NEWS & VIEWS


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EPIDEMIOLOGY

Dimensions of superspreading

Alison P. Galvani and Robert M. May

Analyses of contact-tracing data on the spread of infectious disease, combined with mathematical models, show that control measures require better knowledge of variability in individual infectiousness.

The SARS epidemic was notable for the existence of 'superspreaders' who infected dozens of people, whereas other infectious individuals infected few or none. Were SARS superspreaders anomalies, or are superspreaders characteristic of most infectious diseases? What effects does heterogeneity in infectiousness have on disease emergence and control? On page 355 of this issue, Lloyd-Smith *et al.*[1] provide insight into such questions, and more.

The first question any ecologist asks about an invasive species is: what is the invader's intrinsic capacity for population increase? To answer this, the species' basic reproductive number, R_0, is measured by the average number of offspring per capita that survive to reproductive age. For a directly transmitted infectious disease, be it polio, smallpox, SARS, HIV/AIDS or some newly emerging pathogen, R_0 is the average number of infections produced by an infected individual in a susceptible population[2]. If R_0 is less than one, a self-sustaining epidemic is not possible (at least without further pathogen evolution). If R_0 exceeds one, then although early stochastic fluctuations may extinguish the invader, an epidemic is possible. If R_0 is large, an epidemic is virtually certain.

Initial work in this area largely treated individuals in populations as having an equal chance of transmitting disease — that is, as being homogeneous — and ignored stochastic fluctuations in transmission capability. However, studies of gonorrhoea[3], and of HIV/AIDS[4], could not explain epidemiological patterns without acknowledging heterogeneities in patterns of sexual-partner acquisition, including the disproportionate influence of superspreaders. Similarly, knowledge of heterogeneous parasite burdens is fundamental to accurate modelling of helminthic diseases[5,6]. Explanations of epidemiological patterns of malaria also depend on understanding heterogeneous biting by the mosquito vector[7].

These observations led to the proposal of the 20/80 rule[2,8], which suggests that roughly 20% of the most infectious individuals are responsible for 80% of the transmission (Fig. 1, overleaf). This rule has been applied mainly to helminthic and sexually transmitted diseases[7]; for other directly transmitted diseases, such as smallpox or influenza, heterogeneity in infectiousness has been neglected. The superspreading that seemed to fuel the 2003 SARS epidemic was largely treated as anomalous in most models, but it highlighted the need for a reassessment of heterogeneous infectiousness[9].

Lloyd-Smith *et al.*[1] address this point by posing infectiousness as a continuous variable, and formulate an unambiguous and universally applicable definition of superspreaders as those who transmit more infection than is predicted by a homogeneous 'null model'. The authors analyse data from eight human infections, including SARS, measles, smallpox, monkeypox and pneumonic plague, to show that superspreading occurs across the board, although to a greater or lesser extent depending on the disease. Heterogeneity is greatest for SARS and least for Ebola haemorrhagic fever.

Analysis of the epidemiological dynamics shows that, for a given R_0, both the probability that an epidemic will take off, and the subsequent course of the epidemic, are affected by such heterogeneity. These results may be appreciated intuitively. For a given value of R_0, high heterogeneity in infectiousness implies that relatively few individuals are responsible for most of the transmission — or conversely, that many individuals do not transmit at all. In turn, such small numbers tend to generate pronounced stochastic fluctuations in the initial stages of the epidemic. Consequently, a heterogeneously infectious emerging disease will be

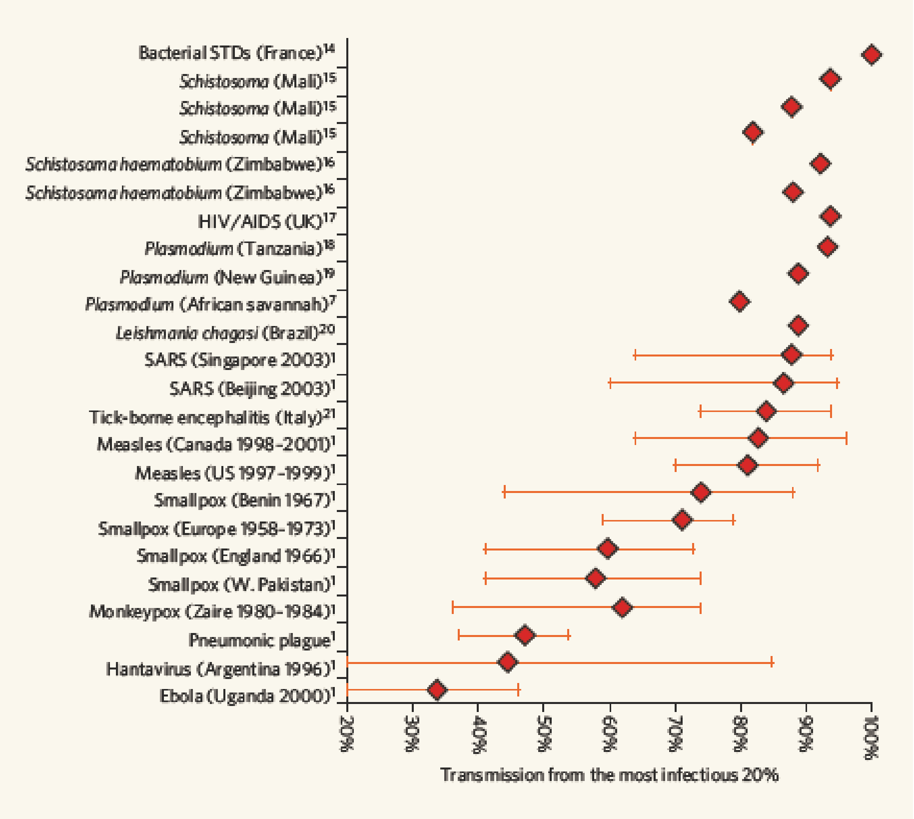

Figure 1 | Heterogeneity in infectiousness for a range of diseases. The measure used is the 20/XX index, which quantifies the proportion of the transmission (XX%) that results from the most infectious 20% of the population. Confidence intervals are included where available. The interval for tick-borne encephalitis (Italy)[21] indicates possible values depending on assumptions made about host susceptibility. STDs, sexually transmitted diseases; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; SARS, severe acute respiratory syndrome.

less likely to generate an epidemic, but if sustained, the resulting epidemic is more likely to be explosive. Thus, it is dangerous to underestimate a disease on the basis of frequent 'failed' attempts, as exemplified by bird flu.

The authors highlight the practical implications of their work. Control efforts should aim to identify the highly infectious superspreaders, and target vaccination or other interventions at them. In this way, the outbreak may be halted sooner, and with fewer people treated, than if efforts are directed at random individuals. Furthermore, Lloyd-Smith *et al.* distinguish between individual-specific and population-wide control measures (for example isolating individual patients as opposed to advising an entire population to reduce the behaviours associated with transmission). They show that individual-specific strategies are more likely to exterminate an emerging disease than population-wide interventions, because the former increase heterogeneity in infectiousness.

Comparisons can be drawn between these new findings[1] and work on heterogeneities in contact patterns among individuals (for example in SARS[10], or sexually transmitted diseases such as HIV/AIDS[4]) and among groups (foot-and-mouth disease, for instance[11]). Earlier research on contact patterns led to a generalized theorem (ref. 2; equation 12.23), which was based on the following reasoning. We can estimate the proportion, p^*, to be vaccinated or otherwise treated in order to eradicate infection in a homogeneous population ($p^* = 1 - 1/R_0$). However, if we take advantage of the heterogeneity, and target the more infectious or more sexually active individuals (depending on the disease), then we can achieve our aim by treating a smaller proportion than is estimated by p^*, as echoed in the results of Lloyd-Smith and colleagues. This general result, first discovered in the epidemiological literature in the mid-1980s, also applies to the structure of information-technology networks in relation to targeted versus random 'viral' attacks[12].

There are also differences between the work of Lloyd-Smith *et al.* and work on heterogeneities in contact patterns. Given that contact rates govern the likelihood both of becoming infected and of passing on infection, models based on heterogeneous contact rates have assumed perfect correlation between infectiousness and susceptibility. Consider HIV/AIDS, where in the simplest case $R_0 = \beta Dc$, with β being the transmission probability (a measure of the infectiousness of an infected individual), D the duration of the infectiousness, and c the average rate at which new sexual partners are acquired. Heterogeneities among individuals with respect to β or in D do not directly affect R_0 as such: the quantities β and D enter the dynamic equations linearly, and the appropriate values for estimating R_0 are just the simple averages.

By contrast, the distribution of partner-acquisition rates enters nonlinearly; those with more partners are more likely to acquire infection by virtue of their higher activity, and they are also more likely to transmit infection. Consequently, the epidemiologically appropriate 'average partner-acquisition rate', c, is not the mean of the distribution, but rather the mean-square divided by the mean. An incorrect result is obtained for R_0 when the average of the partner-acquisition or contact distribution is used. (This observation, incidentally, helps explain how large geographical variation in HIV incidence can arise from differences in the tails of such distributions.) In contrast, Lloyd-Smith *et al.* evaluate heterogeneity in overall R_0 (integrating all contributing factors), and assume that infectiousness is not correlated with susceptibility. As they note, the reality probably lies somewhere in between, with some intermediate level of correlation between infectiousness and susceptibility.

Although there is a considerable advantage in targeted control measures if highly infectious individuals can be identified before they have transmitted infection[1,8], this is easier said than done. In the case of sexually transmitted diseases and contact patterns, however, Cohen *et al.*[13] formulated a seemingly paradoxical method for achieving this aim, without directly identifying the active individuals. This procedure is based on the realization that one's contacts will on average be more highly connected within a contact network than oneself, simply by virtue of being a contact. Thus, highly connected individuals can be identified for intervention by first picking individuals at random, and then selecting randomly among their acquaintances. In this way, highly connected individuals are identified with minimal effort. Moreover, this procedure can be carried out either before or after an outbreak.

Among the next steps to be taken are further parametrization of heterogeneity for different diseases and for the same disease in different settings, and determination of the characteristics of emerging diseases that are likely to exhibit the most pronounced heterogeneity. Heterogeneous infectiousness, and its extreme manifestation of superspreading, are likely to be general properties of disease transmission in populations. The ambitious aim of controlling disease emergence will require a better understanding of those properties, which is most likely to be achieved through the combination of data analysis and epidemiological theory exemplified by Lloyd-Smith and colleagues' study. ■

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NANO-OPTICS

Gold loses its lustre

Roy Sambles

The perfect lens would immaculately reproduce an image of an object, with no light losses in the transition. The strange optical properties of a gold nanostructure bring the prospect of such a component into sharper focus.

As one luckless wooer in Shakespeare's *The Merchant of Venice* discovers, all that glisters is not gold. But what if gold did not 'glister' at all; what if it could, in fact, be made transparent? Such a material would be precious in itself — a potential basis for a 'perfect' lens. Writing in this issue, Grigorenko and colleagues (page 335)[1] present convincing evidence that they have produced nanostructured gold with remarkable optical properties. Although not quite perfect lens material, what they have made is a significant step towards that end.

Grigorenko and colleagues' gold demonstrates, when illuminated by visible light of certain polarizations and at certain incident angles, a characteristic known as negative permeability. To understand the context of this statement, we require some definitions. First, the permeability, μ, of a material expresses the extent to which an applied magnetic field is enhanced in that material: the higher the permeability, the more magnetic a material can become. A second, similar quantity, the permittivity ϵ of a material, relates to electric fields. In this case the definition is slightly different: large, positive permittivities are found in materials — namely insulators, or 'dielectrics' — that respond to an externally applied electric field to produce a distribution of stored charge that reduces the electric field within them. Finally, both the permeability and the permittivity of a material are related to its refractive index, n — the degree to which it bends incident electromagnetic radiation, such as light. This relationship is defined by the formula $n = (\mu\epsilon)^{1/2}$.

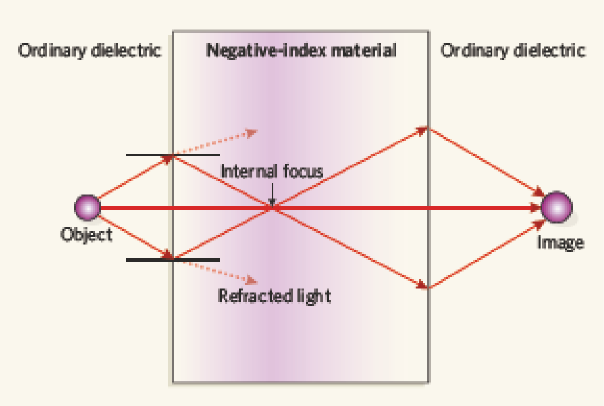

Figure 1 | Reverse swing. Light waves (arrows) from an external source will, at the interface between two materials of different refractive indices, bend towards or away from the normal to the interface (dotted arrows) but never beyond the normal. This limitation is overcome if one of the materials has a negative refractive index. The same thing happens at the second interface of the material, so it acts as a perfect lens, reproducing an image of an object. A conventional lens, which requires a curved surface, can never produce a perfect image because it will always fail to refocus the light that comes from the object in the form of decaying (evanescent) waves. Thus the image will not contain the information about the object carried by these waves.

So why is the negative permeability of Grigorenko and colleagues' material exciting? In answering this, it is important to appreciate that even normal metals are quite extraordinary in their response to light. Free electrons within metals readily respond to the electric field of incident electromagnetic radiation and thereby cancel it almost completely, provided that this field does not oscillate too quickly; so below a certain field frequency, called the plasma frequency, the real part of a metal's optical permittivity is negative. (Expressing permittivity as a complex number with a real and imaginary part is a mathematical construct that allows the wave nature of the fields involved to be taken into account; the imaginary part of permittivity, scaled by the imaginary unit i, is associated with the scattering of electrons and resultant heating in the material.)

Gold, for an incident electric field at red wavelengths, has an optical permittivity of about $-10+2i$, coupled with a normal, positive permeability. Taking these facts into account and using the formula for n, it can then be calculated that the refractive index of gold must be almost entirely imaginary. This is the mathematical equivalent of saying that the metal is opaque — it acts as a barrier to light, with the amplitude of the incident electric field decaying exponentially once inside the surface.

If the permeability of a metal such as gold were to be negative instead of positive, however, it turns out that it would have a negative refractive index[2,3]. Such a material will bend light in the opposite direction to normal materials, lending them their potential as perfect lenses[3]: a flat sheet of the material would focus the light to a perfect image on the other side of the sheet (Fig. 1).

This concept of materials of negative refractive index has been tested in the microwave region of the electromagnetic spectrum[4]. Here, it proved not too difficult to fabricate a resonant metallic material from components known as split-ring resonators, which have both negative permittivity and negative permeability for a small range of incident frequencies. But making a similar material that is responsive at higher frequencies in the visible range is not so easy, as it would require nanoscale split-ring resonators. Grigorenko and colleagues' contribution[1] is to overcome this barrier to a certain extent. They use nanofabrication procedures to make a patterned surface comprising tapered gold posts arranged periodically in pairs. Over a limited frequency range in the visible spectrum, these pairs behave as small, high-frequency bar magnets, much as split-ring resonators do when used at microwave frequencies. A characteristic of such bar magnets at optical frequencies is that they act to cancel the magnetic component of the incident radiation (Fig. 2, overleaf) — much like the action of the electrons in a metal is to