Investing in Exposure

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The problems of the overwhelming amount of medical literature have been thoughtfully highlighted in the *PLoS Medicine* editorial “Drowning or Thirsting: The Extremes of Availability of Medical Information” [1]. It is of vital importance to medical professionals that they improve on their skills of sifting through the huge amounts of literature that are made available to them every month. But this task becomes exponentially more difficult in the less-developed world, where basic knowledge of medical literature is limited [2].

There are no alternatives to the good analytical skills that come through continued exposure to medical literature. This exposure should begin at the medical student level. Exercises such as those requiring medical students to analytically criticize medical literature can go a long way in developing reading skills.

The second issue is that of disseminating the literature that has been published. Access to reliable health information has been described as “the single most cost-effective and achievable strategy for sustainable improvement in health care” [3].

A useful strategy could be making less-expensive paper versions of medical journals widely available in less-developed countries. Publishers should be willing to look into this approach. Regional copies of journals can be produced locally and inexpensively. This will boost the circulation of medical journals. Medical professionals will not mind a little compromise in the quality of paper in a journal, so long as they are able to afford it at a low price.

The business model of offshore call centers can serve as a useful one in the case of publishing low-cost copies of medical journals. Companies have shifted their call centers to less-developed countries where services are available at very low costs. The costs of publishing are likewise bound to be cheaper in the less-developed countries; therefore, journals can be produced at affordable prices. If this model can be followed by multinationals, why is it not possible for a cause as noble as publishing medical literature?

Another approach could be that journal volumes could be condensed, so that only research relevant to the local area is published in the local version of the journal. The Internet’s widely spreading use as a resource can be of vital value in substantially quenching the thirst of professionals. The wide availability of Internet access in Pakistan [4], for example, helps the cause of disseminating information. Internet access such as that given through the platform of HINARI or the Ptolemy project [5] is also a viable option. But these networks need to be expanded to include more countries and individuals [6].

One should hope that investing in improving exposure of health professionals to medical literature will help improve their practices and the quality of healthcare that they provide to impoverished populations in their local area. The need of the hour is to be innovative and be ready to embrace new and thoughtful ideas for the collective good of humanity.

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References


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Hyperinfectivity in Cholera: A New Mechanism for an Old Epidemiological Model?

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Hartley et al. [1] have recently proposed an epidemiological model for the dynamics of cholera that explicitly incorporates a hyperinfectious stage of the pathogen *Vibrio cholerae*, following laboratory findings that passage of the bacterium through the gastrointestinal tract results in a short-lived more highly infectious state. The paper and its commentary [2] emphasize that this model provides a basis for the transmission pathway known as “human-to-human” and demonstrates its importance, relative to the “environment-to-human” pathway, in the “explosive” character of cholera epidemics. Nevertheless, several important points seem to be missing from the discussion.

First, epidemiological models that treat transmission as “human-to-human” do exist in both the older literature [3] and in more recent cholera studies [4,5]. The latter use time series models to explain the interannual dynamics of cholera outbreaks in endemic areas. Their application to the temporal patterns of cholera in both recent and historical records from Bangladesh show that the force of infection is clearly related to previous incidence levels, as expected for “human-to-human” transmission. This work has also shown that environmental variables (El Niño, rainfall) modulate this type of transmission [3], so that the focus on the environment is relevant even for the “human-to-human” pathway.

Second and more importantly, we can ask whether the model of Hartley et al. differs from the standard treatment of “human-to-human” transmission in epidemiological models. In particular, does the so-called “explosive” behavior differ from the well-known exponential growth of cases at the beginning of an epidemic, when there is little or
no immunity built into the population? Inspection of the temporal scales involved in the dynamics tells us that this is not the case: we can collapse their treatment of transmission via a hyperinfectious stage into a more standard direct-transmission formulation. This is because the dynamics of the hyperinfectious stage in the environment are much faster than that of the number of cases, with the average lifespan of a hyperinfectious bacterium (their variable BHI) being on the order of 5 h, whereas an infected individual (their variable I) continues to shed for approximately 5 d. Therefore, to a first approximation, BHI sees I as “constant” for a sufficient length of time to reach “equilibrium” for any given value of I. It follows that this “equilibrium” concentration of the hyperinfectious stage in the environment effectively tracks the size of the infected population; in other words, BHI is simply proportional to I. Simulations of the model with the parameter values of the Hartley et al. paper confirm this expectation for the whole course of an epidemic. We can then get rid of this variable and write the transmission rate as a function of the number of susceptibles and the number of infected individuals, as is traditionally done in epidemiological models. Thus, for purposes of modeling cholera epidemics, we do not need to explicitly represent the hyperinfectious stage, unless the questions and mechanisms we are examining are specifically about this stage (as was the case in Hartley et al.), and “explosive” behavior does not refer to a different type of dynamics than that of standard models for human-to-human transmission.

There is another way, however, in which the epidemics may have been called “explosive” by Hartley et al.: the growth rate of the epidemics in their model is much higher when “human-to-human” transmission becomes dominant relative to “environment-to-human” transmission. This brings us to the important epidemiological quantity known as \( R_0 \), which measures the number of secondary cases produced by an infected individual in a pool of susceptibles, that is, at the beginning of an outbreak. Hartley et al. report a new formula for cholera’s \( R_0 \) (Equation 4 in their paper). There is an interesting discrepancy between Hartley et al.’s \( R_0 \) estimate when “human-to-human” is dominant (\( R_0 \approx 18 \)) and the value we obtain for cholera data for Matlab, Bangladesh (\( R_0 \approx 3 \) (unpublished result)). Our estimate is close to the values Hartley et al. propose when “environment-to-human” transmission is dominant, even though our estimate is obtained from a model of “human-to-human” transmission. As far as we can tell from the information provided, the derived expression for \( R_0 \) in Hartley et al. is an approximation. It appears to hold exactly when the dynamics of both the hyperinfectious and the environmental stage occur on fast temporal scales, quickly “equilibrating” and tracking the number of cases. While this assumption, as we have argued, applies to the hyperinfectious stage, it does not to the environmental one, as demonstrated by similar model simulations. Hartley et al.’s expression for \( R_0 \) would then overestimate the reproductive number of the disease, making it more explosive than it is (see Figure 4 in the paper).

The discrepancy in our estimates has an important consequence: while an epidemic declines from a depletion of susceptibles in the Hartley et al. model, the seasonal outbreaks we observe in Bangladesh are curtailed prior to a significant depletion of susceptibles [5]. This implies that the transmission rate must effectively be decreasing as the epidemic peaks. Indeed, recent observations of vibriophage dynamics in Bangladesh have given rise to the hypothesis that seasonal outbreaks may be self-limiting due to amplification of \( V.\) cholerae-specific phage [6,7]. The dynamics of phage predation are a likely mechanism for the observed reduction in cholera transmission rate at the end of seasonal outbreak.

Despite these differences, both our analyses and Hartley et al.’s model accentuate the need to consider some variant of “human-to-human” transmission to explain cholera dynamics. An important issue is therefore what we should call “human-to-human” transmission. Clearly, the categorization of the two routes of transmission (“human-to-human” and “environment-to-human”) is a simplification, albeit useful for the purpose of modeling the disease, that considers only the two extremes of a continuous axis defined by the strength of the feedback between (previous) cases and transmission rate and by the different temporal scales of transmission. For the “environment-to-human” type, this feedback is weak (in the extreme, nonexistent) as the bacterium concentration in the environment becomes dominated by its survival, population growth, environmental drivers, and the stochastic nature of these processes. At the other extreme, the feedback is strong and the transmission rate is a function of cases. This definition is more general and more practical than the one that restricts “human-to-human” transmission to that mediated by the hyperinfectious state. For issues of control, the more general definition appears more relevant, unless we are considering control measures that would specifically target the concentration of the hyperinfectious stage.

Many open questions remain on the modeling of cholera in connection to transmission pathways. For example, early-warning systems and associated predictive models for endemic and epidemic regions remain to be developed and tested. In contrast, the importance of sanitary conditions, sewage treatment, and clean water for cholera prevention and eradication has been known for a very long time.

Nevertheless, cholera is today in its seventh pandemic and, as a “disease of poverty” [8], continues to represent a significant public health burden around the world. Neither an exclusive focus on the environment nor an emphasis on socio-economic factors alone is sufficient to address the cholera problem today. Developing a better mechanistic understanding of the factors that initiate, amplify, and defuse regular seasonal outbreaks in endemic areas and irregular “epidemic” outbreaks in others should prove valuable to develop viable control strategies for this and other enteric diseases.

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References
Industry and Bioethics: What Price the Relationship?

Mark Boyd, Wendy Rogers

We read with interest the article by Mackie et al. entitled “Lessons on Ethical Decision Making from the Bioscience Industry” [1]. The authors recognize some study limitations, including the possibility of social desirability bias, but fail to address other limitations that in our view seriously weaken the paper.

Firstly, there is no discussion regarding an understanding of the use of the term “ethics” by the authors and bioscience companies. There appears to be an assumption that “ethics” is a straightforward term whose meaning would be agreed by all those engaged in the field. However, the requirements of business ethics, for example, may differ significantly from the requirements of healthcare ethics. When one considers the imperatives of the bioscience and healthcare industries substantially overlap. This study engages with what might be defined as procedural issues, but ignores substantive philosophical issues. The latter may have been beyond the scope of the paper, but if this were the case, it should have been acknowledged.

Secondly, there is no comment upon the authors’ industry links. These are disclosed in their listing of their competing interests and include receipt of industry funding, direct links with companies subject to study, and funding awarded by some of the involved companies after the study. However, there is no discussion of the potential for these links to interfere with study conduct and interpretation. The authors do acknowledge the debate regarding bioethics and links with industry, but such acknowledgements cannot realistically compensate for the conflict of interest faced in the conduct of this particular study. Despite the growing literature on these links, there is no comprehensive analysis of industry-associated bioethics research [2,3]. We cannot therefore confidently claim that there is an observable industry bias in such research. There is, however, overwhelming evidence that bias favourable toward funders occurs in medical research and healthcare prescribing [4–6]. It would therefore seem naïve to believe that bioethicists are in some way immune from factors that demonstrably lead to bias in other disciplines.

In addition to these omissions, the accompanying Perspectives commentary [7] neglects to discuss the implications of the conflicts of interest for the design, conduct, conclusions, and interpretation of the study. There was an allusion to these conflicts, but in this context we would have expected a review to be far more explicit regarding the potentially crucial importance of such conflicts.

Ethicists are wooed by industry precisely because their views and opinions carry weight. This currency will soon become valueless unless researchers, authors, reviewers, and journal editors take a strong stand for intellectual honesty and self-critique in the presence of conflicts of interest.

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Authors’ Reply

We thank Boyd and Rogers for their comments [1] about our article “Lessons on Ethical Decision Making from the Bioscience Industry” [2].

In response to their first point, we would like to refer them to our book, entitled *Biodustry Ethics*, on which our article was based [3]. In the introduction of the book, we provide a discussion about the intersection of traditional medical ethics and business ethics as well as business strategy and...