Epidemic infectious diseases

A novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) isolated at the end of 2019 from a patient in China has spread worldwide causing the COVID-19 pandemic, despite intensive measures to contain the outbreak at the source. Countrywide epidemics have been extensively analysed and modelled throughout the world. Initial studies projected attack rates of around 90% if transmission had been left unmitigated $^{13}$, while subsequent reports noted that individual variation in susceptibility or exposure to infection might reduce these estimates substantially $^{14,15}$ and skew epidemic curves (compare the blue [heterogeneous susceptibility] and green [heterogeneous connectivity] curves with the black [homogeneous]).

**Figure 2: Incidence trajectories under homogeneous and heterogeneous models.** Risk distributions are simulated in three scenarios: homogeneous (black); distributed susceptibility to infection with variance 10 (blue); and distributed connectivity with variance 10 (green). Left panels represent distributions of potential individual risk prior to the outbreak, with vertical lines marking mean risk values (1 in all cases). As the epidemic progresses, individuals with higher risk are predominantly infected, depleting the susceptible pool in a selective manner and decelerating the epidemic. The inset overlays the three epidemic curves scaled to the same height to facilitate shape comparison. Right panels show in red the risk distributions among individuals who have been infected over 4 months of epidemic spread (mean greater than one when risk is heterogeneous, as marked by red vertical lines) and the reduced mean
risk among those who have not been affected (black vertical lines). Models: homogeneous (black) \( dS/dt = -\beta IS \), \( dI/dt = \beta IS - \gamma I \), and \( R_0 = \beta/\gamma \); heterogeneous susceptibility (blue) \( dS(x)/dt = -\beta \int I(u)dxS(x) \), \( dI(x)/dt = \beta \int I(u)dxS(x) - \gamma I(x) \), and \( R_0 = \langle x \rangle \beta/\gamma \); heterogeneous connectivity (green) \( dS(x)/dt = -\beta \int uI(u)du/\int uq(u)du.xS(x) \), \( dI(x)/dt = \beta \int uI(u)du/\int uq(u)du.xS(x) - \gamma I(x) \), and \( R_0 = \langle x^2 \rangle \beta/\gamma \). In heterogeneous models, \( q(x) \) is a probability density function with mean 1 and variance 10, and \( \langle x^i \rangle \) denotes the \( i^{th} \) moment of the distribution. Gamma distributions were used for concreteness.

As models inform policies, we cannot but stress the importance of representing individual variation pragmatically. While much is being discovered about SARS-CoV-2 and its interaction with human hosts, epidemic curves are widely available from locations where the virus has been circulating. Models can be constructed with inbuilt risk distributions whose shape can be inferred by assessing their ability to mould simulated trajectories to observed epidemics while accounting for realistic social distancing interventions

Variation in infectiousness was critical to attribute the scarce and explosive outbreaks to superspreaders when the first SARS emerged in 2002, but what we are discussing here is different. Infectiousness does not respond to selection as susceptibility or connectivity do, i.e. models with and without variation in infectiousness perform equivalently when implemented deterministically and only differ through stochastic processes.

The need to account for heterogeneity in risk to acquire infections is not restricted to AIDS and COVID-19 but is generally applicable across infectious disease epidemiology models. Moreover, similar issues arise in methods intended to evaluate the efficacy interventions from experimental studies as illustrated for vaccines in the sequel.

**HETEROGENEITY AND VACCINE EFFICACY OVER TIME AND ACROSS SETTINGS**

Individual variation in susceptibility to infection induces biases in cohort studies and clinical trials. Vaccine efficacy trials offer a useful illustration of the problem and give insight into the potential solution. In a vaccine trial, two groups of individuals are randomised to receive a vaccine or placebo and disease occurrences are recorded in each group. As disease affects predominantly higher-risk individuals, the mean risk among those who remain unaffected decreases and disease incidence declines. In the vaccine group the same trend will occur at a slower pace (presuming that the vaccine protects to some degree). As a result, the two randomised groups become different over time with more highly susceptible individuals remaining in the vaccine group. The vaccine efficacy, described as a ratio of cases in vaccinated compared to control group, therefore appears to wane (Figure 3). This effect will be stronger in settings where transmission intensity is higher, inducing a trend of seemingly declining efficacy with disease burden. The concept is illustrated in Figure 3 by simulating a vaccine trial with heterogeneous and homogeneous models analogous to those utilised in Figures 1 and 2.

Selection on individual variation in disease susceptibility thus offers an explanation for vaccine efficacy trends that is entirely based on population level heterogeneity, in contrast with waning vaccine-induced immunity, an individual-level effect. As both processes may occur concurrently in a trial, it is important to disentangle their roles, as they lead to different interpretations of the same incidence trend. For example, vaccine efficacy might wane in all individuals, or it might be constant for each individual but decline at the population level due to selection on individual variation. To capture this in a timely manner requires multicentre trial designs with sites carefully selected over a gradient of transmission intensities (e.g. optimally
spaced along the incidence axis in Figure C, F), and analyses performed by fitting curves generated by models that incorporate individual heterogeneity. An alternative and more tightly controlled approach would be to use experimental designs in human infection challenge studies where these are available to generate dose-response curves and apply similar models. These approaches have recently been successfully tested in animal systems.

Figure 3: Vaccine efficacy trajectories under homogeneous and heterogeneous models. A,B,C, Heterogeneous susceptibility or connectivity (gamma-distributed with mean 1 and variance 10); D,E,F, Homogeneous model. Models: (homogeneous) \( \frac{dS_c}{dt} = -\lambda S_c, \frac{dl_c}{dt} = \lambda S_c, \) and \( \frac{dS_v}{dt} = -\sigma l_S, \frac{dl_v}{dt} = \sigma S_v; \) (heterogeneous) \( \frac{dS_c(x)}{dt} = -\lambda xS_c(x), \frac{dl_c(x)}{dt} = \lambda xS_c(x), \) and \( \frac{dS_v(x)}{dt} = -\sigma xS_c(x), \frac{dl_v(x)}{dt} = \sigma xS_v(x). \) Vaccine efficacy is calculated as \( [1 - r_v(t)/r_c(t)] \times 100, \) where \( r_v \) and \( r_c \) represent the incidences in vaccinated and control group, respectively: (homogeneous) \( r_c(t) = \lambda; r_v(t) = \sigma \lambda; \) (heterogeneous) \( r_c(t) = \lambda \int xS_c(x,t)dx/\int S_c(x,t)dx; r_v(t) = \sigma \lambda \int xS_v(x,t)dx/\int S_v(x,t)dx. \)

INDIVIDUAL HETEROGENEITIES AND THEIR INFERENCE USING RISK INEQUALITY METRICS

Heterogeneities in predispositions to infection depend on the mode of transmission but play a role in all high-burden infectious diseases. In respiratory infections, heterogeneity may arise from a variation in exposure of the susceptible host to the pathogen, or the competence of host immune systems to control pathogenic viruses or bacteria. These two processes have multiple
component factors. Some of the most studied are age, patterns of inter-personal contacts, exposure to smoke, nutritional status, pre-existing respiratory illness such as asthma or chronic obstructive pulmonary disease, and the presence of other concomitant diseases such as diabetes and HIV. Enteric diseases have different heterogeneities determined by the source and dose of contaminated sources. Vector-borne parasites, viruses and bacteria may be transmitted by mosquitoes, ticks, snails, and other intermediate hosts, where the risk of onward transmission is affected by heterogeneities in exposure and susceptibility across a complex range of host, demographic, environmental and social factors.

The mechanisms underpinning single factors for infection and their interactions determine individual propensities to acquire disease. These are potentially so numerous that to attain a full mechanistic description may be unfeasible. Even in the unlikely scenario that a list of all putative factors may be available, the measurement of effect sizes would be subject to selection within cohorts resulting in underestimated variances. To contribute constructively to the development of health policies, model building involves compromises between leaving factors out (reductionism) or adopting a broader but coarse description (holism). Holistic descriptions of heterogeneity are currently underutilised in infectious diseases.

Recently, measures of statistical dispersion commonly used in economics have been adapted to describe risk inequality in cancer, tuberculosis and malaria, offering a holistic approach to improve the predictive capacity of disease models. Essentially, this involves stratifying the population into groups of individuals with similar risk, which may be as granular as individual level for frequent diseases, such as malaria or influenza. For infectious diseases which cluster by proximity, such as tuberculosis, stratification can use geographical units. Familial relatedness pertains when there is a clear genetic contribution to risk, such as cancer. By recording disease events in each group, specific incidence rates can be calculated and ranked. Unknown distributions of individual risk are then embedded in dynamic models and estimated by fitting the models to the stratified data. Because they incorporate explicit distributions of individual risk, these models automatically adjust average risks in susceptible pools to changes in transmission intensity, occurring naturally or in response to interventions. Not subject to the selection biases described above, this model approach inherently enables more accurate impact predictions for use in policy development.

CONCLUSION

There is compelling evidence that epidemiologists could use indicators that account for the whole variation in disease risk. Heterogeneity is unlimited in real-world systems and cannot be completely reconstructed mechanistically. Inspired by established practices in demography and economics and supported by successful applications in both infectious and non-communicable diseases, the use and further development of these approaches offers a powerful route to build disease models that enable more accurate estimates of intervention efficacy and more accurate predictions of the impact of control programmes.

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