Too Little of a Good Thing

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.1097/EDE.0b013e31817734ba</td>
</tr>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:25620503">http://nrs.harvard.edu/urn-3:HUL.InstRepos:25620503</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
Too Little of a Good Thing: A Paradox of Moderate Infection Control

Ted Cohen and Marc Lipsitch

Division of Social Medicine and Health Inequalities Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

Department of Epidemiology, Harvard School of Public Health, Boston, MA.

Abstract

Epidemic theory dictates that a reduction in the force of infection by a pathogen is associated with an increase in the average age at which individuals are exposed. For those pathogens that cause more severe disease among hosts of an older age, interventions that limit transmission can paradoxically increase the burden of disease in a population.

Mortality due to infectious diseases dropped precipitously in developed countries decades before the advent of specific interventions such as vaccination or antimicrobial treatment. This decline has been variously attributed to improved nutrition, water purification, and reduced opportunity for transmission. That reducing exposure and risk of infection with pathogens should alleviate morbidity (both for individuals and for communities) is self-evident. But the link between limiting pathogen exposure and improving public health is not always so straightforward. Reducing the risk that each member of a community will be exposed to a pathogen has the attendant effect of increasing the average age at which infections occur. For pathogens that inflict greater morbidity at older ages, interventions that reduce but do not eliminate exposure can paradoxically increase the number of cases of severe disease by shifting the burden of infection toward older individuals. A classic example of such perversity is the increase in the incidence of congenital rubella syndrome observed after vaccination programs that decrease the force of rubella infection but fail to eliminate transmission or ensure adequate coverage of adolescent and adult women.

More recently, researchers have questioned whether the introduction of mass varicella vaccination will result in a higher incidence of herpes zoster among older (mostly unvaccinated) adults. Repeated exposure to varicella circulating in a community appears to reduce the risk of reactivation of a latent infection. Accordingly, Brisson et al hypothesized that a reduction in the force of infection following vaccination could result in a higher number of zoster cases for several decades after the initiation of mass vaccination. Preliminary findings suggest that the incidence of zoster may increase after vaccine is introduced into a community, although this effect has not been consistently observed and larger surveillance studies are currently underway. Ironically (or possibly not, for Merck shareholders), if mass varicella vaccination does cause an increase in zoster incidence in a community, the solution may be to use a second, more potent, vaccine to prevent zoster among older adults. Furthermore, given the high basic reproductive number of varicella and the moderate effectiveness of mass varicella vaccination, transmission is not eliminated even at relatively high levels of vaccine coverage. As such, surveillance studies indicate that mass vaccination is associated with an increasing average age of infection and, in some cases, researchers have documented absolute increases in varicella incidence among older age groups after mass vaccination is introduced.

Correspondence: Ted Cohen, 677 Huntington Avenue, Boston, MA 02115. E-mail: tcohen@hsph.harvard.edu.
Since late infection is associated with greater morbidity, this effect is worrisome. Again, a second dose of varicella vaccination in childhood (as was recently recommended by the Advisory Committee on Immunization Practices in the United States\textsuperscript{14}) may ameliorate this problem.

Proponents of the “hygiene hypothesis,” originally promoted by Strachan\textsuperscript{15} suggest that early life exposure to pathogens enhances the development of the immune system. Hence, excessive sterility of environments resulting in late exposure to pathogens may be responsible for observed increases in the incidence of allergic diseases such as asthma and eczema. While there are several lines of epidemiologic evidence that support this hypothesis\textsuperscript{16}, early infection with several types of bacteria has also been associated with the development of asthma\textsuperscript{17}. Further investigation, and controversy, is no doubt pending.

In this issue of \textit{Epidemiology}, Lavi et al\textsuperscript{18} propose a related explanation for a recent increase in the incidence of listeriosis occurring primarily among middle-aged and elderly individuals in Europe. They suggest that improved food storage and handling practices has reduced but not eliminated exposure to \textit{Listeria monocytogenes} through tainted food products, thus increasing the average age at which individuals are exposed to this pathogen. To close the circle on this argument, they must assume that prior— generally asymptomatic— infection with \textit{L. monocytogenes} is protective against development of disease. Because \textit{L. monocytogenes} is a favorite model organism among those experimental immunologists who work with pathogens, this hypothesis is well supported in animal models. However, definitive work in humans has not yet been done.

As in previous studies of congenital rubella syndrome and herpes zoster, Lavi et al\textsuperscript{18} present their hypothesis in the language of mathematics. Their simple models of the natural history and transmission of \textit{L. monocytogenes} allow for clear communication of the key fundamental assumptions that underlie the dynamical behavior of the system. They use their model to describe conditions under which the net effect of reduced exposure will be detrimental (ie, an increase in the number of cases of listeriosis) and when reduced exposure will simply result in an upward shift in the age distribution of cases. A strength of this modeling approach is that ambiguity is minimized and falsifiable claims are made plain. Others who are displeased with simplifying assumptions made by the authors can modify or extend the model, and examine whether the results are dependent on these choices.

The argument presented by Lavi et al\textsuperscript{18}—that the recent rise in listeriosis incidence is the indirect effect of reducing exposure—is appealing for both its simplicity and its similarity to phenomena observed for other pathogens that exhibit age-specific morbidity. Even so, other explanations for this upsurge remain possible. For example, while no common strain of \textit{L. monocytogenes} has been identified in a large number of the cases, the emergence of a particularly virulent clone (or clones) may still be responsible for the recent increase in case numbers seen in some European countries. Changes in food distribution and handling practices in combination with new risk behaviors (ie, dietary habits) could also have increased the exposure of the at-risk population. Data for trends in exposure are weak (and the most marked improvements occurred many decades ago), the details of human immunity to \textit{L. monocytogenes} are not yet well understood, and the interventions that reduce exposure to this pathogen are nonspecific. Thus, additional evidence to support Lavi et al's\textsuperscript{18} hypothesis will be difficult to identify. One potentially supportive piece of evidence, which unfortunately is not available in the current data, would have been a corresponding increase in incidence in pregnant women (the other group besides elderly at risk for severe \textit{L. monocytogenes} disease) decades prior to the increase observed among the elderly. Still, even in the absence of further supportive evidence, this explanation may be preferred for its parsimony until contradictory data become available. Clearly, the most important assumption on which this explanation rests...
is that the duration of protection conferred by prior \textit{L. monocytogenes} exposure in humans is long lasting or can be readily boosted by repeated exposure. If future research fails to detect such robust protection afforded by previous exposure, we suspect that these authors would be the first to abandon this hypothesis.

\textbf{Biography}

TED COHEN is an Assistant Professor of Medicine at Harvard Medical School and an Associate Scientist in the Division of Social Medicine and Health Inequalities at Brigham and Women's Hospital. He is interested in the transmission dynamics of infectious diseases, especially TB and HIV. MARC LIPSITCH is a Professor of Epidemiology at Harvard School of Public Health and uses experimental, epidemiological, and mathematical approaches to study infectious disease transmission and immunity, focusing on \textit{Streptococcus pneumoniae}.

\textbf{REFERENCES}