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The Enter-net and Salm-gene databases of foodborne bacterial pathogens that cause human infections in Europe and beyond: an international collaboration in surveillance and the development of intervention strategies

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SUMMARY

The free movement of people and foodstuffs between countries are effective ways of distributing disease internationally. There is a requirement for a mechanism whereby data and information on potential outbreaks of foodborne pathogens can be disseminated rapidly to those who need to know. The Enter-net dedicated surveillance network provides this mechanism, complemented by the Salm-gene molecular typing network. Data on epidemiological and microbiological features on current cases, as well as background levels of infections are immediately available within the Enter-net databases. The Salm-gene network with its database of harmonized salmonella PFGE patterns from the participating European countries provides immediate, and electronically exchangeable, DNA fingerprints of outbreak strains. This prompt electronic dissemination of information regarding unusual events with international implications ensures that public health interventions can be implemented and cases of foodborne disease prevented.

INTRODUCTION

Foodborne pathogens do not respect national boundaries. It is now common for a foodstuff to be manufactured or harvested at one place and then distributed. This distribution can be within a country, across economic regions [such as the European Union (EU)], continents or even worldwide. Over €50 000 million worth of agrifoods (foods derived from agricultural sources, a frequent vehicle for foodborne pathogens) from countries in at least five continents were imported and distributed within the 15 EU countries in 1999 [1]. This demonstrates the size of this market.

Free movement of people and goods between countries can be effective ways of distributing disease internationally [2, 3]. An international response is required to combat these threats. Enter-net is a network that does this by conducting surveillance of foodborne pathogens internationally, predominantly within Europe [4]. Participating EU countries include Austria, Belgium, Denmark, England, Wales and Northern Ireland, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Scotland, Spain and Sweden (plus Norway and Switzerland within Europe). From autumn 2003 the EU Accession Countries; Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Malta & Gozo, Romania, Slovakia and Slovenia, have also been included in the network, as has Iceland from the European Economic

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Area countries. Countries outside the EU that formally participate in the network include Canada, Japan, South Africa and New Zealand; there are also informal links with many other countries.

A complementary research project, Salm-gene [5], enhances this network to provide common, harmonized molecular typing methods, and facilitates the rapid electronic transfer of the images captured by them in a digitized format. Countries participating in the Salm-gene network are: Austria, Denmark, England & Wales, Finland, Germany, Italy, The Netherlands, Scotland, Spain, with France acting as the software compatibility advisor.

Urgent enquiries regarding events with potential international implications and the early recognition of infections caused by contaminated foods, coupled with the prompt electronic dissemination of associated information ensures that public health interventions can be implemented and cases of foodborne disease prevented. These ensure the health of participating countries' citizens. We describe the role of Enter-net and Salm-gene in meeting these aims.

Objectives of Enter-net and Salm-gene

The specific aims of Enter-net and Salm-gene are as follows:

Enter-net

To maintain international databases of bacterial enteric pathogens (*Salmonella* and Verocytotoxin-producing *Escherichia coli*), which are readily available to those who need to develop intervention strategies to combat outbreaks of enteric disease.

To provide a mechanism for the rapid dissemination of urgent enquiries on unusual events that may have international implications.

To recognize and investigate international outbreaks, and contribute to intervention strategies through appropriate national agencies.

Salm-gene

To enhance the Enter-net salmonella database by using well-established molecular methods of strain subtyping, coupled with the electronic transmission of bacterial DNA fingerprints.

Bacterial foodborne infections have a major impact on both individuals unfortunate enough to be infected with the pathogenic bacteria involved, and also in terms of socioeconomic consequences, on the health services of member countries. In combination, these linked projects aim to improve the quality of life of citizens by reducing the impact of foodborne bacterial infections to both the individual and to the community.

Implementation

A key aspect of both Enter-net and Salm-gene is the development of rapid methods of information and data flows in relation to foodborne bacterial pathogens for all participating countries. This is achieved by the formation of two complementary networks, involving key microbiologists and epidemiologists from each country, feeding epidemiological and microbiological information on unusual events, supplemented by routine data, electronically on a regular basis to a coordinating centre at the Health Protection Agency (HPA) Communicable Disease Surveillance Centre (CDSC), based at Colindale, London, UK. The information and data received are then disseminated throughout the whole network.

Enter-net incorporates basic microbiological and epidemiological strain and outbreak data into the international databases. The strain characteristics are ascertained using internationally recognized schemes for serotyping, phage typing and antimicrobial susceptibility testing (AST) [6], and are maintained by international EQA (External Quality Assurance) schemes for serotyping and phage typing of *Salmonella*, the serotyping of VTEC, and AST for salmonellae.

The Enter-net *Salmonella* database is complemented by an electronic database of DNA characteristics of salmonella strains, based primarily on pulsed-field gel electrophoresis (PFGE) which is being developed within the Salm-gene project. The Salm-gene PFGE database comprises digitized DNA fingerprints incorporated within a BioNumerics software framework. PFGE gels are prepared using harmonized methods, with agreed running conditions [5]. A panel of strains for DNA subtyping by PFGE has been distributed to all participating laboratories for regular (3–6 monthly) external quality assurance of gel profiles (Fig.).

The electronic transmission of the resultant gel images to the hub in Colindale obviates the necessity for sending strains through the postal system for typing at designated community reference laboratories and can result in the almost instantaneous recognition of a common strain causing outbreaks simultaneously in several different countries [7]. This DNA strain

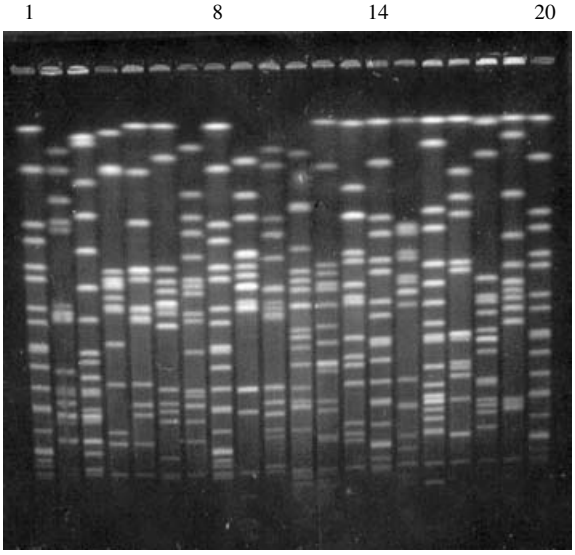

Fig. Salm-gene EQA panel for *Salmonella enterica*. Lanes 1, 8, 14, 20, *S. enterica* Braenderup (H9812, PulseNet); 2, Typhimurium DT104; 3, Typhimurium DT208; 4, Enteritidis PT4; 5, Enteritidis PT6a; 6, Hadar PT11; 7, Virchow PT47; 9, Agona PT15; 10, Heidelberg; 11, Indiana; 12, Montevideo; 13, Mbandaka; 15, Livingstone; 16, Anatum; 17, London; 18, Senftenberg; 19, Poona.

database can be complemented when appropriate by the incorporation of sequence data relating to the identification of specific drug-resistance genes, e.g. β-lactamases, chloramphenicol and dihydofolate reductase genes, or the identification of chromosomal mutations conferring resistance to specific antimicrobials (e.g. for resistance to quinolone antimicrobials by gyrase mutational analysis – GAMA [8]). Currently the Salm-gene database is only available online to the 10 countries participating in this project. However, once the methodology is finalized the database will be made available to all Enter-net participants.

A summary of key findings from both Enter-net and Salm-gene is made available to appropriate agencies, both nationally, e.g. the Food Standards Agencies within the Member States, or internationally, e.g. the European Food Safety Authority, for the development and application of appropriate intervention strategies to combat the spread of infection within or across national and international boundaries.

Both projects have dedicated websites (http://www.salmgene.net/ and http://www.hpa.org.uk/hpa/inter/enter-net_menu.htm). These incorporate both public and private (members only) viewing areas. Public health colleagues in related areas, e.g. veterinary microbiology and food hygiene, both within Europe and globally, also receive information through the coordinating centre about Enter-net and Salm-gene activities and are encouraged to access the relevant websites for regular updates.

Microbiologists and epidemiologists from laboratories in participating countries receive regular training and updates in the methods used in both the Enter-net and Salm-gene projects. Such training may take the form of secondments, which may last for up to 6 months, or focused workshops. For example a two-day training workshop in bioinformatics for Salm-gene participants was held in the spring of 2004. Phages for the typing of *S.* Enteritidis and *S.* Typhimurium are prepared and distributed by the HPA Laboratory of Enteric Pathogens (LEP), and representatives from participating countries spend time at the LEP for training in phage-typing techniques. In addition to these activities the Enter-net workshop is held annually and is hosted by a different country to foster the European ownership of, and participation in, the network. At this workshop all countries are represented and there are presentations of key microbiological and epidemiological findings relating to the recognition and control of foodborne disease within Enter-net countries. Likewise there is an annual Salm-gene workshop for all participants, and regular workshops for all staff engaged in the project for technical and scientific updates.

Complementary epidemiological and microbiological techniques are used in these projects. The basic epidemiological techniques include methods such as trend analysis and case-control studies, coupled with the development and management of international databases, statistical analyses of the epidemiological data and dissemination of resulting information.

All participants have access to the data outputs. Raw data are held in restricted databases; analysed data are available via the Internet. Results of investigations are regularly published in peer-reviewed journals. The methods developed within Enter-net and Salm-gene are amenable to expansion and can be utilized by primary identification and typing laboratories for other fields within the food chain, e.g. food and water, environmental and veterinary laboratories. Active collaboration is maintained with scientists and others in these areas to facilitate outbreak control and the development of intervention strategies.

Resources

The financial resources to coordinate the Enter-net in Europe come from the European Commission (EC)

Table. *Examples of international outbreaks of bacterial food poisoning recognized through Enter-net and Salm-Net, 1994–2002*

Year	Organism	Cases	Countries involved	Vehicle implicated	Ref.
1994	*Shigella sonnei*	100+	England & Wales, Germany, Norway, Scotland, *Sweden*	Lettuce	[9]
1995	*Salmonella* Stanley	200+	Finland, *USA*	Alfalfa sprouts	[10]
	S. Dublin	30+	France, *Switzerland*	Cheese	[11]
	S. Tosamanga	28	Eire, England & Wales, France, Germany, Sweden, *Switzerland*	None confirmed	[12]
1996	*S.* Agona	4000+	Canada, *England & Wales*, Israel, USA	Kosher snack	[13, 14]
	S. Anatum	19	Eire, *England & Wales*, France, Scotland	Dried baby milk powder	[15, 16]
1997	*E. coli* O157	15	Denmark, England & Wales, *Finland*, Sweden	Water (Fuerteventura)	[17]
	S. Livingstone	100+	Austria, Czech Republic, Denmark, England & Wales, Finland, Germany, The Netherlands, Norway, Sweden	Travel to Tunisia	[18]
1998	*S.* Newport	100+	*England & Wales*, Finland	None confirmed	[19]
1999	*S.* Paratyphi B	309	Denmark, England & Wales, Finland, Germany, Ireland, *Norway*, Sweden, Switzerland	Turkish holiday resort	[20]
2000	*S.* Typhimurium DT204b	392	*England & Wales*, Germany, Iceland, The Netherlands, Scotland	Lettuce	[7, 21]
2001	*S.* Livingstone	54	*Norway*, *Sweden*	Fish pie	[22]
	S. Stanley	100+	*Australia*, *Canada*, England & Wales, Scotland	Peanuts (China)	[23]
	S. Oranienburg	500+	Austria, Belgium, Denmark, Finland, *Germany*, The Netherlands Sweden (product in Canada), Croatia, Czech Republic	Chocolate (Germany)	[24, 25]
	S. Typhimurium DT104	100+	Australia, Canada, England & Wales, Germany, Norway, *Sweden*	Halva (Turkey)	[26]
2002	*E. coli* O157	21	*England & Wales*, France	Cucumber from Belgium	[27]

Index countries are italicized.

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RESULTS

Since the formation of Enter-net (as Salm-Net) in 1993 numerous food-related outbreaks of enteric pathogens have been recognized and public health intervention strategies have been developed and coordinated wherever possible (Table).

Since the initiation of the Salm-gene project in 2001 the phenotypic methods of strain typing used in Enter-net have been augmented by DNA-based subtyping, coupled with the rapid electronic exchange of DNA profiles as well as epidemiological data. To ensure worldwide coverage, the methods used within Salm-gene are compatible with those used in the PulseNet networks in the United States, Canada, Asia Pacific and Latin America [28] and the same reference strain of *S.* Braenderup is used.

Examples of successful outbreak recognition and intervention which have been facilitated by the combination of phenotypic and molecular typing coupled with the rapid exchange of microbiological and epidemiological data include the investigation of an international outbreak of salmonellosis between May and October 2001 in which the vehicle of infection was peanuts in their shells imported from China. In this outbreak the most important serotypes were

Stanley and Newport and cases were identified in England & Wales, Scotland, Australia, and Canada. Isolates of *S.* Stanley from peanuts and human patients were indistinguishable by PFGE [23]. Rapid sharing of electronic DNA images was a crucial factor in delineating the outbreak, which highlighted global problems caused by the international movement of foods originating from countries with a high incidence of endemic salmonellosis. In December 2001 a potentially massive international outbreak of salmonellosis in several European countries and North America was averted following the exchange of PFGE profiles and epidemiological data through the Salm-gene and Enter-net networks [24, 25]. The causative agent here was chocolate contaminated with *S.* Oranienburg. The contaminated product was used in several brands that were regularly consumed by children. Although over 500 infections were recognized over a period of 6 months, the withdrawal of this product undoubtedly contributed to the control of a potentially debilitating outbreak amongst a vulnerable population subset over the Christmas period.

In outbreaks such as those listed above, following the rapid identification of the contaminated product public health interventions have included: public warnings issued by appropriate authorities; withdrawal of the product; information about product contamination relayed to the source country; and development of control measures to prevent contamination at source. The added value to public health investigations which has been provided by the Enter-net and Salm-gene networks includes not only outbreak recognition resulting in withdrawal of the product and the prevention of subsequent infections, but also a major saving on resources to the health services of the participating countries in the event of major outbreaks of foodborne infection.

Learning points and conclusions

Key learning points from the Enter-net and Salm-gene projects in combating international outbreaks of foodborne pathogens include:

- The importance of 'good practice' in all aspects of the projects, coupled with rigorous quality assurance for all participating laboratories.
- The harmonization of typing methods, including both phenotypic and molecular (DNA-based) typing.
- The integration of traditional and newly developed methods of strain identification and typing.
- The rapid transfer of information and epidemiological and microbiological data.
- Common databases containing epidemiological and microbiological data, including DNA fingerprint analyses.
- Networking – developing personal contacts and building professional trust and confidence between participating countries.
- The rapid communication of findings to relevant medical and scientific personnel in the participating countries and elsewhere, to first-line medical practitioners in the community and hospitals, and to authorities responsible for food safety.
- Maintaining transparency of information and ensuring that such information is placed in the public domain.

The Enter-net and Salm-gene networks are working in tandem to provide an interactive network for the rapid identification and investigation of international outbreaks of foodborne pathogens facilitated by the globalization of food supplies. The added value of these networks is that they rapidly disseminate information on contaminated foodstuffs to allow the timely implementation of public health interventions, and hence protect the European and international populations from infections with foodborne bacterial enteric pathogens.

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APPENDIX

Enter-net

Project leaders: O. N. Gill, W. J. Reilly, H. R. Smith.
Scientific coordinator: I. S. T. Fisher
Administrator: F. Stalham
Current participants. **Austria**: F. Allerberger, C. Berghold, R. Strauss. **Belgium**: J.-M. Collard, G. Marchant, D. Pierard. **Canada**: L.-K. Ng, P. Sockett. **Denmark**: P. Gerner-Smidt, K. Mølbak, F. Scheutz. **England & Wales**: S. J. O'Brien, E. J. Threlfall, L. R. Ward. **Finland**: M. Kuusi, A. Siitonen. **France**: H. de Valk, P. Grimont. **Germany**: A. Ammon, H. Karch, H. Tschäpe. **Greece**: K. Mellou, P. T. Tassios, A. Vatopoulos. **Ireland**: M. Cormican, P. McKeown. **Italy**: A. Caprioli, I. Luzzi, A. Tozzi. **Japan**: N. Okabe, H. Watanabe. **Luxembourg**: P. Huberty-Krau, F. Schneider. **The Netherlands**: W. van Pelt, Y. van Duynhoven, W. Wannet. **New Zealand**: F. Thomson-Carter, D. Phillips. **Norway**: J. Lassen, L. Vold. **Portugal**: C. Furtado, J. Machado. **Scotland**: J. Coia, J. Cowden, M. Hanson. **South Africa**: K. Keddy. **Spain**: A. Echeita, G. Hernández-Pezzi. **Sweden**: Y. Andersson, S. Löfdahl, R. Wollin; **Switzerland**: H. Hächler, H. Schmid. Plus the many other contributors who have been involved in the project over the years, and in the many investigations of international outbreaks.

Salm-gene

Project coordinator: E. J. Threlfall
Participants. **Austria**: C. Berghold. **Denmark**: P. Gerner-Smidt. **England & Wales**: I. Fisher, A. Gatto, O. N. Gill, J. Green, S. J. O'Brien, T. Peters. **Finland**: A. Siitonen, S. Lukinmaa, U.-M. Nakari. **France**: P. Grimont. **Germany**: H. Tschäpe. **Italy**: I. Luzzi. **The Netherlands**: W. Wannet. **Scotland**: J. Coia. **Spain**: A. Echeita. Plus all the technical personnel within the laboratories of each participating country.

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