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INTERVENTION STUDIES AND THE DEFINITION OF DOMINANT TRANSMISSION ROUTES

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A common approach to assessing the relative importance of different transmission routes is to eliminate transmission through one route and assume that the ratio "number of cases eliminated:number of residual cases" measures the relative importance of the eliminated route *vis-à-vis* the residual transmission route. A quantitative model is used to generate synthetic data similar to those analyzed by epidemiologists. These data are analyzed using this conventional procedure and the inferences drawn from the synthetic data compared with the causal relationships structured into the model. The implications for the analysis of real-world data are analyzed by examining data on the importance of water and other transmission routes for cholera in Bangladesh.

cholera; diarrhea; environmental exposure; epidemiologic methods; models (theoretical); water

A SIMPLE (HYPOTHETICAL) EXPERIMENT IN DISEASE TRANSMISSION

The characteristics of the bacterium

The enteric bacterium, *Bacterium experimentus* causes a distinctive diarrhea. Extensive dose-response experiments have been conducted with human volunteers. The results, presented in figure 1, indicate that the dose-response relationship is precisely log-linear. The relationship can be expressed mathematically as follows for doses of up to 100 organisms:

$$\text{Probability of infection} = 0.5 \log_{10} (\text{dose}).$$

The Experiment

Different concentrations of the bacteria in water are prepared in the laboratory. Red cups contain exactly 70 bacteria, blue cups contain exactly 30 bacteria, and white cups contain no bacteria.

Three identical groups, of 100 volunteers each, are identified. Each volunteer drinks the contents of two or three cups according to the experimental design shown in table 1. In table 1, too, the expected number of cases of diarrhea in each group is calculated according to the known dose-response relationship.

Observations on diarrhea in the three groups are made, and it is observed that the number of cases was predicted perfectly in each case. *B. experimentus* proves an excellent bacterium for experiments!

Epidemiologic analysis of the data

Two epidemiologists, both with extensive experience in evaluating the impact of environmental interventions on health, are presented with different portions of the data in table 1. They are asked to draw conclusions on the relative contri-

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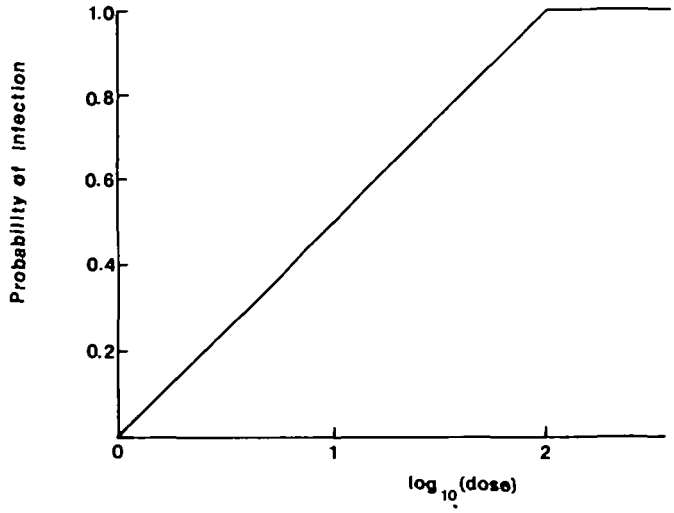

FIGURE 1. Dose-response curve for *B. experimentus*.

butions of the red, blue, and white cups to the development of disease in the volunteers.

The first epidemiologist is presented with the data in table 1 pertaining to Groups A and B. To this epidemiologist, Group A represents a group that is exposed to infection through several transmission routes, while Group B represents a group with similar exposure except that "route blue" is eliminated. Noting that the number of cases in Group B is only slightly smaller than the number of cases in Group A, the epidemiologist concludes that "route blue does not constitute an important transmission route" and that "virtually all transmission is through routes red and white."

The second epidemiologist is presented with the data of table 1 pertaining to Groups A and C. Following precisely the same rationale, he concludes that "some transmission takes place through route red, but the majority of transmission takes place through routes blue and white."

The two epidemiologists meet to discuss the epidemiology of the disease caused by *B. experimentus*. They discuss the importance of each transmission route. The first epidemiologist tells the second that his data clearly show that blue is not an important route. Since the second epidemiologist's data show that blue and white together constitute an important route, they agree that white must be the major transmission route.

The work of the epidemiologists is done. With great confidence they pronounce "route white" to be the dominant transmission route, adding that "route red" constitutes a transmission route of secondary importance while "route blue" accounts for very little transmission.

TABLE 1

Development of disease in experimental groups

Group	Each subject ingests contents of:	No. of organisms ingested	Probability of infection = 0.5 $\log_{10}$ (dose)	No. of cases
A	Red + blue + white	70 + 30 + 0 = 100	1.00	100
B	Red + white	70 + 0 = 70	0.92	92
C	Blue + white	30 + 0 = 30	0.74	74

Assessment of the epidemiologic methodology

To summarize: "Red", which actually accounts for 70 per cent of transmission, is considered to be a route of secondary importance; "Blue", accounting for 30 per cent of transmission, is considered to be a route of tertiary importance; and "White", the residual route, which transmits no organisms, appears to be the most important route of all. The lesson is that, if the dose-response relationship is non-linear, if there are several transmission routes, and if the effects on disease incidence of eliminating one transmission route are known, then it is fallacious to assess the relative importance of the eliminated and residual transmission routes by comparing the reduction in incidence due to elimination of the one route, on the one hand, to the residual incidence of the disease, on the other. This error may be referred to as "the residual fallacy."

The residual fallacy in mathematical terms

Consider the case of two transmission routes, and let: R = the number of organisms passing through route R; B = the number of organisms passing through route B; Y_0 = the number of cases prior to intervention; Y_{-R} = the number of residual cases after intervention (i.e., after eliminating R). Therefore: $Y_0 - Y_{-R}$ = the number of cases eliminated by eliminating R.

In the conventional assessment procedure, it is assumed that by comparing the number of cases eliminated (*viz.*, $Y_0 - Y_{-R}$) with the number of residual cases (*viz.*, Y_{-R}), the ratio of R to B can be inferred. That is, it is assumed that:

$$\frac{Y_0 - Y_{-R}}{Y_{-R}} = \frac{R}{B}.$$

Examining the left-hand term it may be seen that, if the dose-response curve is linear, then

$$Y_0 = k_1 + k_2(B + R)$$

and $$Y_{-R} = k_1 + k_2B,$$

whence $$Y_0 - Y_{-R} = k_2R$$

and $$\frac{Y_0 - Y_{-R}}{Y_{-R}} = \frac{k_2R}{k_1 + k_2B}.$$

For a linear dose-response relationship, then, the conventional assumption, *viz.*, that

$$\frac{Y_0 - Y_{-R}}{Y_{-R}} = \frac{R}{B},$$

is valid only if k_1 is approximately equal to zero, which corresponds to a very small minimal infective dose.

If, however, the dose-response curve is log-linear, then

$$Y_0 = k_1 + k_2\log(B + R)$$

and $$Y_{-R} = k_1 + k_2\log B,$$

then $$Y_0 - Y_{-R} = k_2[\log(B + R) - \log B]$$
$$= k_2\log[(B + R)/B]$$
$$= k_2\log(1 + R/B)$$

and $$(R/B)_{\text{inferred}} = \frac{Y_0 - Y_{-R}}{Y_{-R}}$$
$$= \frac{k_2\log(1 + R/B)}{k_1 + k_2\log B}.$$

Thus, $(R/B)_{\text{inferred}}$ is not, as assumed in the conventional evaluation procedure, equal to the actual ratio of R/B.

To obtain an estimate of the magnitude of the error incurred in assuming that $(R/B)_{\text{inferred}}$ is equal to $(R/B)_{\text{actual}}$, consider the case of enteroviruses, organisms for which some detailed dose-response information is available (1). For these organisms the minimal infective dose is very small, whence $k_1 \simeq 0$, and

$$(R/B)_{\text{inferred}} = \frac{\log(1 + R/B)}{\log B}$$

Values of $(R/B)_{\text{inferred}}$ and $(R/B)_{\text{actual}}$ are plotted on figure 2 for a variety of values of $(R + B)$. From figure 2 it is evident that, in all cases of practical interest, $(R/B)_{\text{inferred}}$ is always substantially less than $(R/B)_{\text{actual}}$. That is, the importance of the residual route relative to the eliminated

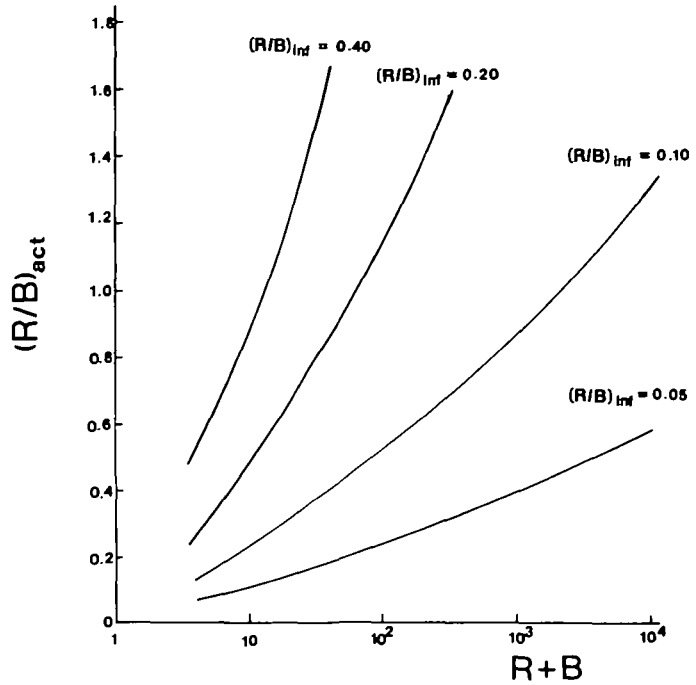

FIGURE 2. $(R/B)_{\text{inferred}}$ for different values of $(R/B)_{\text{actual}}$ and $R + B$. Note: $R/B_{\text{inferred}} = \dfrac{Y_0 - Y_{-R}}{Y_{-R}}$.

route is always greatly exaggerated. Figure 2 also shows that as the number of organisms ingested increases (i.e., $R + B$ increases), the effect of the error becomes increasingly severe. What this means, in practice, is that while a water supply program which reduces exposure to pathogenic organisms by 80 per cent would have a substantial effect on disease where the level of transmission of organisms is relatively low, a program which reduces exposure by 80 per cent would have only a small effect where the level of transmission of organisms is relatively high.

DIARRHEAL DISEASE IN THE REAL WORLD

Do the assumptions built into the hypothetical *B. experimentus* model hold for any significant "real world" diseases? Consider the situation in underdeveloped countries and, in particular, consider diarrheal diseases which are transmitted through the fecal-oral route in such settings.

Dose-response relationships. While extensive information on dose-response relationships for all diarrheal pathogens are not available, available data on important bacterial pathogens (see reference 2) confirm that "as a generalization there is probably a monotonic increase in the risk of infection as the dose increases exponentially" (3).

Transmission routes. Transmission can take place through several routes, with water, food, and person-to-person contact usually considered the most important for fecal-oral diarrheal diseases.

Interventions. In the majority of cases reported in the literature, the intervention involves improvement in the bacteriologic quality of drinking water. This concentration on drinking water is due, in part, to the historic role played by drinking water quality improvements in

eliminating waterborne cholera and typhoid in industrialized countries. And, in part, also due to the fact that improvements in water quality are relatively easy to monitor, because water sources are typically common to whole communities and since bacteriologic examination of water is simple and cheap. The monitoring of food quality, on the other hand, is much more difficult because such monitoring has to take place at the household level at specific times of the day, and it is much more expensive to conduct bacteriologic tests of food samples. The situation with person-to-person contact is still more difficult, because there are so many monitoring sites and no generally-accepted indicators for monitoring the bacteriologic consequences of such contacts. For these reasons, intervention studies, by and large, are studies of the effects of improving water quality.

To illustrate the implications of the *B. experimentus* model in such situations, consider the case of cholera and drinking water in Matlab Thana, Bangladesh. There is a close similarity with the *B. experimentus* model: the dose-response relationship for *Vibrio cholerae* is approximately log-linear (4); multiple transmission routes are possible; data are available on interventions affecting one transmission route (*viz.*, drinking water), while no data are available on the effects of interventions which affect other transmission routes.

The rich literature on the effect of improved water supplies on the incidence of cholera in Matlab (5–8) shows that improvements in drinking water quality alone do not effect major reductions in cholera incidence. Because it is generally assumed that "[if] a significant proportion of the disease is transmitted via drinking water [then] the provision of a safe water supply will have a significant impact on incidence of the disease" (9), these negative results have been interpreted by some analysts (e.g., Feachem (10)) as evidence that cholera is not waterborne in Matlab and that transmission takes place primarily through the "residual" routes of food contamination and person-to-person contact. As the *B. experimentus* case has illustrated, this rationale, which attributes the residual cases of disease to "other" transmission routes may be fallacious.

This example is of particular interest because, through a remarkable recent microbiological-cum-epidemiologic study in Matlab (11), direct microbiologic data are available on the frequency with which *V. cholerae* can be isolated from the different transmission routes. This study shows that while *V. cholerae* could be isolated in 7.8 per cent (28/360) of drinking water samples and 12.9 per cent (106/823) of cooking water samples, the organisms could be isolated in only 0.13 per cent (2/1593) of food samples, 0.30 per cent (2/677) of hand rinses, and 0.00 per cent (0/437) of utensils and food preparation boards.

In this area of Bangladesh, cholera transmission takes place through drinking water, through ingestion of water during bathing, through eating contaminated food and by person-to-person contact. Considering the microbiologic data collected on each of these routes, there can be little doubt that in Matlab most transmission of cholera takes place through drinking water. However, because of the existence of significant secondary transmission through other routes (probably primarily through the ingestion of contaminated water while bathing) and because the dose-response curve is approximately log-linear, elimination of the main route (polluted drinking water) does not lead to large reductions in cholera incidence. In this case, then, the rationale which declares cholera to be non-waterborne because improving drinking water quality does not lead to dramatic reductions in disease *is* fallacious.

This simple model also sheds new light on the recent hypothesis of a "threshold-saturation" phenomenon which suggests that "at the lower end of the spectrum there is a threshold below which investments in community water and/or excreta disposal facilities alone result in little detectable improvement in health status" (12).

Some of the reasoning behind the hypothesis seems to be incorrect. For instance, the authors contend that "reducing the exposure to disease only slightly, say by improving the quality of drinking water only, as occurred in the Bangladesh studies, would not necessarily lead to any measurable improvement in health status" (12). However, the microbiologic data (11) and our model indicate that improving the quality of drinking water *did* effect a major reduction in exposure to *V. cholerae* but that, because of the very high level of transmission in this environment and the effect of a log-linear dose-response curve, this major reduction in exposure translates into only a small reduction in disease incidence. These problems notwithstanding, the model developed in this paper provides strong support for the "threshold-saturation phenomenon" and provides a plausible biologic basis for the existence of such a phenomenon.

Conclusions

This analysis suggests that the following guidelines be used in drawing inferences on the importance of different transmission routes from data on the effect of interventions on disease incidence: If disease incidence falls sharply after introduction of the intervention, the affected route *is* the primary transmission route. However, if the disease incidence does *not* fall sharply, no conclusions can be drawn about the relative importance of different transmission routes.

Thus, for example, John Snow (13) was unquestionably correct in concluding, on the basis of large differences in attack rates for the populations served by polluted and unpolluted water supplies, that cholera was almost exclusively waterborne during the London epidemic of 1854. If, however, the difference in attack rates had been much smaller, Snow could not have concluded that transmission of cholera by water was unimportant and that person-to-person transmission was of major importance in that epidemic.

This negative conclusion on the validity of a widely-used epidemiologic tool is disturbing. How, then, are we to proceed? What inferential methods *can* be trusted in seeking guidance on these vital policy issues?

The analysis presented in this paper suggests that a different and, unfortunately, more complex method might be more appropriate for assessing the impact of any particular intervention. Returning to the *B. experimentus* example, the effect of elimination of "route blue" would be an 8 per cent reduction in disease if no prior improvements were made in "route red", whereas, with prior elimination of route red, elimination of "route blue" would result in a 100 per cent reduction in disease incidence. Similarly, in the case of cholera in Bangladesh, while improvements in the quality of bathing water and food handling and personal hygiene practices would have a negligible effect on the incidence of cholera if drinking water quality were *not* improved, such changes would have a dramatic effect on the incidence of cholera *if* prior improvements in drinking water quality had been made.

The implication is that the effect of improvements in, say, water quality should not be evaluated by the reduction in disease due to water supply improvements in isolation, but rather by the degree to which the improvement in water quality affects the health effects of other (simultaneous or subsequent) essential changes in environmental conditions or personal health practices.

A more generic response to the dilemma raised by the "residual fallacy" is suggested by the response of social scientists to similar methodologic problems (14). The approach would be identical to that followed in this paper, but would draw on more complex and satisfactory simulation models. These models would probably be stochastic and would certainly include other epidemiologically-significant phenomenon such as infection:case ratios and the effect of acquired immunity. These models would be used to generate data sets similar to field data collected by epidemiologists. These synthetic data would then be analyzed by conventional and other analytic methods. For each method, the inferences drawn from the synthetic data would be compared with the causal relationships which were structured into the model. Thus, conventional procedures could either be validated or, if these are, as in the present case, found to be wanting, alternative analytic methods could be identified and tested.

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