

The Use of Farm-to-Fork Surveillance and New Genome Sequencing Techniques to Prevent and Control Foodborne Disease Globally**

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Summary

In the future, it is likely that all clinical microbiological laboratories will have access to DNA sequencing on a daily basis. The technology will become significantly cheaper and quicker than present bacterial identification systems. Given that human infectious diseases have an increasingly global epidemiology (e.g., severe acute respiratory syndrome [SARS], H5N1 avian influenza, influenza, *Salmonella*, and antimicrobial resistance), rapid identification of microorganisms and timely response are crucial for preventing global spread. It is suggested that new technologies (e.g., DNA sequencing), combined with new methodologies for risk assessment and attribution of human infectious disease to the source (animals and/or food), should be used for science-based reduction of the foodborne disease burden at the global level. Systems to enable real-time detection and prevention of infectious diseases should be based not only on the best available collaborative science, but also must have a clear and transparent governance structure with global reach.

Current realities

A significant portion of, if not most, infectious diseases in humans is related to animals. The diseases are caused by zoonotic pathogens (i.e., pathogens shared between human and animal populations). Recent major human outbreaks of diseases that stem from animals include bovine spongiform encephalopathy (BSE) and its human counterpart, Creutzfeldt-Jacobs disease, SARS, avian influenza, and the H1N1 pandemic. Such diseases may jump once to the human population and then spread from human to human (e.g., SARS or H1N1), spread in animals and jump to humans multiple times through human-animal contact with live or dead animals (e.g., avian influenza), or spread in animal populations and then to humans via food (e.g., BSE). Efficient early detection and prevention of such diseases will be possible in the future, based on new DNA sequencing techniques.

It should be realized, though, that the most significant part of the zoonotic infectious disease burden is not related to these unusual pathogens, but rather to a small group of pathogens that cause endemic foodborne diseases. These endemic zoonotic pathogens are responsible for a significant number of “ordinary” disease cases year after year. Endemic diseases typically relate to zoonotic pathogens that are constantly present in a large proportion of certain animal populations and, if not controlled, cause an ongoing and often large disease burden. In addition, the use of antimicrobials in

animal populations (to promote growth and treat sick animals) is creating zoonotic strains resistant to the antimicrobials used to save human lives. The occurrence of these resistant zoonotic pathogens exacerbates the foodborne disease burden in humans.

Old food safety systems have failed to control this significant food-related disease burden for a number of reasons, including intuitive reliance on end-product testing and a lack of inter-sectoral collaboration. Safety cannot be achieved by senseless testing alone, including testing of imported food at borders. Monitoring the presence of pathogens in the end product usually is inefficient because it is impractical to test enough samples to obtain the necessary degree of statistical certainty (Havelaar et al., 2010). Silo thinking in the broader food safety system has also significantly contributed to the relatively sorry state of affairs that exists at present. This mentality has resulted in a situation in which surveillance systems for animals are not at all linked to surveillance systems for food or humans. Thus, for example, *Salmonella* cannot be linked among the animal, food, and human domains. Notably, when countries have succeeded in creating integrated systems spanning both agricultural and human sectors, preventive and control efforts have also been more successful (Wegener et al., 2003). Such inter-sectoral systems have been used to monitor the situation and spread of antimicrobial resistance from animals, via food, to humans. However, coordination of data-gathering efforts is presently missing in many food safety systems, leading to a very weak evidence base, uninformed decisions, and ultimately poor implementation. The result is a lack of political support and generally poor financing of systems and efforts.

The new thinking in food safety relies heavily on the farm-to-table concept (i.e., focusing prevention on the full food-production chain from farm to consumer) and the proactive use of risk assessment. Risk assessment presents a science-based and transparent way of evaluating food safety problems as well as the efficacy of solutions along the full food-production chain. The use of risk assessment to deal with microbiological food safety problems primarily began in the United States and Canada, and moved to the rest of the world throughout the 1990s and 2000s. Guidelines and expert committees for this purpose were defined by the World Health Organization (WHO) and the Food and Agricultural Organization (FAO) in 2000.

Scientific opportunities and challenges

In terms of source attribution, *Salmonella* exemplifies an area where new methods have been created to link the bacteria in animals and food to the infections in humans. In typical food safety systems, *Salmonella* is not compared in animals, food, and humans. Thus, the source of most cases of sporadic human salmonellosis (e.g., pork, chicken, and eggs) cannot be found, ultimately resulting in a lack of upstream prevention (i.e., sporadic cases are not linked together in outbreaks). However, in an effort to relate *Salmonella* in animals/food to the infections in humans, a model was developed to estimate the number of human cases attributable to each of the major animal-food sources (Hald et al., 2004). *Salmonella* subtypes found in animals and food are compared with subtypes found in humans, and annual estimates on the impact of

Salmonella through major animal-food sources are accordingly generated. The model has become a powerful decision-support tool for allocating resources to achieve optimal *Salmonella* prevention and control. This is true for both drug-sensitive (i.e., nonresistant) and antimicrobial-resistant *Salmonella*.⁴ While the case of *Salmonella* demonstrates a significant opportunity in terms of developing new models for source attribution, this precise model cannot at present be applied to other infections. The model is possible for *Salmonella* because of the specific typing methods available for this bacterial genus, as well as the epidemiology of the pathogen, yet for most other pathogens similar possibilities do not exist.

The rate of total genome sequencing has increased tremendously in the past decade. Whole bacterial genomes can now be sequenced in minutes, creating significant new opportunities (and challenges) in term of monitoring, tracing, and attributing foodborne bacterial infections. In principle, the rate and cost of sequencing will not be the limiting factor. Rather, problems will relate to storing, analyzing, and interpreting the enormous amount of bacterial-sequencing data. The genome-sequencing technology will also enable a globally harmonized system for the identification and characterization of bacterial strains. This information will be easy to share among countries, thus enabling global monitoring and tracing of foodborne pathogens. It also enables significantly quicker, more specific, and less expensive characterization of bacterial strains. When a pure bacterial culture is available, results can be achieved within minutes in the field without specialized laboratories. Likewise, sequencing data can be used as the basis for broader source attribution, enabling specific infectious-disease prevention for most zoonotic pathogens. The major challenges lie in achieving global agreement on the specific sequencing technique and in determining ways to transmit and store data.

Policy issues

To contextualize the salient policy issues, it is imperative to bear in mind the following: (i) globally, up to half a billion microbiological isolates are characterized each year in diverse and expensive typing systems involving serology, all of which could be replaced by total genome sequencing for bacteria and viruses; (ii) human infectious diseases have an increasingly global epidemiology — thus, rapid detection and identification of microbial agents and timely response and control are crucial if we want to prevent or control global spread; and (iii) globally standardized, research-based solutions and technological developments are needed for real-time microbiological identification and analysis of information, and such solutions must be implemented with global access and long-term sustainability.

- A standardized methodology to analyze microbiological genomes should be globally agreed on. Included within this should be a system to report, in real time, microbiological identification data together with antimicrobial-resistance characteristics. Such systems should take diagnostic and surveillance needs for animal, food, and human health sectors into account. Policy-level debate and

⁴ For example, in 2005, it was estimated that 60% of all *Salmonella* infections acquired in Denmark came from Danish meat and 40% from imported meat. However, when examining the multiple antimicrobial-resistant isolates or fluoroquinolone-resistant isolates, more than 90% of infections were attributed to imported meat.

decisions are needed in an international forum with much inclusiveness and transparency.

- A capacity to assemble, process, and handle large data quantities over Web-based systems should be developed to create a global database of microbiological strain DNA-sequence data.
- The governance structure for such an interactive global DNA-sequence database and system needs to be transparent, be inclusive, and consider information-sharing constraints. Policy-level consideration of implications and timelines for such constructs is needed.
- Data-gathering efforts related to food contamination and foodborne disease must be coordinated so systems to efficiently prevent foodborne diseases are based on solid evidence. Likewise, monitoring, surveillance, and control efforts should be geared toward enabling common goals.
- Establishment of global source-attribution models should be based on full genome sequencing linking the specific animal and food sources to human infections at national, regional, and global levels. The outcome can be used to track and evaluate the spread of microbial pathogens and antimicrobial resistance, as well as to set and monitor targets for contamination and disease reduction. A clear and transparent global governance system is needed for this to succeed.
- There should be increased standardization of information on microorganisms, including information on the relationship between antibiotic use in agri-/aqua-culture and antibiotic resistance in foodborne pathogenic microorganisms. It is also important to document and evaluate specific intervention strategies for prevention of antibiotic-resistant microorganisms.

References

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The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Jørgen Schlundt (see above). Dr. Schlundt initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Dr. Schlundt. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Schlundt, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- Foodborne diseases are an immediate global concern. They negatively impact societies through associated morbidity, mortality, and substantial health care-related costs. The present foodborne disease burden warrants action at global, national, and local levels to prevent the transmission of these diseases.
- Source attribution is an example of a successful strategy for the prevention and mitigation of foodborne diseases. Source attribution has demonstrated its value in Denmark where, despite being limited in terms of the microbes involved, it led to significant reductions in foodborne illnesses, deaths, and associated health care costs. Accordingly, similar systems should be established worldwide.
- Source attribution systems must draw on the One Health approach by utilizing data from as many sources as possible (e.g., combining data from human health and veterinary systems). While data collected from processing plants, farms, food, and patients are all critical elements of source attribution, more emphasis should be placed on data from the farm because that information allows disease management decisions to be implemented at the primary production stage.
- For a source attribution system to be successful, it must be global in design (i.e., collecting and analyzing data across national borders) and have the participation of both the food industry and regulatory agencies. The system should also be designed to catalog as many microbes as possible to broaden its application to non-foodborne microbial infections.
- Extensive advances in DNA sequencing technology have played a large role in the feasibility of source attribution. A global source attribution system would still take several years to put in place, but would be viable with appropriate political support. Given that the benefits (e.g., reduced morbidity, mortality, and health care expenditures) outweigh the cost of developing and implementing a source attribution system, intergovernmental agencies and governments should encourage and champion the development of such a system.
- Countries must more widely communicate with each other regarding their foodborne disease control strategies. When communication is lacking, successful strategies (e.g., Denmark's source attribution system) go unnoticed and are not replicated in countries where they could have great impact. Additionally, data sharing (e.g., genetic material) should be encouraged to accelerate the development of disease prevention methods, such as vaccines.

Current realities

Globally, thousands of people die each year from diseases transmitted to humans through food. While it was suggested that most of the bacteria that are transmitted to humans via the global food supply originate from animals, it was acknowledged that source attribution is not frequently employed to establish a causal link.

A Pew Charitable Trust report recently estimated the health care-related cost of foodborne disease at approximately US\$152 billion yearly to the United States alone. There are also tremendous resource expenditures to implement point-of-import testing of food as a safety measure. This procedure was perceived as less useful than point-of-production testing.

It was noted that Denmark has implemented a system of source attribution, which is currently focused on *Salmonella*. The system is based on the premise that, if animals are the suspected cause, microorganisms in food, animals, and humans should be compared to determine the true source. There is a significant amount of data available on *Salmonella* (found in chicken, eggs, pork, etc.) to support a comparison of the strains found at the farm, in food, and in patients. This source attribution allowed Danish authorities to attribute a number of disease outbreaks to a specific source. It was strongly argued that source attribution is only truly successful if testing is performed at the farm level (i.e., the source), alongside testing in food and in affected patients.

Concern was expressed that, currently, common foodborne diseases are not a serious enough priority within public health programs, especially in the United States. Attention was drawn to an announcement made by the U.S. Centers for Disease Control and Prevention (CDC) that *Salmonella* infections in the U.S. have increased during the last 15 years. Meanwhile, the European Union has made significant efforts to reduce *Salmonella* in poultry. Differences between the E.U. and U.S. systems of food safety were also clarified. The E.U. system relies more heavily on measures implemented at primary production stages (e.g., farms), while the U.S. system relies more heavily on measures implemented at the processing stage (e.g., slaughterhouses).

Due to the tremendous progress made in DNA sequencing technology, it has become much easier to decode genomic data. The Smithsonian Institution's "Barcode of Life" initiative was highlighted as a successful application that has emerged from such advanced DNA sequencing technologies. There are numerous collaborative projects focusing on genetic sequencing that have taken place. For instance, the National Institutes of Health (NIH) has worked with the E.U. to fund the International Human Microbiome Project (IHMP), which was recognized as a successful international collaboration. The IHMP aims to characterize the human microbiome and, hopefully, identify its role in disease pathogenesis. It took approximately two years to overcome the ethical and data sharing issues that posed problems for this initiative and to develop the necessary protocols. Ten other organizations have joined the consortium working together on the IHMP, and the project now includes representatives from countries across five continents. Such collaboration was cited as an example of a framework that could be imitated to establish a global source attribution program for foodborne diseases.

It was noted that other international frameworks also help countries negotiate with each other on data sharing. For example, a database of microbes involving approximately 160 countries was favorably discussed. The U.S. Food and Drug Administration (FDA) has made a large investment in a total genome sequencing facility, including spending significant resources on a supercomputer for sequencing purposes. These points underscored the current, worldwide interest in the use of DNA technology and the need for avenues to share the results of such research.

Scientific opportunities and challenges

Despite evidence demonstrating endemic diseases comprise the main burden of foodborne diseases, it was recognized that significant resources are reactively expended on managing foodborne disease outbreaks. It was contended that a more anticipatory approach based on an effective attribution system is needed, on both national and international levels, to prevent and mitigate foodborne diseases. Some concerns were raised regarding barriers to such source attribution systems, including the costs of such endeavors and the level of collaboration that could truly be achieved across borders. It was acknowledged that a high level of participation is necessary to achieve a system of global attribution. Such a major commitment can be justified by the associated health care-related cost of foodborne illness in the U.S. alone (i.e., US\$152 billion annually).

There was general consensus that a global foodborne disease attribution system is both necessary and feasible. It was agreed that it may be necessary to implement such a system through a tiered approach because each country has differing capacities in infrastructure and human resources. Such a disease attribution system could eventually allow for real-time assessment of global trends related to pathogens and emerging diseases. This would accordingly move the focus beyond epidemics to include management of endemic diseases. It was proposed that, if political will can be garnered, such a system could be established within 10 years. Involving less-wealthy countries in the design and implementation of such a program will not only provide a broader source of data, but the associated training and capacity-building would provide these countries with the opportunity to bypass the mistakes made by wealthier countries in foodborne disease management.

The debate concerning how technological advances (e.g., DNA sequencing) have provided a significant opportunity for greatly improving food safety through extensive source attribution focused on identifying the benefits that could be realized by patients. Considerable enthusiasm was displayed vis-à-vis the possibility of a global source attribution system, which would significantly shorten the diagnosis-to-treatment time of patients by providing real-time data. Such a system would embody the One Health approach to disease management, be applicable to other fields such as environmental health, and provide yet another opportunity for transdisciplinary collaboration. Involving industry in the development and implementation of the source attribution system is imperative, particularly for accelerating the implementation of necessary technologies.

It was argued that an important first step in developing a source attribution system would be to establish the current baseline of microbial prevalence. The baseline information required would need to be gradually accumulated over time as data are collected and analyzed. This proposal stimulated debate on the feasibility and affordability of such a system. It was noted that the resulting long-term savings from reducing foodborne illness costs would more than offset the costs of developing and implementing such a system.

For source attribution to be successful, the data collected must be shared with other countries to increase the value of such information and to allow a global picture of foodborne microbes to emerge. A source attribution system has great potential to move beyond solely addressing foodborne microbes and could be expanded to include other microbes of interest. Such a global database of microbes would be an invaluable tool to the medical community since patients could be treated more easily and quickly, thereby possibly preventing disease outbreaks and loss of life. Human health professionals are often inconsistent in performing or reporting the results of microbial tests, especially since this is not always mandatory. Because of this inconsistency, gaps in essential source attribution data have been routinely identified. Likewise,

there was some disagreement over the feasibility of monitoring and collecting data at the farm level in countries with vast numbers of farms although it was noted that the number of farms is irrelevant when appropriate statistical sampling methods are employed.

While it was suggested that the U.S. should adopt some of the food safety measures employed in the E.U., it was not clear whether comparable efforts would be obtained in the U.S. This difference of opinion was exemplified by concerns that U.S. industries such as those involved with poultry would be reluctant to support the stringent measures necessary to establish an effective model. It was countered that the poultry industry in Denmark was instrumental in establishing the Danish *Salmonella* program. To be successful, direct industry incentives may be needed to promote the degree of participation that is essential to support any successful attribution program. There are, of course, inherent incentives for industry to cooperate, including the reduction of microbial contamination and outbreaks that can be economically damaging to the food industry.

Intellectual property rights issues and social-based controversies (e.g., privacy rights) related to gene typing, which would generate the enormous amount of gene sequencing required by a source attribution system, were extensively discussed during the debate. It was recognized that to effectively address pandemic outbreaks (e.g., the H5N1 influenza outbreak in Southeast Asia), a framework is needed that facilitates easy access to the pathogen strains necessary for research (particularly pertaining to vaccine manufacturing). Several potential barriers were mentioned. For instance, some countries have felt cheated when the genetic material they provided was later used to create vaccines they could not access and/or afford to purchase. Specifically, a case was mentioned where a vaccine was field-tested in a particular country, but once the vaccine was approved and produced it was too expensive to be used within the test country. This example illustrates the ongoing challenges related to corporate and social responsibilities.

It was lamented that countries are unaware of successes such as Denmark's in addressing food safety challenges. It was generally agreed that such successes should be reported and shared, so that others could benefit from them.

Policy issues

While the advances made in technology (e.g., DNA sequencing) can have a major impact on improving food safety through extensive source attribution, the political will and policies needed to support and use these advances are generally absent. Nonetheless, a global source attribution system would be a significant benefit to the public worldwide and, therefore, serious efforts to implement it must be made. The magnitude of such an undertaking could be justified when compared with the enormous health care costs of foodborne diseases. As a related proposal, it was also suggested that import testing expenditures could be shifted to point-of-production testing and monitoring for data. Data from testing and monitoring could then be used in the attribution system. Such an undertaking, however, would require support from a given country's political leadership.

For a source attribution system to be truly global, it must include less-wealthy nations. Therefore, greater understanding is needed regarding how to streamline and implement a tiered system that recognizes the differing capacities of various countries. Additionally, it was noted that a global source attribution system would require worldwide harmonization of standards.

Because microbes evolve over time, an effective source attribution system will require a robust surveillance system that is constantly monitoring microbes. A baseline of circulating microbes

must be established and standard protocols for monitoring will be needed to ensure uniformly useful data.

There was some agreement that non-European countries should follow the E.U.'s mandate to reduce food contamination and microbial foodborne diseases, such as *Salmonella*. Discussion on this point indicated that the reduction in microbial contamination in the E.U. occurred as a direct result of the E.U.'s goal-oriented program. While no clear alternative pathways were suggested, it was contended that it is possible for countries to achieve the required contamination reduction through differing mechanisms as long as the same outcome is achieved.

The need for a global initiative to address intellectual property rights and focus on sharing genetic material, was widely expressed. This initiative would provide a framework to share genetic material and data, not only through ongoing research, but also during times of crisis (e.g., the 2009 H1N1 pandemic). The current absence of such a framework delays rapid data dissemination, which is a detriment to protecting the public (e.g., hindering the timely production of vaccines). However, it must be recognized that such information generally originates from resource-poor countries, which are often reluctant to share data or samples because they generally have not garnered direct benefits from data sharing in the past (e.g., sharing genetic material has not regularly stimulated improved access to vaccines via subsidies). To ameliorate obstacles to data sharing and achieve political support for sharing efforts, it was suggested that these types of source attribution and intellectual property issues must be initially addressed at the highest leadership level possible — prime ministers or presidents. It was noted that value would be optimized by communicating data through existing reporting structures and frameworks, such as those managed by the Food and Agriculture Organization (FAO) or the World Health Organization (WHO).

Successes, and especially failures, in dealing with foodborne disease issues must be shared internationally to enable countries to either emulate achievements or avoid mistakes made by others. It was emphasized that information-sharing difficulties underscore the need for a functioning communication system, both regionally and internationally. Some proposed that it may be possible to strengthen existing communication networks within organizations such as FAO or WHO. Others felt that new international organizational efforts are required.

Changing focus from responding to foodborne disease outbreaks to addressing endemic foodborne disease issues was a common suggestion that was strongly supported. By concentrating on endemic foodborne diseases, the occurrence of outbreaks will lessen and treatment time of cases will also be reduced. Thus, it was generally agreed that a narrow focus on outbreak response is not a sound public health strategy.