Preparing for Emerging and Unknown Threats: Public Health

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In this presentation, I will discuss:

- Factors affecting emergence or re-emergence of threats
- A framework for considering research needs, and
- The potential role of biotechnology innovation.

I will focus on food safety with concentration on infectious diseases. What I will talk about *vis-à-vis* food safety will be equally conceptually important in terms of animal and plant diseases. All three are important to food security both in terms of availability of foods and the ability of developing countries, in particular, to trade food in the global marketplace as a source of hard currency; it's important that they have access to North America and Europe.

Much of what I will say in terms of research needs and potential tools will be equally applicable to food defense, although I will not emphasize that subject. Anything that I say about the emergence of a new foodborne disease is equally important in terms of the re-emergence of a foodborne disease. I define re-emergence as a known agent that "pops up" in new forms or locations, and the example I like to use is *Clostridium botulinum* because about every 10 years it goes through a rediscovery period. It originally started in Germany as an issue in fermented meats. Then as canning became more important it showed up in canned products. In the early 1960s, it appeared as infant botulism, an infectious rather than a toxigenic agent. It has shown up in the past 10 to 12 years in adulterated cosmetics and it is now a food-defense concern. Also, we are seeing increasing numbers of cases of adult "infant botulism," *i.e.* colonization of the intestinal tracts of adults where it produces toxin.

Emergence/Re-Emergence

Regarding emergence of a new food-safety concern, two important factors involve genetics. One is the pure chance of a change in a microorganism as a result of normal low-probability evolutionary events. And the second is that drivers can "push" microorganisms to change rapidly in potentially predictable ways. My working hypothesis is:

> *The emergence or re-emergence of a new food-safety concern is primarily the result of societal, technological or environmental changes that are primarily the result of human activities.*

Although we cannot predict far into the future, like weather forecasting (versus climate change):

- We can look at current trends to anticipate events in the near term (5 to 10 years), and
- We can establish a network for data-gathering to enable such forecasts.

Food-borne disease is dependent on the "balance" between the biological agent, the consuming population, and the food. Based on my working hypothesis above, as long as that is stable and the dynamic balance is maintained, there should be a minimum emergence of disease. The problem is that there is nothing about foods, there is nothing about the food industry, there is nothing about consumers and there is nothing about microorganisms that stays the same. They are in a continuing state of dynamic flux. That flux is increasing, which means that the rate of emergence is increasing.

Drivers

Global Demographics

One of the drivers causing disease emergence is global demographics. The burgeoning population is facilitating the secondary spread of agents by increasing interpersonal contact. Also, with the exception of sub-Saharan Africa, average age in all parts of the world is increasing, and, as populations age, susceptibility to infectious diseases increases. Furthermore, in many countries, rates of obesity are escalating along with related chronic diseases that increase susceptibility to infectious agents. Furthermore, birth rates are falling in much of the world, largely because parents have increased expectations of their children reaching adulthood. This affects the political landscape in terms of acceptable risk, particularly *vis-à-vis* infants and young children. And there are child substitutes: the sensitive issue of pets has important political overtones.

Global Food Industry

The food we consume comes from all over the world. Food-borne diseases that were previously limited geographically can now be disseminated widely. We have moved from what used to be microbiologically stable commodities to fresh products shipped via increasingly complex supply chains. It is possible to get to almost anywhere in the world within 48 hours. Accordingly a new biological agent could be disseminated worldwide via people or products within that time.

Processing

There has been a continuing trend toward milder processing of food, which may result in selection of mocroorganisms with increased resistance. "What doesn't kill you makes you stronger" is true for infectious agents. Also there is a perception that organically produced foods are safer, which may be true if the concern is over pesticide residue, but is not true microbiologically. And then there is a reemergence of the consumption of uncooked foods. This reflects the fact that we have been encouraged to eat more fresh produce and increasing demands mean that it is brought in from all over the world. It is transported in two-week segments from the tip of South America all the way to Alaska to ensure that fresh produce is available to us every day of the week. It used to be that cantaloupes were available in New Jersey for just two weeks in the year. Now they are available year-round. And there's a reemergence of consumption of raw milk and similar products. People have forgotten that unpasteurized milk used to be a source of tuberculosis. And since raw tuna, in sushi in particular, is popular and more nutritious than the cooked alternative, raw beef, raw liver and raw chicken are also being eaten as sushi, particularly in Japan, with several attendant outbreaks of foodborne disease. Japanese public-health officials are trying to convince the public to quit eating raw chicken.

Bacterial Gene Transfer

The importance of horizontal gene transfer between bacteria cannot be overstated. *E. coli* provides a good example. In the 1890s, it was thought to be non-pathogenic, whereas new strains continue to emerge through gene transfer causing various kinds of foodborne disease (Figure 1.).

- **1890's: First used as a non-pathogenic indicator of fecal contamination**
- **1940's: Implicated as a cause of infantile diarrhea**
- **1970's: Role of enterotoxigenic strains as foodborne pathogens**
- **1980's: Role of O157:H7 and other EHEC as a cause of hemorrhagic colitis and hemolytic uremic syndrome**
- **1990's: Identification of other classes of pathogenic *E. coli*, some of which may be foodborne**

Figure 1. Importance of horizontal gene transfer—*Escherichia coli*.
(EHEC = enterohemorrhagic *E. coli*)

Research Needs

Breaking the Disease Cycle

What knowledge and tools do we need to do the following three things?

- Anticipate and prevent the emergence of diseases from new, infectious agents. Although this is potentially the most cost-efficient approach, it is conceptually the hardest and it is difficult to obtain funding to look at something that hasn't happened yet. On the other hand, it is encouraging to see an RFA for this kind of work within the USDA Agriculture and Food Research Initiative (AFRI).
- Eliminate or contain the emergence of diseases before they become established. This can be achieved only within a short time window because many agents are hard to get rid of once they are established.
- Eradicate emerging pathogens that have become fully established in a new niche. This is particularly difficult with organisms that have multiple reservoirs and vehicles.

Anticipating/Preventing Emergence

In anticipating and preventing, a basis is needed for selecting the microorganisms that are most likely to be involved, to avoid investment of funds in an organism or group of organisms that is of low risk or has little impact. There is need to know what portion of the population and what foods or food technologies are likely to be involved. And, with this approach, it is necessary to have the technologies and strategies available to intervene in the riskiest situations.

As an example, during the past ten years, *Cronobacter sakazakii* has emerged as a food-borne pathogen in neonates. Although there are multiple sources for this organism, a furor arose because it was associated with powdered infant formula. We now know that a variety of other Enterobacteriaceae are occasionally associated with this type of infection, causing bacteremia, meningitis and necrotizing colitis, again in neonates. We also know that neonates aren't the only ones consuming powdered formulas. The biggest growth market in powdered formulas is actually at the other end of the age scale; they are being recommended increasingly as nutritional supplements for seniors and geriatric patients. It's noteworthy that seniors constitute the most rapidly growing segment of the population in the United States with susceptibilities similar to those of neonates. Their immune systems are starting to decrease, and, through achlorhydria, they produce less gastric acid, begging the question, "Should we be monitoring assisted-living centers for incidences of infections from Enterobacteriaceae?"

Eliminating/Containing Emergence

To eliminate or contain emergence of a disease before it becomes established, rapid identification of the new agent and cases is needed, as is identification of vectors, vehicles and reservoirs to determine its origin and how it is infecting humans. Also needed is an effective means of quarantining the emerging pathogen. However, "quarantine" raises hackles because of the days when immigrants were sent to Roosevelt Island for six months to two years if they had symptoms of tuberculosis. And an effective means of eliminating the pathogen from localized agricultural and environmental sources is necessary. Finally, an effective means for removing conditions that are fostering emergence must be developed.

Probably the best example is severe acute respiratory syndrome (SARS) caused recently by a coronavirus. It is noteworthy that SARS is now identified as a foodborne pathogen that is transmitted person-to-person. This respiratory agent is closely related to a virus found in civet cats and other animals in Chinese live markets. It appears that bats were the original source of the virus, particularly the Chinese horseshoe bat that then infected civet cats that also inhabit tree canopies. In the civet, an intermediate host for the virus, a mutation occurred that extended host range to humans who readily transfer it by respiratory means. Massive international efforts by a number of governments and intergovernmental agencies resulted in total control. It involved a massive quarantine whereby people with symptoms were barred from international travel. Live-animal markets in China were closed. Parts of hospitals in Canada were quarantined, preventing people from entering or leaving. Sources and intermediate hosts were rapidly identified and intermediate hosts were removed to break the infection chain; civets are no longer available for purchase in China. Evidence indicates that the problem resulted from a loss of habitat for bats outside of China, forcing their migration into China and infection of local bats, which, in turn, infected the civet cats.

Eradicating an Established Pathogen

To eradicate a fully emerged pathogen and its ability to cause disease, understanding of the following factors is needed:

- The etiology of the disease
- The ecology of the organism
- Mode of dissemination of virulence factors
- How to decrease human susceptibility
- Whether alternative food production, processing, marketing and consumption tools are available
- Means of effective communication to convince people of the need to change their ways, and
- Mobilization of political will and funding.

Such projects typically cost hundreds of millions of dollars. How much money was spent to eradicate small pox?

To date, no established foodborne disease has been completely eradicated. The closest is the poliovirus, which has not been fully eradicated. Others are in a state of control, but can reemerge if controls are ignored or are circumvented. Two that immediately come to mind are brucellosis and tuberculosis. The latter is particularly troubling because of the emergence of antibiotic-resistant strains. It is extremely difficult—and may be impossible—to eradicate pathogens that are free-living or have multiple hosts.

Research Needs

Basically there are two types of research needs. Short-term acute needs and longer-term needs.

Acute

With a new emergence, the need is to assemble an international research team immediately. Application of significant resources is needed; international establishment has to be prevented in less than a month.

Longer Term

Longer term needs include informatics to rapidly identify emergence events, rapid means for detecting and characterizing new pathogens, proactive approaches to predict where and when emergences are likely, and technologies for preventing them. Although difficult, unintended-consequence analyses should be done—by broad groups of knowledgeable people—to think through and quantify likely outcomes from changes in technology, marketing, *etc*.

Biotechnology's Role

Any discussion of emerging pathogens must include enterohemorrhagic *E. coli* strain O104:H4, the cause of the outbreak of foodborne disease in German in May 2011, which demonstrated the potential contributions of rapid, advanced biotechnology. The fact that the genome was sequenced within a week was amazing. On the other hand, having that information and making sense of it are not the same thing. I still haven't figured out how an organism that has no known attachment factor actually caused disease. None of the press releases that I saw provided insight into why it became a pathogen. Even the most advanced tools will be ineffective if the basic incident-command system is flawed.

Stopping Promiscuity

Infections by *E. coli* O157 in the United States and around the world have decreased dramatically in recent years. The problem is, infections by other enterohemorrhagic strains of *E. coli* (*e.g.* O104:H4) are likely to continue as long as *E. coli* exists and is capable of horizontal transfer of genes. O104 is not a new emergence; it's an extension of O157 because of the gene-transfer process. Whether gene-transfer can be stopped is hard to say. Certainly total elimination of *E. coli* from the food supply is virtually impossible. Taking a serotype approach has been successful here in the United States in the short run. However, it's becoming clear that it will not be successful in the long run, and so a new approach is needed.

What conditions foster promiscuity in food production and processing, and in specific animals, *etc*.? Are technologies or conditions available, or can evolutionary pressures be brought to bear, to suppress horizontal gene transfer? Is it possible to predict which strains are most likely to become the next source of foodborne enterohemorrhagic infection? *E. coli* O104 was not seen as a threat until it emerged; public policies were focused on six other serotypes.

Overcoming Diversity

Some pathogens, like *Salmonella enterica*—the leading cause of foodborne disease in the

United States—thrive because there are so many serotypes. With over 2,400 serotypes, no effective vaccines exist. Effective immunity would require both humoral and mucosal responses, but no common antigen is currently available. Compounding this, a high percentage of carriers are asymptomatic. About one in ten Americans carrying salmonella show no signs of it.

What factor do all salmonellae have in common that we can take advantage of in formulating new biotechnologies to prevent foodborne outbreaks? The rate of infection by salmonella has been constant for 20 years, although the primary vehicle has changed, from *S. enteritidis* to *S. enterica*. Furthermore, outbreaks of disease associated with fresh produce are significantly more common.

Predicting Emergence

If the number of hurricanes that will hit the United States each year can be predicted, why can't foodborne-disease emergence—and what new organisms will appear—be predicted? Forecasting weather is based on models, a lot of data-gathering and hard-core computational activities. We could develop models that are based on understanding factors that influence genetic stability and on understanding the impact of environmental, economic and demographic factors. It will require a team effort because the simulation modelers don't understand infectious diseases and infectious-disease people don't understand modeling.

Sentinel Populations

This was mentioned *vis-à-vis* elderly people. It provides the strongest opportunity of predicting where new emergences will occur. We need to start monitoring populations, locales and foods that carry inherently more risk in terms of food-born disease, for example:

- The very young, the elderly and the debilitated
- Foods that are consumed without cooking (fresh produce), and
- Areas of high population density and poor sanitary infrastructure.

Biotechnology may provide new tools to assist in this endeavor.

Long Standing Unfulfilled Needs

I have been asking for these research items for 15 years. I have put out RFAs, underpinned by significant funding, to try and get people to do this work and have been unsuccessful.

Sample Size

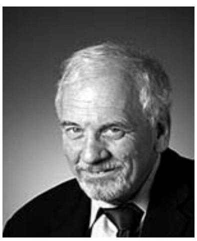
Dealing with food, sample size determines method sensitivity; as the sample becomes smaller, assay sensitivity is lost. With a sample weight of 2 µg, minimum sensitivity is somewhere between 3,000 and 5,000 organisms, providing only a 50% chance of detecting the organism. Molecular biologists need training in sampling statistics. In the papers I review, it is common to find, in discussions of new detection systems, poor understanding of how to calculate lower limits of sensitivity.

Assessing Immune Status

During an outbreak of foodborne disease, assessment of immune status of potentially exposed individuals is problematic. A non-invasive, rapid, field-deployable, inexpensive tool is needed—similar to a breathalyzer, for example—to provide a fairly accurate estimate of a person's current immune status. It would help in risk assessment to determine what factors need emphasis.

Concluding Remarks

We need to foster "just in time" research, particularly when responding to an emerging situation. We need to assemble research teams quickly, properly resourced, who understand how they fit into the overall structure. The longer the time between emergence and control the more it will cost both in public health and in dollars. There is need to think in terms of "right sized" technologies. Most of our food is produced by a few companies and many other companies produce a small percentage of our food. In order to solve emerging foodborne disease problems we need to think both high tech and low tech. And we need to look at the world like the microorganisms we are trying to control look at it, to find out what makes them tick. Their basic goal is to reproduce, but I encourage thinking of how a microorganism—as it is getting ready to merge—actually thinks and that will help us figure out where it is going to pop up.



Robert Buchanan, director of the University of Maryland's Center for Food Safety and Security Systems, received his BS, MS, MPhil, and PhD degrees in food science from Rutgers University, and postdoctoral training in mycotoxicology at the University of Georgia. Since then he has 30 years experience teaching, conducting research in food safety, and working at the interface between science and public-health policy, first in academia, then in government service at both the USDA and FDA, and most recently at the University of Maryland.

Dr. Buchanan's scientific interests are diverse, and include extensive predictive microbiology, quantitative microbial risk assessment, microbial physiology, mycotoxicology, and HACCP systems. He has published widely on a broad range of subjects related to food safety, and is one of the co-developers of the widely used USDA Pathogen Modeling Program. Buchanan has served on numerous national and international advisory bodies. He is a permanent member of the International Commission on Microbiological Specification for Foods, and has been the US delegate to the Codex Alimentarius Committee on Food Hygiene for 10 years.