Chapter 20
Populations, Patients, Germs and Genes: Ethics Of Genomics and Informatics in Communicable Disease Control

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20.1 Introduction

Infectious diseases are still among the major causes of morbidity and mortality worldwide. Current estimates are that each year – mainly in developing countries – 500 million people become ill and more than 1 million die from malaria; 2 million of the 33 million people living with human immunodeficiency virus (HIV) infection die of acquired immune deficiency syndrome (AIDS); and 1.7 million of the 14 million with active tuberculosis (TB) die from it (WHO 2000, 2007, 2009). Millions of children, particularly, die each year from respiratory and diarrheal diseases, the rates of which are largely determined by political, socioeconomic and environmental factors. Although there has been a progress in the control of vaccine preventable diseases in developing countries, vaccines for malaria, TB and HIV/AIDS remain elusive and increasing antimicrobial resistance makes treatment difficult, even when it is available.

In industrialized countries, food-borne, respiratory and healthcare associated infections (HAIs) cause significant excess morbidity, mortality and healthcare costs. In the USA each year, an estimated 1.7 million HAIs cause ~100,000 deaths; 76 million food-borne diseases lead to 5,000 deaths. Many of these infections and deaths could be prevented if evidence-based control measures were properly implemented (Mead et al. 1999; Klevens et al. 2007). Clearly "smarter" strategies are needed to control communicable diseases.

Modern technology has enabled large scale screening for human genomic markers of susceptibility or resistance to infection and comparative studies of microbial genomes and is providing new knowledge about relationships between humans and

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disease-causing microbes. This knowledge will reveal new targets for vaccines, antimicrobial agents, diagnostics and disease surveillance, which can be exploited to improve disease prevention, control and management.

Because infectious (or communicable) diseases affect communities – rather than merely independent individuals – new strategies to control and prevent infection involve complex relationships within and between populations. The disproportionate burden of communicable diseases among the most disadvantaged populations provides a challenge for new technology to improve disease prevention and control where conventional strategies have failed.

20.2 Infectious Diseases Ethics

The emergence of the discipline of human bioethics in the 1950s and 1960s coincided with a prevalent (but, with hindsight, unwarranted and dangerous) belief that the problems of infectious diseases had been solved by sanitation, immunization and antibiotic therapy. The much-quoted pronouncement that "it is time to close the book on infectious disease" is usually attributed to former US Surgeon General William Stewart. Although there appears to be no evidence that he ever actually said this, "the sentiment was certainly widely shared" at the time (Sassetti and Rubin 2007). This widespread complacency remained largely unchallenged throughout most of the twentieth century. It was dispelled by the unfolding of HIV pandemic and the plethora of other emerging and re-emerging infectious diseases that followed (or in some cases preceded) it, but it had already contributed to the gross neglect of infectious diseases by bioethicists (Smith et al. 2004; Francis et al. 2005; Selgelid and Selgelid 2005). AIDS was a rare exception, but many of the ethical issues it raised – confidentiality, discrimination, patients' rights and sexual freedom – were not specifically related to its status as an infectious disease.

Belatedly, this neglect is now being addressed; infectious diseases have at last come to the attention of bioethicists. During the twenty-first century, public health ethics has become a rapidly growing sub-discipline of bioethics, and much of the public health ethics literature has focused on infectious disease in particular. In addition to AIDS, attention has especially focused on severe acquired respiratory syndrome (SARS), pandemic influenza planning and issues related to bioterrorism (Reid 2005; Thompson et al. 2006; Miller et al. 2007). There has also been debate about the ethics of issues such as: intellectual property rights, relating to antimicrobial agents and their implications for the access to essential treatment of infectious diseases (Gupta et al. 2005) and the relationship between marketing of antimicrobials and the emergence of antibiotic resistance (Selgelid 2007).

Although infectious diseases are no longer the most common cause of death worldwide, they are still major contributors to illness, loss of productivity and premature death in developing countries and among poor and disadvantaged people everywhere, despite the long history of successful prevention and control. Communicable diseases have implications far beyond their effects on individual sufferers and their

immediate families. Because they can be rapidly fatal in previously healthy people and their spread is often unpredictable and indiscriminate, they can cause fear, panic, social disruption, political overreaction and victimization, out of proportion to the actual disease burden or risk (Smith et al. 2004). The explosive, but relatively short-lived, spread and high mortality of SARS in 2003 led to international socioeconomic repercussions affecting tourism, trade and international relations and costing billions of dollars. Disproportionate responses are often exacerbated by the florid language used by media and politicians, with analogies to terrorism or war ("flesh-eating"; "silent killer"; "superbug"; "plague"; "attack"; "struck down"). The fact that many communicable diseases are preventable or can be successfully treated can provoke recriminations against individuals or institutions, which are perceived to have failed.

Infectious disease ethics occupies a position between the individualistic perspective of conventional bioethics and the traditionally more collective approach of public health and incorporates elements of both. The former emphasizes the right of individuals to make decisions about their health, based on their own interests or preferences (autonomy), limited only by the potential of those decisions to harm others (the harm principle). The latter is based on utilitarian principles, whereby decisions are determined by the best overall outcomes (in terms of aggregate and/or average human well-being), even if some individuals may be disadvantaged as a result. Recently, Margaret Battin and colleagues have suggested a new approach – that ethical decision-making about infectious diseases should take place behind a Rawlsian "veil of ignorance", a concept developed as the basis for making fair decisions about distributive justice (Battin et al. 2009; Rawls 1971). They propose that patients with infectious diseases – and indeed anyone – can be seen, actually or potentially, as both a victim and a vector of infection (Battin et al. 2009). Behind the "veil of ignorance", the decision-maker does not know her actual status – victim and/or vector – but acknowledges that she could be, or could become, either.

Infection affects communities, not just individuals; everyone is both part of a human social network and host to billions of micro-organisms which can spread from person to person. Most of these microbes are benign or even essential to health, but a minority are potentially harmful to people carrying them or to others with whom they interact. Levels of susceptibility to infection vary between individuals, as determined by, *inter alia*, where and how they live, their age, underlying health, nutritional status, life-style choices and genetic makeup and the measures they take to protect themselves, such as immunization. No one can be reliably protected from infections due to respiratory viruses, food-borne bacteria or pathogens spread by mosquitoes. Like the patient with fever and cough or diarrhea, each of us is a potential victim and a potential vector. Ethical infectious disease policy will respect the interests of both patients with infections – who want care and protection, without discrimination – *and* of the rest of the community who seek protection from infection. The latter include not only apparently healthy individuals, some of whom are unwitting carriers of potentially dangerous pathogens, but also people at increased risk of infection, because of underlying disease or genetic predisposition.

In this chapter we explore how recent advances in microbial and/or human genomics and modern information technology can improve our understanding of

communicable diseases and provide better strategies to manage, prevent and control them. We try to anticipate and suggest ways to meet the social and ethical challenges that will arise. Some ethical issues, such as those relating to research in developing countries or human genomics, are neither new nor specific to communicable diseases and have been debated at length. Others, which arise from application of new microbial diagnostics and pathogen profiling, enhanced communicable disease surveillance and informatics, have been explored less extensively, if at all. We examine issues such as informed consent, privacy and confidentiality, autonomy, resource allocation, quality control, compliance with evidence-based practice and disease surveillance, prevention and control, in these contexts, from behind a "veil of ignorance," by assuming that anyone could be victim or vector of infection.

20.3 Challenges in Infectious Diseases Genomics Research

20.3.1 Genetics and Disease Susceptibility

It is well established that susceptibility to infection varies between individuals and that a component of this variation is inherited (Cooke and Hill 2001). For example, malaria parasites are known to have contributed, over millennia, to the evolution of the human genome, by selecting gene mutations, such as those causing sickle cell disease and glucose-6-phosphate deficiency (G6PD) that enhance survival of heterozygous carriers living in malaria-endemic areas (Daily et al. 2008). Differences in susceptibility to malaria and TB have been recognized between different but closely related ethnic groups (Modiano et al. 1996); and large epidemiological, twin and genetic studies have provided insights into the hereditable proportions of susceptibility or resistance to a number of infectious diseases. There are well documented associations between certain human leukocyte antigen (HLA) genes and susceptibility to severe malaria, rapid progression of HIV infection to AIDS, development of overt TB disease or leprosy and hepatitis B carriage (Cooke and Hill 2001). However, HLA genes account for only a small component of genetic susceptibility to infection, which (like many other types of disease) is apparently determined by interactions between many different genes, acquired characteristics (e.g., nutrition, previous exposure) and environmental factors.

Sequencing of the human genome and advances in metagenomics have provided opportunities to search more broadly for genetic traits that contribute to infectious disease susceptibility and host–pathogen interactions that can be targeted by new vaccines or drugs. Genome-wide mapping and analysis of hundreds of polymorphic markers in family groups and matched case/control studies of diseases of interest are currently underway. The aim is to identify genomic regions linked to communicable disease risk. These studies are difficult, because the diseases most suited to this type of investigation are most common in the poorest countries with limited health (and research) infrastructure and whose residents are understandably wary of possible exploitation by researchers from rich countries (Cooke and Hill 2001).

20.3.2 The Malaria Genomic Epidemiology Network

The MalariaGEN project illustrates some of the ethical challenges involved in human genomics research. It was established in 2005, with joint funding from the Gates Foundation and the Wellcome Trust. Members of this network of independent investigators contribute to a central DNA repository and to databases of core phenotypic data. One of the goals of MalariaGEN is to determine why only a small proportion of children develop life-threatening malaria, in communities where all children are repeatedly infected with the malaria parasite, *Plasmodium falciparum*. Researchers are using the technique of genome-wide association (GWA) analysis, which involves mapping half a million or more single nucleotide polymorphisms (SNPs) in thousands of individuals – without the need for whole genome sequencing – to identify sequence variants that correlate with disease risk, using statistical inferences based on common patterns.

The study has the potential to benefit millions of children but involves the complex methodological, social and ethical challenges which are common to any clinical research in developing countries or human genomics research anywhere. The involvement of numerous independent investigators, in rich and poor countries, from disciplines as varied as clinical and community medicine to state-of-the-art genomics and bioinformatics, requires a balance between standardization and uniformity of practice, on the one hand, and the need for sensitivity to diverse cultural settings, on the other (The Malaria Genomic Epidemiology Network 2008).

Informed consent and privacy. Children with severe malaria often die within hours of the admission to hospital. This raises logistical issues of recruiting subjects, classifying clinical phenotypes correctly and collecting specimens for genetic studies, without compromising medical care in the resource-poor settings where most cases occur. Language and cultural barriers complicate effective communication with the parents of potential research participants. It can be difficult to convey the distinction between diagnosis and medical research. Unfamiliar concepts must be explained in the local language – perhaps through the use of metaphors drawn from local experience – but even then there may be misunderstandings. Guidelines for obtaining informed consent, without creating undue anxiety, are being developed and carefully evaluated by MalariaGEN researchers, in collaboration with local communities.

Actual and perceived protection of the anonymity of research participants and their communities is critical to the development of trust between researchers and participants. In the MalariaGEN project, local databases which contain both phenotypic and genotypic data are designed to comply with appropriate ethical guidelines to ensure data security. A data access committee oversees researchers' access to individual genomic data. Qualitative research is underway to identify the concerns, of community members and other stakeholders, about the collection and use of ethnicity data in relation to genomic epidemiology, which could result in stigmatization if misused. Although it is commonly claimed that

the use of de-identified data cannot harm research subjects, this is not necessarily so; research findings can sometimes lead to the development of policies or behaviors that are harmful to (e.g., ethnic) groups of which the subject is a member. This kind of risk should be explained to parents of potential research subjects as part of the informed consent process. Guidelines are essential for the publication and release of ethnicity data to provide maximum scientific benefit while respecting and protecting the interests of participants and their communities.

Ownership of data and intellectual property. When many different research groups and parent institutions are involved, ownership of data and intellectual property is complex and potentially contentious. There is often institutional pressure on researchers to patent any discoveries with the potential for commercial development. The principle agreed by MalariaGEN is that intellectual property protection will be sought only if it will facilitate the translation of research results into affordable health benefits for the populations most in need. Any resulting financial gains will be returned to the participating communities.

20.3.3 The Human Microbiome Project

The Human Microbiome project (McGuire et al. 2008) is another multicenter program, which entails familiar ethical, legal, and social challenges in a novel setting. It is an investigation of the relationship between humans and microbial societies that inhabit all body surfaces and play a vital role in human health. It will establish a database of microbial DNA and RNA, based on sampling of 15–18 mucosal and skin sites from about 250 healthy individuals aged between 18 and 40 years of age, about half of whom will provide a follow-up set of samples within 12 months. Blood will be collected and stored for human genome and immune response investigation from a subset of around 10 participants. Extensive demographic and medical historical data will be collected.

Informed consent, respect for autonomy, and communication. Disclosure of the possible risks involved in providing samples for this project is difficult because of the current dearth of knowledge about the human microbiome and what future research questions may arise from linking microbial with human genomic data. As in other areas of research involving biobanking, there is controversy as to whether participants should be asked to give consent only for specific investigations already planned or blanket consent for future research. Almost by definition, blanket consent involves consent to research that neither subject nor researcher may, at the time it is given, be able to understand or predict. It has been argued, however, that requesting general consent is acceptable so long as participants are well informed about the uncertainties, and there is a strong governance structure to protect the privacy of participants and ensure that future research is consistent with their expectations (Caulfield et al. 2008). This would generally involve the appointment of an independent multidisciplinary monitoring body, including lay representatives, to

promote public trust and ensure respect for participants' autonomy; therefore, blanket consent would be limited to future research approved by this body.

It is likely that analysis of the preliminary results of this project will identify characteristics of individual microbiomes, which could affect the health of the participant (e.g., risk of obesity or type 2 diabetes or changes due to medical interventions, such as antibiotic therapy). The point at which information, which could affect lifestyle or medical decisions, should be shared with participants or their physicians will be controversial. The study will almost certainly identify healthy individuals who are infected or colonized with potential pathogens that could cause future disease, under circumstances which are currently unpredictable and likely to vary between individuals. Should participants be told that they are potential victims or vectors if the level of risk is unknown? Researchers are unlikely to be qualified to manage potential clinical issues; at what stage should a medical practitioner be consulted, if at all?

The answers will depend on the validity and clinical significance of the findings and whether the participant has expressed a desire to know the results. For example, identifying nasal colonization with *Staphylococcus aureus* would require a different response from the discovery that the participant has asymptomatic genital infection with a sexually transmissible pathogen, which is a potential risk to others. If there were no apparent risk (e.g., of infection) to others, the participant's "desire to know" may be a key consideration. For this kind of research, discussion and negotiation on details regarding disclosure of findings to the subject and/or others should arguably become a more important part of the informed consent process.

Data confidentiality and security. Confidentiality of individual genomic and microbiomic data will compete with the need for researchers to share data and will depend on the extent to which data can be linked to individuals. For the human microbiome project, microbial DNA sequence data will be coded and released into publicly accessible databases, but clinical information and individual human DNA data will be coded and stored in controlled-access databases for later correlation with microbial data. Only aggregate human genomic data will be released into public databases. Whether, how, and by whom data are linked remain controversial because of the existing uncertainty about the extent to which microbial data can reveal individual identity and could be used to stigmatize individuals or groups. These are among the risks that will be discussed with participants when seeking informed consent.

Representativeness and justice. In most clinical research projects, subjects are selected and so not truly representative of the whole population. This means that the risks and potential benefits are not equally shared and the results may not be generalizable. The human microbiome project excludes children and older adults, to ensure that interpretation is not complicated by metabolic changes related to growth, puberty, or aging. However, subjects are chosen to include as many racial and ethnic groups as possible even though this could risk identifying false associations due to unrecognized confounding factors. While these problems are often unavoidable, they must be recognized and accounted for in the data analysis and conclusions.

20.4 Application of Pathogenomics and Informatics Research to Communicable Disease Diagnostics and Prevention

Over the past half-century or so, the natural histories of many human infectious diseases have changed, often fundamentally and often as a result of deliberate or unwitting human intervention. For example, immunization has (actually or almost) eliminated a few (smallpox, polio, and measles) and has controlled many other diseases (diphtheria, rubella, tetanus, hepatitis B). However, although vaccines are available, they have been less successful in controlling some diseases (e.g., pertussis, TB, influenza), and immunization remains elusive for many (e.g., most respiratory and diarrheal diseases, malaria, and HIV infection). Antimicrobial agents are available for the treatment of many types of infection but, with few exceptions, their efficacy has been compromised by the development of resistance in target pathogens. On the other hand, changes in land and water use, agriculture, animal husbandry, transportation, climate, or lifestyle, as well as increasing numbers of people who are immunocompromised because of AIDS or immunosuppressive drug therapy, have led to the emergence of new and opportunistic human pathogens which were once regarded – if they were recognized at all – as animal, rather than human, pathogens or as harmless commensals.

Recently, studies of microbial genomes have helped explain many of these phenomena at the molecular level and have led to changes in anthropocentric concepts of pathogens and commensals. In future, they will reveal new ways to protect humans from illness and death by identifying new targets for antimicrobial agents or vaccines. At least one genome (and often several) of all significant human pathogens has now been fully sequenced. Comparison of genomes of different strains of the same and related species can provide extensive information about microbial evolution and the relative importance of different types of genetic variation (e.g., mutation, insertion, deletion, duplication, recombination, or lateral transfer) and how they occur. We now know that many of the genes that determine virulence or antibiotic resistance are transferred on mobile genetic elements (plasmids, bacteriophages, transposons, pathogenicity islands) between different strains or species; this can dramatically amplify the effects of selection pressures (see Chap. 12 for details). These mobile elements can be exploited in the development of diagnostic and surveillance tools, but they also complicate the interpretation of test results and attempts to control disease transmission.

20.4.1 Diagnostics and Antibiotic Resistance: Ethical Implications

Increasingly sophisticated "smart" diagnostics, which are currently under development, will potentially allow more sensitive and specific pathogen detection and profiling (Sintchenko et al. 2007) which could significantly improve communicable disease

diagnosis, management, and control. If their benefits are to be fully realized, the predictive values of new tests (i.e., the ability to predict whether or not the patient has the infection which the test is intended to diagnose) must be thoroughly evaluated, with reference to clinical outcomes not just through comparisons with existing diagnostic methods. Moreover, the evaluation should not end with their introduction into routine practice.

Currently, the microbiology laboratory's task is to identify a relevant pathogen in a clinical specimen and report it, with an antibiotic susceptibility profile, if appropriate. Conventional diagnostic methods are relatively slow, and the interpretation of results is often subjective. For example, whether or not a pathogen is identified and reported in a culture from a site with normal flora may depend on the skill and experience of the laboratory scientist. The interpretation of the result depends on clinical information, which is often not available to the scientist, and technical information which may not be available to the clinician – such as the type and quality of specimen, diagnostic method used, and the pathogen strain. The clinician's interpretation of the result will often determine the antibiotic choice, but if this is inappropriate, the outcome may be compromised (Khatib et al. 2006; Chapman et al. 2008).

In the near future (and to some extent already), multiplexed nucleic acid detection (NAD) systems, which target 10s, 100s, or even 1,000s of highly specific nucleic acid sequences, will identify, in virtually real-time, any of a large number of possible pathogens relevant to the site of the specimen or the clinical syndrome. At the same time, they will also determine whether the pathogen identified carries specific virulence determinants or antibiotic resistance genes and/or whether its profile is similar to those of pathogens isolated from other people (a cluster of infections) (see Sect. 20.4.2). New or unusual pathogens can be included in these systems at little or no extra cost, which will save time by identifying less common or less obvious pathogens sooner than is currently possible.

In a clinical research setting, the ability to study the prevalence and clinical associations of many different species or genetic markers simultaneously will provide new knowledge about the etiology, epidemiology, and pathogenesis of infectious disease syndromes and interactions between species. Multiplexed NAD systems will allow inclusion of species which are usually harmless commensals but occasionally are potential pathogens, copathogens or opportunists (Wang et al. 2008; Masue et al. 2007; Mckechnie et al. 2009). With appropriate analysis of clinical, epidemiological, and microbial data, this will help define their role and the circumstances, if any, in which they cause disease.

Properly designed clinical research studies (currently, a rarity in diagnostic microbiology) will clarify the circumstances in which the detection of virulence or antibiotic resistance markers in mixed flora is significant (Table 20.1). For example, genes that encode resistance to newer β-lactamase and carbapenem antibiotics or vancomycin are often carried in commensal gut flora, but can be transferred to virulent Gram negative bacilli (such as *Enterobacteriaceae*) or enterococci, respectively, under selection pressure from antibiotic therapy (Chapman et al. 2008; Iredell et al. 2006). Multiresistant *Enterobacteriaceae* or vancomycin resistant enterococci (VRE) are much more likely

Table 20.1 Examples of nucleic acid detection methods to detect virulent and/or antibiotic resistant pathogens and potential interpretation problems

Species	Gene marker(s)	Potential confounders	Indication for testing
Methicillin resistant *Staphylococcus aureus* (MRSA)	Methicillin resistance gene – *mec*A – or other SCC*mec*[a] genes; *S. aureus* species-specific gene – *nuc*	Other methicillin resistant staphylococci in same specimen (false positives); sequence variation in SCC*mec* (false negatives)	Screening for carriage (nares, groin etc); rapid identification in blood culture
Vancomycin resistant enterococci (VRE)	*van*A, *van*B, *vanB*2/3 (genes encoding vancomycin resistance)	Enteric anaerobes and streptococci carrying *vanB* (Ballard et al. 2005)	Screening – rectal swabs
Clostridium difficile	*tcd*A, *tcd*B or *tcd*C (toxin genes)	Not all *C.difficile* isolates contain relevant toxin genes	Diagnosis of diarrhea
Diarrhegenic *E. coli*	Shiga toxin – stx1, stx2+/−*eae*; +/−other toxin/virulence genes	Genes may be present but not expressed; sequence variants	Diagnosis of diarrhea
Various commentals and environmental bacterial species	Antibiotic resistance genes or transmissible elements	Genes may be carried, harmlessly by commensals	Screening to guide future therapy or infection control

[a] SCC*mec* is the staphylococcal cassette chromosome (a mobile genetic element), which carries the methicillin resistance gene *mecA*

than commensal or environmental bacteria to cause disease or spread to other patients and are more difficult to treat than their antibiotic susceptible counterparts.

However, even after careful evaluation, in a research setting, there are pitfalls in the translation of new diagnostic methods into practice. Although the interpretation of conventional microbiological results is often empirical and subjective, it is based on years of experience. Faster and more sensitive methods will provide more information, more timely and reproducible results and detection of a broader range of pathogens than conventional methods; they may uncover new infectious disease syndromes or identify previously unrecognized carriers. Confirmation that a new (and usually more expensive) assay will improve clinical outcomes requires ongoing prospective analysis of reliability and cost-effectiveness, which is difficult in a diagnostic laboratory setting. However, without it, the use of new assays could lead to unnecessary therapy or medicalization of "normal" conditions.

For example, screening patients for carriage of multiresistant organisms, such as methicillin resistant *Staphylococcus aureus* (MRSA) using rapid NAD methods, can improve hospital infection control by allowing more timely and appropriate isolation of patients and can guide appropriate antibiotic therapy. However, the sensitivity and specificity of some NAD methods differ from those of conventional methods, leading to potentially adverse consequences. Failure to identify some carriers (Thomas et al. 2008) will increase the risk of transmission to other patients. On the other hand if NAD assays identify more carriers than conventional methods, it can be difficult to distinguish increased sensitivity from false positive results. Either way, it will mean that more patients will be isolated, possibly unnecessarily (Humphreys 2008), which is costly, can adversely affect clinical care (Stelfox et al. 2003) and may cause unnecessary anxiety.

These uncertainties emphasize the importance of not only carefully evaluating the performance characteristics of a new test, but also of defining its purpose and clinical impact. Is it performed for the benefit of the patient on whom it is performed or for the benefit of other patients? While benefits to other patients may justify screening and isolation of patients who are colonized with multiresistant organisms, the degree of benefit, cost-effectiveness, and possible alternative strategies to achieve similar results must be assessed (Jeyaratnam et al. 2008; Wenzel et al. 2008; Buhlmann et al. 2008). A key question in public health (and infection control) ethics is: how great must the expected danger to public health (or to hospital patients) be to justify involuntary isolation of an individual who is a potential source of danger? Assuming that the appropriate metric of danger to public health is the "disability-adjusted life year" (DALY), for how many DALYs (x) would confinement of a person (e.g., a carrier of MRSA) for time t be justified, assuming that the free movement of that person could be expected, on average, to result in x or more DALYs?

The effects of changes in test turn-around times, reliability and predictive values, on patient care should be critically assessed, as new diagnostic methods are introduced. As part of this assessment, the point at which clinical research – with its ethical safeguards such as the informed consent of subjects – merges into routine practice will need to be defined. We need to develop standards for interpretation and reporting of the results of new diagnostic tests, in consultation with clinicians, to improve consistency. At present, introduction of new diagnostic and screening methods generally

occurs independently in individual laboratories; test evaluation is often limited to comparison with existing methods and continued satisfactory performance in quality assurance programs, as required by accreditation bodies. Differences between methods used by different accredited laboratories suggest that some are "better" than others, but this information is not readily accessible to clinicians or patients and the criteria on which choices are based are often poorly defined. New tests are usually more expensive that conventional methods. It is usually assumed – and often true – that any increased costs are justified by better patient outcomes and savings elsewhere, but formal cost-effectiveness studies that are needed to confirm this are rarely done. Even if extensive evaluation demonstrates that a new method can improve patient outcomes and/or reduce costs, introduction of the test is often prevented or delayed because of the difficulty of transferring costs (and savings) between cost centers.

In summary: the widespread application of the new science of pathogenomics to infectious diseases diagnosis – with appropriate prospective evaluation of the clinical impact – should not only improve outcomes, but also provide a better understanding of many aspects of human infection and disease such as:

- The spectrum of diseases caused by known pathogens
- The possible infectious etiology of diseases of unknown cause
- The ecology of human microflora and factors that affect them
- The incidence and significance of colonization with different strains of known pathogens and of carriage, by commensals or opportunistic pathogens, of virulence or antibiotic resistance genes
- Potential interactions that may affect virulence, simultaneous carriage of combinations of pathogens, and/or commensal species
- The routes and mechanisms of transmission of pathogens between people and of genes between different microbial strains or species

20.4.2 Strain Typing for Pathogen Tracking

Surveillance is essential for disease control. It has been described as "the eyes of public health" (Fairchild et al. 2008). Although laboratory-confirmed cases of infectious diseases represent a small minority of notified cases (and an even smaller proportion of all cases), laboratory notification is more specific, reliable, and consistent than clinician notification. For many notifiable infectious diseases, simple species identification of the pathogen is inadequate and strain typing is required to monitor trends or to investigate outbreaks. However, until recently, the efficacy of surveillance has been limited by the fact that conventional strain typing methods are relatively slow, insensitive, and often performed only by specialized public health laboratories. Recent developments in microbial genomics have led to the development of faster and more discriminatory methods (see Chap. 2, 4, and 17), but their introduction has been limited and haphazard, in part because of inadequate recognition of the importance of improved strain typing methods, for disease control.

Delays of 2–3 weeks, in obtaining strain typing results mean that recognition of outbreaks is delayed and subsequent investigation of the cause is compromised. For example, in cases of food-borne disease, it may be impossible to identify a common food source, because victims cannot remember what they ate weeks before. Outbreaks involving large geographic areas, which are investigated in different jurisdictions and laboratories, may only be recognized after very large numbers of people have been affected, if at all.

In the early stages of the 2009 "swine flu" outbreak, there was no rapid strain typing method to distinguish the novel influenza H1N1 strain from other circulating H1N1 seasonal influenza A strains. This meant that many recent travelers to Mexico, where the outbreak began, or to the USA or Canada, where human-to-human transmission was reported early, were isolated for many days, awaiting results from the few reference laboratories able to identify the strain (initially, only after it was isolated in cell culture). However, sequences of several relevant antigen genes (hemagglutinin [H], neuraminidase [N], and polymerase [P]), from "swine flu" H1N1 strains isolated in different parts of the world, were published (http://www.ncbi.nlm.nih.gov/genomes/FLU/SwineFlu.html) within a very short period. This meant that culture-independent strain identification and typing methods soon became available to diagnostic laboratories around the world and played an important role in subsequent surveillance and control.

The availability of culture-independent diagnostic and strain typing systems for many pathogens of public health importance will make it possible for diagnostic laboratories to simultaneously identify relevant pathogenic species and their strain profiles, in a single assay, and report the results to public health authorities, within hours. Faster recognition and investigation of outbreaks will limit the number of cases and reduce the risk of new outbreaks. Some rapid strain typing methods are already available and in use. However, like diagnostic methods, new strain typing methods need to be carefully evaluated to ensure that their use translates into better public health outcomes. Unfortunately, the variety of different methods, the speed with which they are already being introduced, and limited funding for surveillance studies make prospective evaluation of risks, costs, and benefits, difficult. In addition, prospective evaluation will be impracticable without easy access to patient demographic, clinical, and outcome data and will be impracticable without sophisticated informatics tools to analyze these data.

20.5 Information Science and Technology for Patient Management and Communicable Disease Control

20.5.1 Health Information Systems

Rapid advances in medical science and therapeutics and increasing specialization have increased the demand for more accessible diagnostic, epidemiological, and

therapeutic information, interpretive reporting of diagnostic test results, and clinical decision support systems. Electronic patient records (EPRs), networked with relevant clinical databases and information systems, are a logical response to these needs and are predicted to improve the quality, efficiency, safety. and reduce the cost of healthcare (Hillestad et al. 2005). They could also significantly improve disease surveillance and control (Friedman 2006; Chaudhry et al. 2006) and population health.

Linking clinical data from EPRs with microbiological results will enhance and personalize clinical decision support, e.g., for antibiotic prescribing (Sintchenko et al. 2008; Thursky et al. 2007). Linking clinical information with strain typing data will allow comparison of strains from different patients, in order to identify linked cases or outbreaks and to define their limits in space and time, much more rapidly than is currently possible (Gallego et al. 2009). Prospective surveillance of aggregated clinical, diagnostic, pathogen profile, and outcome data will help identify previously unrecognized risk factors or microbial strains which are associated with more severe disease or adverse outcomes. They will provide a basis for risk assessment tools to alert public health or infection control practitioners to the need for quarantine or investigation of contacts. The elements of an integrated clinical and public health information system may include:

- On-line laboratory test order entry and reporting systems
- Rapid, microbiological diagnosis and strain typing
- Access to components of individual EPRs, including demographics and relevant medical history (e.g., medical or environmental risk factors, presenting complaint, and laboratory test results)
- Data mining/analysis software that can identify and interpret epidemiological links
- Risk assessment and decision support systems to guide public health or infection control action
- Online prescribing and decision support to guide antibiotic therapy, if required, based on laboratory results and clinical history

20.5.2 Practical Application

Imagine this (future) scenario (only some components of which are currently plausible or - some would argue - even desirable):

- A patient presents with symptoms of an infectious disease; the doctor records the clinical findings in the EPR and orders diagnostic tests online.
- An informatics program with appropriate scanning software will scan the EPR for relevant demographic and medical risk factors and may prompt the doctor to seek additional information (e.g., about recent travel, diet, or contacts).
- The program will analyze the clinical data, provide a differential diagnosis and a list of appropriate laboratory tests, and recommend empirical antibiotic therapy,

if indicated, based on therapeutic guidelines, local susceptibility data and the medical history. (Artificial intelligence systems capable of making diagnostic and management decisions are still largely aspirational).

- The doctor will confirm, change, or override the laboratory test orders or prescription before transmitting them, electronically, to the laboratory and pharmacy, respectively.
- A pharmacy information system will establish that the drug dose is correct and will check for possible interactions with other current medications before the drug is dispensed and ready for the patient to collect, along with a personalized information sheet about precautions and potential adverse side-effects.
- The laboratory request form and a list of specimens required will be available when the patient arrives at the specimen collection center; specimens will be delivered to the laboratory and processed rapidly.
- If a relevant pathogen is identified, appropriate strain typing and/or antibiotic susceptibility testing will be performed. A personalized laboratory report, with interpretative information, will be generated and sent immediately or after review by a clinical microbiologist.
- The treating doctor's report may include a modified recommendation for treatment (e.g., a different antibiotic, based on the pathogen susceptibility or a recommendation to discontinue treatment); in some cases, a warning of potential complications (based on patient and pathogen profiles) will be added.
- If the infection is notifiable a second report will be sent, automatically, to the relevant public health authority. The strain profile will be compared with those of other strains in a database linked to similar laboratory databases within the same jurisdiction, country or, potentially, internationally.
- This analysis will identify outbreaks and monitor the geographic and temporal distribution of different strains in different populations, which may provide early warning of the emergence of new strains or detect potential vaccine failures. Spatial and temporal parameters for the detection of outbreaks due to the same strain will be modifiable to account for varying geographic areas or time periods from a few days to months or years.
- If an outbreak is identified, the report may also list other individuals infected with the same pathogen strain and any relevant medical or epidemiological risk factors (recorded in their EPRs) and suggest appropriate public health action or a possible common source or index case.

The use of integrated clinical and laboratory systems and informatics tools, linked to decision support systems, with continuous analysis and feedback of epidemiological, clinical, outcome and other data, could improve our understanding of disease epidemiology. It would enable assessment and improvement of the predictive accuracy (likelihood ratios) of diagnostic and pathogen profiling methods and the efficacy and cost-effectiveness of treatment and preventive interventions; it should improve clinical outcomes. Nevertheless, as with other novel health management systems, if there is inadequate validation or precautions against inappropriate use, it could lead to unnecessary anxiety, the stigmatization of

infected patients, unwarranted infringement of liberty (if coercive public health restrictions are inappropriately applied) and increased healthcare costs.

20.6 Ethical Implication of Improvements in Biosurveillance

20.6.1 Electronic Patient Records

EPRs are computerized medical records, which allow storage, easy retrieval, searching, and sharing of different types of medical and non-medical data (including laboratory results). Many different EPR systems have been described but are still in limited use in hospitals and healthcare systems. Many potential benefits – including better medical care, reductions in medical errors and litigation, and significant cost savings – have been claimed, but, so far, there is limited hard evidence to support the claims. A report commissioned by the Rand Corporation, in 2005, suggested that the introduction of EPRs could save >$US 80 billion in healthcare costs in the USA (Hillestad et al. 2005). However, this has been recently disputed by physicians from Harvard Medical School hospitals – where EPRs have been in use for many years – who claimed that, despite some real benefits of EPRs, the projected cost-savings and quality improvement were exaggerated (Groopman and Jartzband 2009). They expressed concern about the potential use of EPRs to gather evidence about costs, which could be used to limit the use of expensive medical or surgical interventions, and warned against the introduction of expensive technology without rigorous evaluation and evidence.

There has been very little analysis of the potential improvement in disease surveillance by the use of EPR data (and, to our knowledge, none specifically related to communicable disease control). In paper-based medical systems, "privacy is protected by chaos" (Rothstein 2008), records are fragmented and often difficult to compile or locate. EPRs can facilitate the optimal use (mining, analysis, linkage) of data to improve health outcomes and save lives. To achieve this, EPRs would need to be universal (everyone has one), longitudinal (cradle – or womb – to grave) and networked with each other and with other information systems (Fairweather and Rogerson 2001); for example, in the USA, the Nationwide Health Information Network (NHIN) is being established to develop electronic formats that will make records of different types that are compatible and transportable across networks and across the country.

The characteristics which make EPRs most useful are also those that cause most public concern about the potential for inappropriate access and use. Patients will be reluctant to disclose intimate information, no matter what the potential public benefit, if they fear that it could be used to their disadvantage by government officials, employers or insurance companies. Safeguards based on sound ethical principles will be needed to protect privacy and to prevent harm or disadvantage to individuals while promoting public health and gaining optimal benefit from limited public health resources.

Despite increasing concern and legislation relating to the privacy of personal information (e.g., in Australia, the Federal Privacy Act, 1988 – http://www.austlii.edu.au/au/legis/cth/consol_act/pa1988108/), health information is generally treated as a separate category of personal information (e.g., New South Wales [NSW] Health Records and Information Privacy Act, 2002 – http://www.lawlink.nsw.gov.au/lawlink/privacynsw/ll_pnsw.nsf/pages/PNSW_03_hripact). If the use of health information for disease surveillance were to be expanded, there would be certain requirements for the protection of privacy, such as:

- Development of ethical standards for the development, implementation, evaluation and modification of bioinformatics software programs for the storage and analysis of patient data (Gotterbarn and Rogerson 2006)
- Publicly debated, transparent and binding software and hardware standards to protect privacy, confidentiality, integrity and security of data
- Clearly defined principles governing access to identified data for the purposes of disease surveillance or research, including by whom and under what circumstances access is allowed, how it will be monitored and under what circumstances the individual must either give consent or be informed that their record has been accessed

Breaches of privacy may be objective (i.e., resulting in fraud or denial of a service or of freedom) or subjective (i.e. resulting in second or third parties having access to intimate information, which may cause distress, without objective harm). These different consequences may need to be considered differently in assessing the risks associated with the use of EPRs. It has been suggested (Dyson 2008) that the best way to prevent breaches of privacy would be to allow individuals to control access to their own data. However, informed consent for the selective release of medical records (McKinney et al. 2005) would be difficult to obtain and is unlikely to be practicable if data are to be accessible in an emergency or for disease control purposes.

A number of standards exist already, including some designed to protect confidentiality of data transferred across national borders in compliance with international health-related applications e.g., International Organization for Standardization (ISO) 22857:2004 (Kalra and Ingram 2006).

20.6.2 Communicable Disease Notification and Surveillance

Even for communicable disease surveillance, some data can be de-identified and used to monitor trends in disease rates, to identify risk factors and to assess the effectiveness of public health interventions. However, communicable disease surveillance often requires individual patient identification to allow contact tracing, outbreak investigation and the implementation of appropriate control measures and to determine the outcomes. For example, under the NSW Public Health Act, 1991 (http://www.austlii.edu.au/au/legis/nsw/consol_act/pha1991126/), disclosure of

certain data is allowed, but there are strict principles governing the collection, storage, access and use of information. In practice, there is little public opposition to the notification of identifiable, personal information to health authorities for communicable disease surveillance, which is accepted as necessary in the public interest. However, this may be, in part, because current communicable disease surveillance systems are generally slow, insensitive, and nonspecific. They are relatively ineffective in detecting, preventing, or interrupting disease outbreaks (Eng and Eng 2004) but also difficult for unauthorized individuals to access and use inappropriately. Thus, privacy is protected by "information friction" (Dyson 2008). The type of future networked EPRs and databases envisaged in the scenario above will be more effective than conventional systems, but potentially more at risk of abuse, with more serious consequences.

Protection of genetic or infectious diseases data is necessary to prevent objective breaches of privacy, such as harassment or stigmatization, which could lead to denial of insurance or jobs. However, improvements in disease control, based on efficient surveillance across large populations could not be achieved if large numbers of people refused to participate because of fear that results could be misused. Denmark has one of the most advanced EPR networks, which allows individuals to block information in their records. This option is reported to be rarely exercised but greatly valued (Rothstein 2008). At present, the disclosure of health information for public benefit is often regulated by laws that are so broad that, in practice, no limits are placed on their scope. EPR networks could, paradoxically, protect privacy more effectively, by allowing limits to be imposed on the scope of data that could be accessed. Scanning software could be programmed to select only information relevant to a specific purpose, using 'contextual access criteria' – software algorithms which specify that, for an enquiry of type X, only data A, B, and C are needed.

Networking of EPRs and other information systems raises new issues relating to informed consent. For effective disease surveillance, all patient records would need to be accessible to data scanning software. Limiting the data that can be accessed to what is relevant may be theoretically possible but defining, in advance, what is relevant may be difficult. Informed consent for individual investigations or routine surveillance would be impracticable. It will, therefore, be important that the implementation of electronic health data management systems and their use for disease surveillance be preceded and accompanied by adequate information, public debate, transparency and appropriate safeguards.

20.6.3 The Use of New Laboratory Data

Networking laboratory information systems. The use of laboratory data for electronic disease surveillance would require that laboratory results from different laboratories mean the same thing. While this may seem obvious, existing differences in result interpretation, predictive values of different methods and lack of consensus on optimal methods, mean that considerable harmonization of laboratory practices will

be required. Different laboratory management structures, funding sources, referral patterns, and accountabilities between private and public laboratories or between primarily diagnostic and reference/public health laboratories will make this difficult, but not impossible.

Laboratory staff and directors are often reluctant to share details of tests numbers or methods, quality assurance programs are generally conducted anonymously, and accreditation authorities are required to maintain strict confidentiality, in relation to procedures (including any deficiencies) within individual laboratories. Clearly, issues of trust, commercial confidentiality and quality assurance will need to be addressed at the same time, as details of, laboratory testing methods and interpretation and compatibility of different types of information system.

The ability to generate personalized interpretive laboratory reports based on demographic and clinical data in the EPR would assist clinicians who are often unfamiliar with rapidly changing laboratory methods and their interpretation. The ability of the laboratory information system to rapidly identify a possible outbreak, by identifying clusters of microbial isolates with similar genetic profiles could significantly reduce the size and impact of communicable disease outbreaks. Personalized, targeted decision support can potentially reduce inappropriate antibiotic use, healthcare costs (Sintchenko et al. 2005), the emergence of drug resistance and adverse drug effects.

The use of laboratory data for clinical quality and safety. Laboratory information systems can be used by health authorities to monitor the quality of patient care in individual hospitals (Fairweather and Rogerson 2001) by gathering statistics about infections which develop after a patient's admission to hospital – such as *S. aureus* or specifically MRSA blood stream infections. This has benefits for both potential patients and the general public who arguably have a right to information about the quality of care in hospitals to which they may be admitted in future. In some countries, data related to HAIs are publicly reported, and the occurrence of cases judged to be preventable may incur penalties. For example, the Centers for Medicare and Medicaid Services (CMS) in the USA have recently announced that they will no longer reimburse healthcare facilities for costs related to certain HAIs that could have reasonably been prevented through the use of evidence-based guidelines (http://www.idsociety.org/newsArticle.aspx?id = 6,852).

Many health professionals and administrators are concerned about financial penalties for "preventable" infections and about possible misinterpretation of publicly reported HAI rates because of differences in case-mix and reporting systems (Stone et al. 2005) between hospitals. Some commentators fear that hospitals may refuse to care for high-risk patients who are more likely to develop infections. However, electronic reporting and data scanning software have the potential to analyze individual patient risk factors and adjust incidence data according to the differences in case mix between different types of hospital.

Like most other applications, the use of surveillance data for quality assurance has the potential to improve patient care and the performance and accountability of individual clinicians and healthcare organizations, but there is, also the potential for misuse, breaches of confidentiality and data security not only for patients, but also for professionals, who are usually very wary of any type of performance monitoring.

20.6.4 Surveillance Ethics: A New Paradigm

Advances in surveillance technologies raise the need for the development of frameworks and guidelines for surveillance ethics. Research ethics has traditionally been a central theme of bioethics discourse, for which monitoring guidelines and procedures are well established in health and research institutions, but the ethics of disease surveillance is a relatively unexplored area in need of debate. On the one hand, there are questions about the technical similarities and/or differences between surveillance and research and how they affect practice, if at all (Fairchild and Bayer 2004). In theory, these may be the questions of definition and semantics, but there are currently major differences, which may or may not be justified, in the way these two areas are perceived by practitioners and funding bodies. From an ethical perspective, the key question is whether there are *morally relevant* differences between research and surveillance such that the ethical requirements for the former should not also apply to the latter. According to research ethics, for example, informed consent is paramount and the interests of the individual are supposed to take priority over those of science or society (Declaration of Helsinki - available at: http://www.wma.net/e/policy/b3.htm). Given that research and surveillance are similar insofar as both aim to generate information to promote health outcomes, the crucial questions are whether, why and how much, if at all, ethical requirements for disease surveillance should be less stringent than those of biomedical research.

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