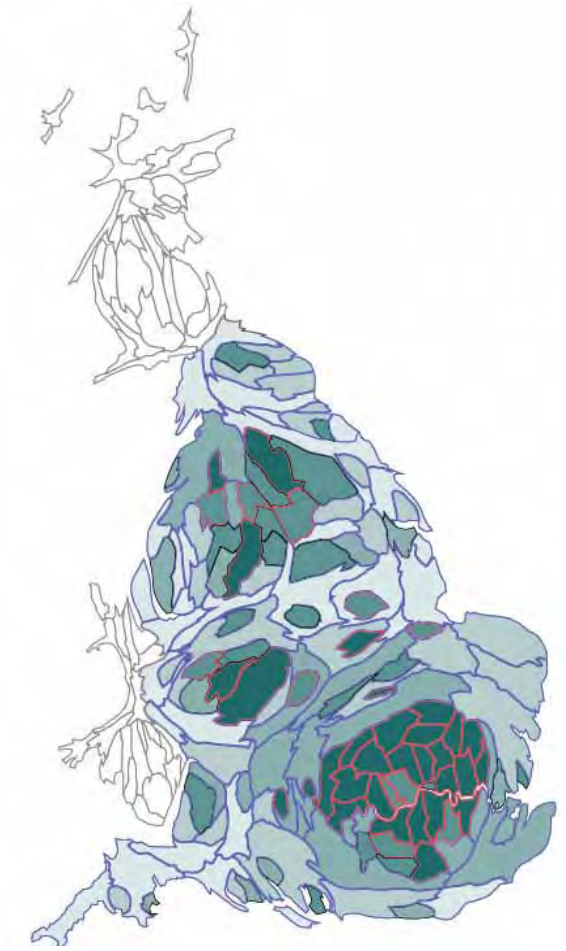
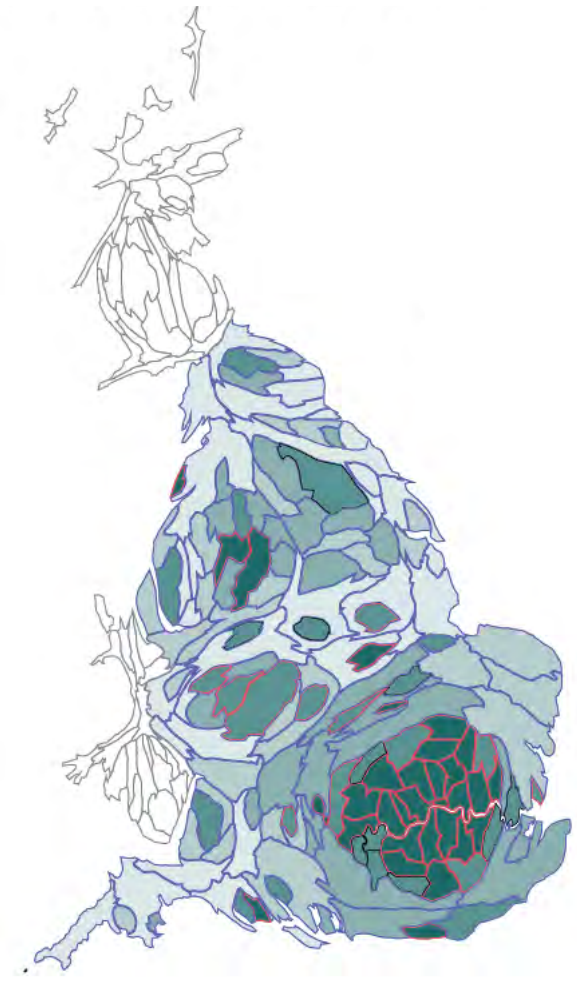
Annual Report of the Chief Medical Officer

Volume Two, 2011

Infections and the rise of antimicrobial resistance





Dear Reader

My annual report is published in two volumes. Volume One, "On the State of the Public's Health", was published in November 2012. It focused on epidemiology and surveillance, using innovative visualisation techniques to display data on over 130 health topics. I have had a lot of positive feedback about Volume One and plans are already underway to build upon this repository of information.

It is my intention to release a second volume of my annual report each year. Whereas Volume One is broad in scope, Volume Two is an in-depth review into a specific issue. This year I am addressing infection and antimicrobial resistance.

Antimicrobial resistance is a very real threat. If we have no suitable antibiotics to treat infection, minor surgery and routine operations could become high risk procedures. I am making 17 recommendations to named organisations to address this threat. As with Volume One, all the data used to produce images in this report are available in Microsoft Excel files, by local authority (where possible) via data.gov.uk

Yours ever

Sally C

Prof Dame Sally C Davies

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Editors and authors

This report could not have been produced with the generous input of the following people and their teams.

Editor

David Walker[1,2]

1 Regional Director of Public Health, East Midlands
2 Deputy Chief Medical Officer (Designate), Department of Health

Editor

Tom Fowler[1,2]

1 Locum Consultant in Public Health, Department of Health
2 Honorary Research Fellow, University of Birmingham

Project Manager

Orla Murphy[1]

1 Chief Medical Officer's Events and Project Manager, Department of Health

Chapter Authors

Chapter 1

Sally C Davies[1]

1 Chief Medical Officer and Chief Scientific Advisor, Department of Health

Chapter 2

Mike Catchpole[1], Sarah Tomkins[2], Paul Cleary[3]

1 Director of Infectious Disease Surveillance and Control, Health Protection Agency
2 Senior Scientist (Epidemiology), Health Protection Agency
3 Regional Consultant Epidemiologist, Health Protection Agency North West

Chapter 3

Anthony Kessel[1], James Wilson[2], Ibrahim Abubakar[3], John Watson[4], Richard Pebody[5], Maria Zambon[6], Gayatri Amirthalingam[7], Aileen Kitching[8], Mary Ramsay[9], Gwenda Hughes[10], Valerie Delpech[11], Emma Savage[12], Sarika Desai[13], Ellen Bloomer[14], Peter Goldblatt[15]

1 Director Public Health Strategy and Medical Director, Health Protection Agency
2 Lecturer in Philosophy and Health, Director, Centre for Philosophy, Justice and Health, University College London
3 Professor in Infectious Disease Epidemiology, Research Department of Infection and Population Health, University College London and Tuberculosis Section, Respiratory Diseases Department, Health Protection Agency
4 Head, Respiratory Diseases, Health Protection Agency
5 Consultant Epidemiologist, Head of Influenza and Acute Respiratory Virus Surveillance section, Health Protection Agency
6 Director of Reference Microbiology, Health Protection Agency
7 Consultant Epidemiologist, Immunisation, Hepatitis & Blood Safety Department, Health Protection Agency
8 Speciality Registrar (Public Health Medicine), Health Protection Agency
9 Consultant Epidemiologist, Health Protection Agency
10 Consultant Scientist (Epidemiology), Health Protection Agency
11 Consultant Epidemiologist, Health Protection Agency
12 Principal Scientist STI Surveillance, Health Protection Agency
13 Senior Scientist (Epidemiology), Health Protection Agency
14 Research Fellow, UCL Institute of Health Equity, University College London
15 Deputy Director, UCL Institute of Health Equity, University College London

Chapter 4

David Wyllie[1], Lily O'Connor[2,3], Sarah Walker[2,3], Jim Davies[3], Elizabeth Sheridan[1], Susan Hopkins[1,4], Tim Peto[2,3], Derrick Crook[2,3]

1 Public Health England
2 Oxford University Hospitals NHS Trust
3 University of Oxford
4 Royal Free London NHS Foundation Trust

Chapter 5

Keith W Ridge[1], Kieran Hand[2], Mike Sharland[3], Ibrahim Abubakar[4], David M Livermore[5]

1 Chief Pharmaceutical Officer, Department of Health
2 Consultant Pharmacist, Anti Infectives, University Hospital Southampton NHS Foundation Trust

3 Professor of Paediatric Infectious Diseases, Paediatric Infectious Diseases Unit, St George's Healthcare NHS Trust
4 Professor in Infectious Disease Epidemiology, Research Department of Infection and Population Health, University College London and Tuberculosis Section, Respiratory Diseases Department, Health Protection Agency
5 Professor of Medical Microbiology, Norwich Medical School, University of East Anglia, Norwich

Chapter 6

Mike Sharland[1], Shamez Ladhani[2], Mary Ramsay[3], Paul Heath[4], Sonia Saxena[5], Elizabeth Koshy[6], Alex Bottle[7], Jo Murray[8], Paul Griffiths[9]

1 Professor of Paediatric Infectious Diseases, Paediatric Infectious Diseases Unit, St George's Healthcare NHS Trust
2 Paediatric Infectious Diseases Consultant, St George's University London
3 Consultant Epidemiologist, Health Protection Agency
4 Professor of Paediatric Infectious Diseases, St George's University London
5 Clinical Senior Lecturer, Imperial College London
6 NIHR Doctoral Research Fellow, Imperial College London
7 Senior Lecturer in Medical Statistics, Imperial College London
8 PhD Student, Imperial College London
9 Professor of Virology, University College London

Chapter 7

Michael Levin[1], Mike Sharland[2]

1 Professor of International Child Health, Imperial College London
2 Professor of Paediatric Infectious Diseases, St George's Healthcare NHS Trust

Chapter 8

Nigel Field[1], Laura Shallcross[2], Russell M Viner[3], Robert W Aldridge[4], Anne M Johnson[5]

1 NIHR Academic Clinical Lecturer, University College London, and Public Health Registrar, London Deanery
2 MRC Clinical Research Fellow, University College London, and Public Health Registrar, London Deanery
3 Professor of Adolescent Health, University College London
4 Wellcome Trust Research Training Fellow, University College London and Public Health Registrar, London Deanery
5 Professor of Infectious Disease Epidemiology, University College London

Chapter 9

E L C Ong[1]

1 Consultant Physician and Honorary Senior Lecturer, Department of Infection & Tropical Medicine, Royal Victoria Infirmary, Newcastle upon Tyne

Chapter 10

John Watson[1], Colin Brown[2], Gavin Dabrera[3], Elizabeth Sheridan[4], Nicola Lovett[5], Christopher P Conlon[6]

1 Head, Respiratory Diseases, Health Protection Agency
2 Academic Clinical Fellow in Infectious Disease and Microbiology, Health Protection Agency
3 Specialist Registrar (Public Health), Health Protection Agency
4 Consultant Microbiologist, Health Protection Agency
5 Specialist Registrar in Geratology, Oxford University Hospitals NHS Trust
6 Reader in Infectious Diseases and Tropical Medicine, University of Oxford

Chapter 11

edited by Tom Fowler[1,2]

with substantial contributions from

Kevin Dean[3], Martin Stewart-Weeks[4], David Cooksey[5], Stephen J Fowler[6], Paul Dark[7], Ashley Woodcock[8], Sue Hill[9], Tom Fowler[1,2], David Walker[10,11], David M Salisbury[12], Sharon Peacock[13,14], Danny Altman[15], Stephen Wyllie[16], Mike Catchpole[17], Andrew Hall[18], Derrick Crook[19]

1 Locum Consultant in Public Health, Department of Health
2 Honorary Research Fellow, University of Birmingham
3 Healthcare Director, Cisco Internet Business Solutions Group
4 Director, Global Public Sector Practice, Cisco Internet Business Solutions Group
5 Chair, Aegate Limited
6 Lecturer and Honorary Consultant Respiratory Medicine, University of Manchester
7 Reader and Honorary Consultant Intensive Care Medicine, University of Manchester
8 Professor of Respiratory Medicine, University of Manchester
9 Chief Scientific Officer, Department of Health
10 Regional Director of Public Health, East Midlands
11 Deputy Chief Medical Officer (Designate), Department of Health
12 Director of Immunisation, Department of Health
13 Honorary Consultant Microbiologist, Health Protection Agency
14 Clinical Microbiologist, University of Cambridge
15 Professor of Immunology, Imperial College London
16 Head, Zoonoses Team, Department of Environment, Food and Rural Affairs
17 Director of Infectious Disease Surveillance and Control, Health Protection Agency
18 Professor of Epidemiology, London School of Hygiene and Tropical medicine
19 Consultant Microbiologist, University of Oxford

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Chapter 1

Chief Medical Officer's summary

Chapter author
Sally C Davies[1]

1 Chief Medical Officer and Chief Scientific Advisor, Department of Health

Introduction

My annual report must fulfil two functions; to provide an assessment of the state of the public's health, and to advise government on where action is required. To achieve this I have decided to produce two volumes of my annual report. The first volume is a compendium of the data and information used to describe the health of the population. The narrative of this second volume (hereafter referred to as "this report") fulfils the independent advocacy role of the Chief Medical Officer.

Volume One is available at http://www.dh.gov.uk/health/2012/11/cmo-annual-report/, and contains data on trends and spread of many of the infectious diseases discussed in this report.

The purpose of this report

This report sets out my response as Chief Medical Officer to the challenges and opportunities facing us in the prevention, diagnosis and management of infectious diseases. It includes a series of recommendations that are framed as challenges for action.

Historically, the annual reports of the Chief Medical Officer for England have provided an important record of the health of the nation and highlighted the major health and public health challenges facing government. This report continues that tradition, primarily focusing on the health challenges we face, but it is different to those of preceding years. Firstly, it is thematic, focussing on a specific field of health and disease. Secondly, it draws upon the expertise of a broad range of leading clinicians, academics, experts and service providers to highlight the problems faced by policy-makers, doctors and research scientists when tackling existing and emerging threats from infectious diseases. I intend to take this approach and focus on a different theme each year.

The choice of infectious diseases

I have chosen infectious diseases as the subject for my first in-depth report for a number of reasons;

- Globally, this group of diseases represents the greatest cause of death and burden of disease. In developed countries, following the success of vaccination and antimicrobial drug therapy, infectious diseases have been overtaken in prominence by chronic diseases such as heart disease and cancer, but the threat has not gone away. New infectious diseases are emerging every year and older diseases which we managed to control are re-emerging as they become resistant to our antimicrobial drugs.
- As advances in medicine in other areas extends lives, it is also creating new groups of generally older individuals that are particularly vulnerable to infection, such as those immunosuppressed due to cancer treatments and organ transplants.
- The supply of new antimicrobial agents has slowed and levels of antimicrobial resistence are increasing, limiting our treatment options.

It is essential that we continue to develop our defences against infectious disease and to do this we must align policy, science, innovation and clinical excellence.

The intended audience for this report

This first chapter, as my response to the infectious disease challenges identified in this report, is primarily aimed at politicians and policy makers. When we look at our successes in controlling meticillin-resistant *Staphylococcus aureus* (MRSA; an 84.7% reduction by 2011 from the 2003/4 peak) and *C. difficile* (a 53% reduction by 2011 from 2008), we can see that action with political will behind it can have a tremendous effect. This is particularly the case when there is cross party agreement on priorities.

In this report, I identify those issues that require specific focus and action by our politicians.

As well as recommendations aimed at politicians, there are recommendations that I look to policy makers, commissioners and providers of health and public health services to act upon. These focus on the need for appropriate education of health professionals and the public, particularly around antimicrobial resistance, the need for developing and implementing surveillance methods, which should be particularly robust around the infectious disease risks that represent the greatest threats, and the need for a greater focus on prevention. Within this chapter, I specifically identify to whom particular recommendations are addressed.

The remainder of the report consists of the chapters written by a number of internationally recognised experts asked to provide an assessment of the key issues facing us in infectious diseases. These chapters were written to inform me, as Chief Medical Officer, of the areas I need to champion for action. The chapters were written independently by the authors[i] and represent their views rather than mine, but they are also the basis on which my calls for action are made.

There is a remarkable consensus around the key underlying issues, even though there was some disagreement around specific actions necessary and which areas should be prioritised first. As such, these chapters will be of most interest to people with a need for a more detailed understanding of the issues and the evidence base for my recommendations. This includes the scientific community, health and public health professionals involved in the prevention, control and treatment of infectious diseases and

i Minimal editing was also undertaken by the editors of the report to ensure greater consistency of structure and style. All changes were agreed by chapter authors.

some policy makers. It is also likely to be of interest to other countries facing similar challenges.

The report is not aimed at the general public but as it addresses issues that affect all of us, it will be useful to those with an interest in this area.

The evidence base for the recommendations

The process for the development of the report is new. Experts drawn from diverse organisations including universities, hospitals, policy teams, industry, the Health Protection Agency and the Department for Environment, Food and Rural Affairs (Defra) collaborated in a series of workshops to identify important and emerging issues in the field of infectious diseases. The focus was on opportunities and threats that could inform the development of policy and practice. Some of these experts were then invited to take the lead to produce chapters to describing the most important infectious disease challenges as they affect individuals throughout the various stages of their lives. These chapters address the different issues of infectious disease across the life stages (perinatal, child, adolescent and young adult, adult and older adult).

Three issues emerged which cut across all the life stages and there was consensus that their importance required specific, separate pieces of work. These were:

- the emergence of microorganisms (bacteria, viruses, fungi and parasites) that are resistant to antibiotics and other antimicrobial drugs,
- healthcare-associated infections, which are a concern for all people accessing health services, and
- the social and environmental context in which infections occur.

These issues are the subject of separate expert reviews in the report. Finally, a group of experts was convened to consider the future challenges and opportunities in infectious diseases. This focused on producing specific pieces on the opportunities offered by developing technologies in vaccines and the emerging science of genomics, allied to the developing science of "Big Data".

The approach taken in this report is essentially to harness expert review and opinion on the challenges facing us. This report is not intended to be a comprehensive guide to infectious diseases. Based on their knowledge and experience, our experts have deliberately been selective in the issues that they chose to highlight.

I do not address pandemic influenza preparedness in depth. This has been the focus of Chief Medical Officer annual reports in the recent past. Instead our focus was on areas where there are new opportunities to advance my understanding and our ability to combat infectious diseases.

In compiling this report I have been mindful of the existing government advisory mechanisms in the field of infectious disease. I have endeavoured to avoid straying into those areas except to try and link up different strands of work to describe the overarching challenges that we face.

The importance of infectious diseases

Mortality rates for infectious diseases have declined in all developed countries over the last few decades. Part of the decrease is due to improvements in hygiene and sanitation but the introduction of mass vaccination programmes and effective medical treatments has dramatically reduced the mortality rate. However, infections are still a major cause of death in the very young and in the elderly, particularly in those with coexisting chronic disease. It is therefore, important to recognise that infections are still a major cause of illness in England.

In 2010, in England, infectious diseases accounted for 7% of all deaths, 4% of all potential years of life lost (to age 75)[ii] and were also the primary cause of admission for 8% of all hospital beds days[1]. They are responsible for a large proportion of sickness absence from work. In the UK in 2011, around 27.5 million days were lost due to minor illnesses, such as coughs, colds and 'flu. This represented 21% of all days lost and was the most common reason given for sickness absence.[2]

Despite the decline in mortality rates, the burden of disease and the economic impact of infections and infectious diseases, estimated in chapter 2 as approximately £30 billion each year, remains high.

A characteristic of infectious disease which separates it from other types of illness is that the causative factors undergo constant and rapid change. Progress in the management of other conditions can be viewed as a stepwise progression, as understanding of the aetiology and pathogenesis of the disease increases. In the case of infections, we have learned that microorganisms also progresses and as we develop new prevention and treatment options, so the microorganism can evolve resistance mechanisms to defeat us.

In the last 50 years, we have developed a wide array of vaccines and antimicrobial drugs which have been effective in winning battles against infections, though the origins of both immunisation and antibiotic use go back much further than this.

The next 50 years may be very different. Resistance of microorganisms to our drugs is increasing and organisms are emerging with resistance to a wide variety of agents, rendering them ineffective, so we risk losing "the war". The supply of new replacement antimicrobial agents has slowed dramatically and we face the prospect of a future where we have far fewer options in the treatment of infectious

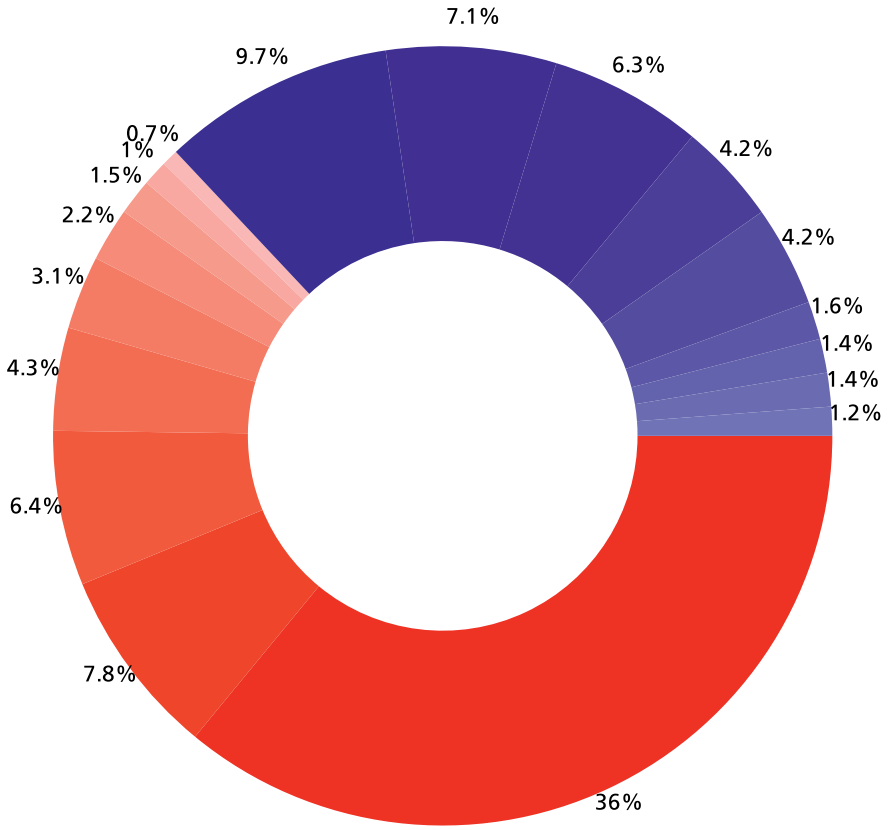
ii Where an infectious disease is recorded as the primary cause of death.

disease and infections that, previously easy to control, will become much more significant threats to health. Standard surgical procedures, such as hip replacements, could become riskier with widespread antimicrobial resistance, as would treatments that result in immunosuppression, such as chemotherapy or organ transplant, which rely on the ability to treat infections that, occur in this very vulnerable group of patients.

The challenges we face are changing. We need to move beyond a limited focus on MRSA and *C. difficile* to a wider focus on infection control and antimicrobial resistance. As discussed in chapter 5, new challenges are emerging, such as those around Enterobacteriaceae (*Escherichia coli (E. coli)*, and *Klebsiella* related species), which are now the most frequent agents of hospital-acquired infection. *E. coli* alone accounts for around 36% of the bacteraemias (blood stream infections) compared to MRSA, which now accounts for only 1.6%. More concerning is the suggestion that mortality in patients due to multi-resistant *E. coli*, is approximately 30%, compared with 15% for those with antibiotic susceptible *E. coli*. The implications of these issues for politicians and policy makers are discussed here but covered in detail in chapter 5, where the chapter authors estimate that 5,000 patients die of Gram-negative sepsis each year, half due to a resistant organism.

An indication of the potential ongoing threat of infectious diseases is the degree to which these diseases increase in incidence when public health control programmes break down. International examples of this include the failure of immunisation programmes in some Eastern European states following the collapse of the Soviet Union in the 1980s. This led to major outbreaks of diphtheria[3], a disease which

Figure 1.1: Organisms causing blood stream infections in adults in England, Wales and Northern Ireland, April 2011-March 2012

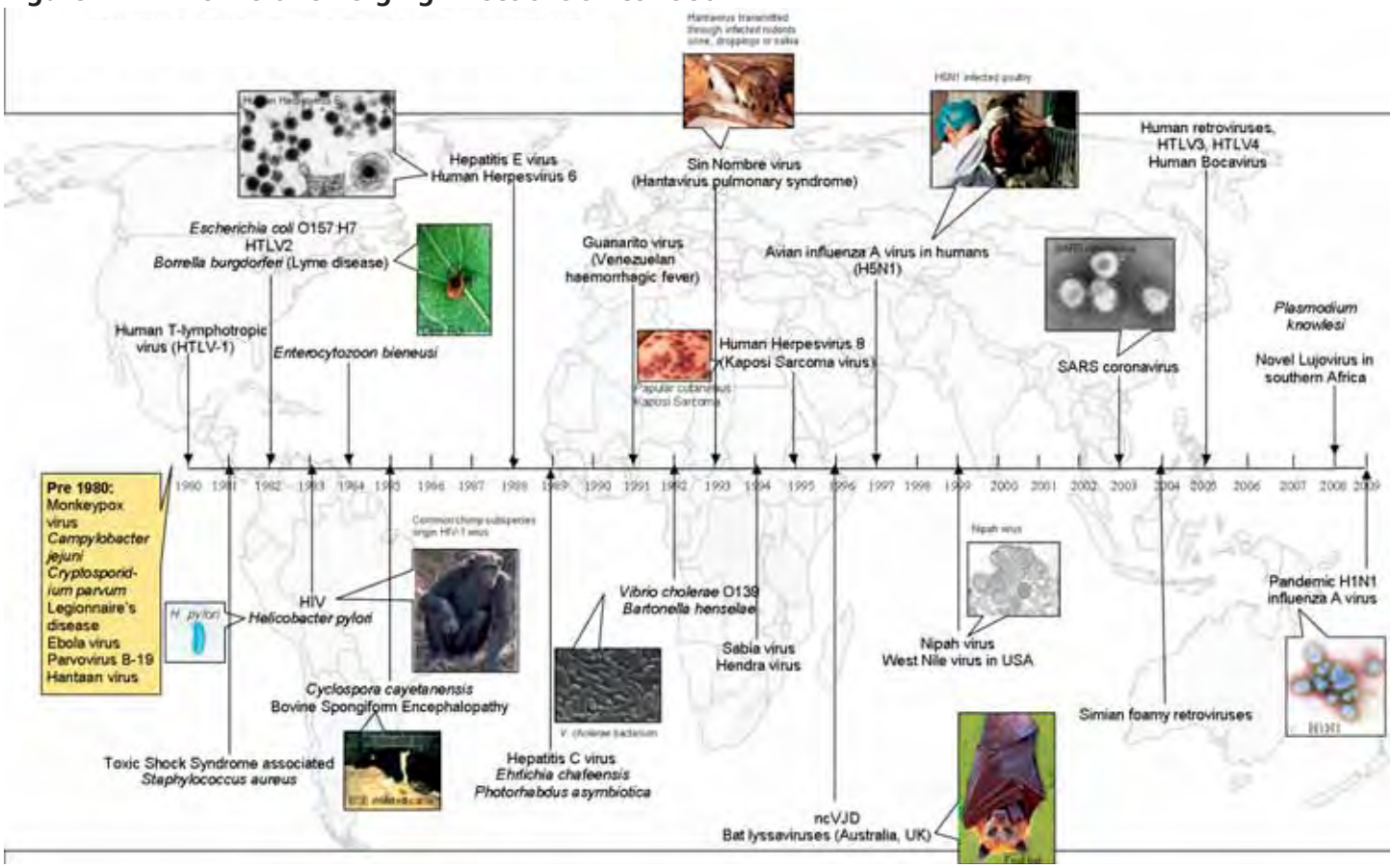


Gram negative
- Eschericha coli - 36%
- Klebsiella spp. - 7.8%
- Other Gram-negative - 6.4%
- Pseudomonas spp. - 4.3%
- Proteus spp. -3.1%
- Enterobacter spp. - 2.2%
- Bacteroides spp. - 1.5%
- Serratia spp. - 1.0%
- Acinetobacter spp. - 0.7%

Gram positive
- Staphylococcus aureus (MSSA) - 9.7%
- Non-pyogenic streptococci - 7.1%
- Enterococcus spp. - 6.3%
- Streptococcus pneumoniae - 4.2%
- Other Gram-positive - 4.2%
- Staphylococcus aureus (MRSA) - 1.6%
- Group B Streptococci - 1.4%
- Group A Streptococci - 1.4%
- Diphtheroids - 1.2%

Source: HPA. English National Point Prevalence Survey on Healthcare Associated Infections and Antimicrobial Use, 2011: Health Protection Agency, England; 2012. Note: excludes 13,206 episodes of bacteraemia with coagulase negative staphylococci.

Figure 1.2: Timeline of emerging infections since 1980



had become rare in Europe. Recent rises in the incidence of HIV infection among injecting drug users in Eastern Europe have also coincided with contractions in the public health infrastructure for HIV prevention as a result of financial constraints.[4] This rise in HIV was also driven by changes in individual behaviour, when a move to the use of injectable amphetamine-based drugs meant that there was a higher frequency of injecting with increased risks of exposure to infection. In the UK, the decline in MMR (Measles, Mumps and Rubella) immunisation rates following unfounded concerns over vaccine safety has resulted in outbreaks of measles and mumps in communities with low immunisation rates.

The ability of microorganisms to change over time has also led to the emergence of completely new infectious diseases. In the last 30 years we have seen the discovery of a new disease almost every year (see figure 1.2). Many of these are of major significance such as HIV, Legionnaires disease, *Campylobacter* and the Coronavirus which caused the SARS outbreak.

The recent influenza pandemic in 2009 highlighted the capability of infectious pathogens to threaten health globally and very quickly. Our national response to the pandemic was effective and robust. It reflected the enormous amount of preparation and planning in preceding years. We need to retain this capacity to respond, but also to detect future threats to health through effective disease surveillance and diagnostic capability.

The importance of a life course approach

The epidemiology of infectious disease is shaped by the interaction between the characteristics of the causative agent (the virus, bacterium, or other microorganism), the host (the person exposed to the infection), and the environment (including animal hosts, food, water and other environmental sources and environmental conditions. For HCAIs this includes hospital environment, design, fixtures, fittings, cleaning procedure and staff behaviours. The differences between the patterns of infectious disease seen at each life stage in the life course is determined by differences in these interactions, particularly in respect of host and environment factors.

In the earliest stages of life the immune system has not yet had a chance to develop protective responses to many infectious disease agents, making children particularly prone to infectious diseases that are easily spread by close contact (if they have not been vaccinated, or there is no vaccine available), especially when they start to mix with other children in nurseries or schools.

During adolescence and adulthood behavioural factors have a significant influence on the epidemiology of infectious diseases associated with those life stages. For example sexually transmitted infections are distributed between different population groups according to patterns of sexual

behaviour, and injecting drug use behaviour effects the epidemiology of hepatitis C infection.

As medical interventions become available for non-infectious diseases that are more common in the later stages of life, such as non infectious cancer and diabetes, so the pattern of disease in older adults will change. This reflects environmental factors such as undergoing surgery or simply being in hospital and host factors such as reduced immunity as a result of disease or medical treatment. Thus we are now seeing the paradoxical emergence of new infectious disease threats, and the re-emergence of infections that had previously been thought to be a problem of the past, as a direct consequence of the success of modern medicine. Examples include the increased risk of infection in general, but also of unusual infections such as invasive fungal disease, in patients being treated for non-infectious diseases, such as patients on immunosuppressive treatments for cancer or inflammatory disease. Similarly, the widespread use of antimicrobial drugs to treat infectious disease has given rise to the emergence of *C. difficile* as a major cause of healthcare associated infection, and the emergence of resistant forms of opportunistic bacteria (e.g. *Pseudomonas*, *Klebsiella*, Acinetobacter, among many others) is causing infections in hospitalised, vulnerable patients. When this is coupled with the fact that our population is growing and aging, it seems plausible that the area where there will be greatest growth in burden of infectious diseases is older adults.

A more detailed description of the current epidemiology of infectious diseases and how they relate to the different life stages is given in Chapter 2.

Key areas for policy and political action

In considering the evidence and opinions presented in the subsequent chapters, I have 4 general recommendations respecting

- Antimicrobial resistance[iii]
- Surveillance
- Prevention
- Education and training of the health and care workforce

There is a need for politicians in the UK to **prioritise antimicrobial resistance** as a major area of concern, **including it on the national risk register** (specifically, the 'National Security Risk Assessment') and pushing for action internationally as well as in local healthcare services. I have already requested that it be **placed on the Department of Health's strategic risk register** and am pleased that action has been taken accordingly. Following discussion with myself, **the Department for Environment, Food and Rural Affairs (Defra) supervisory board also agreed to a recommendation that antimicrobial resistance be placed on their strategic risk register** (as of December 2012). This now needs to be taken up as a cross government priority.

The focus also needs to expand from MRSA and *C. difficile* to include all issues around antimicrobial resistance, but in particular Carbapenemase resistance in Gram-negative infections such as *Klebsiella.*

Antimicrobial resistance is a ticking time bomb not only for the UK but also for the world. We need to work with everyone to ensure the apocalyptic scenario of widespread antimicrobial resistance does not become a reality. This is a threat arguably as important as climate change for the world.

Challenges and opportunities

- Antimicrobial resistance is increasing worldwide, the government needs to:
  - ⇨ put antimicrobial resistance on the national risk register (specifically, the 'National Security Risk Assessment')
  - ⇨ implement effectively the UK 2013-2018 cross government antimicrobial resistance strategy
  - ⇨ improve global leadership and action, particularly around the development of new antibiotics and preserving the effectiveness of existing antibiotics (antibiotic stewardship)
- Education and awareness needs to be improved around
  - ⇨ antimicrobial resistance, strategies for prevention and antibiotic stewardship, which should be part of routine curricula for all clinical professionals
  - ⇨ raising awareness of antimicrobial resistance and appropriate antibiotic use among the public, managers and professionals
- Surveillance systems – Public Health England and the NHS Commissioning Board need to
  - ⇨ develop surveillance systems to underpin their strategies for prevention and antibiotic stewardship
  - ⇨ monitor infection
  - ⇨ monitor antimicrobial (in particular antibiotic) prescribing
  - ⇨ monitor antimicrobial resistance (AMR)
  - ⇨ link this information to other Health and Care datasets to inform future action
- Diagnostic technology for infection – rapid diagnostics that allow movement away from broad spectrum treatments to more tailored approaches is a key area of innovation
  - ⇨ genomic technologies have a major role to play in the future and we need to be prepared to take advantage of this
  - ⇨ developments in point of care diagnostics are also particularly important as these have the potential to substantially increase the speed of diagnosis.

iii Whilst there are subtle differences between 'antibiotic' and 'antimicrobial' the two terms are used here to mean medicines that are used for the treatment of bacterial infections in humans and animals.

There is a **need for improved surveillance around infections and particularly around antimicrobial resistance**. It is clear that there is the potential to do much more, particularly through the linkage of existing data. In Chapter 11 the 'Big Data dynamic care and collaboration' discussion illustrates some of the potential future directions that use of more open data could lead to. The evidence presented in chapter 3 (Social Determinants) demonstrates the health inequalities associated with infectious disease and the need for linking infectious disease data to wider health determinant data as part of Joint Strategic Needs Assessments (JSNAs). Yet while all chapters highlight potential benefits of greater linkage of information, there remain a number of logistical and technical barriers to greater linkage of data. **Politicians, both nationally and locally, need to acknowledge the value of improving health surveillance systems.** They should be driving this work by explicitly giving a stronger mandate to this work.

All infectious diseases are potentially preventable and **a greater emphasis needs to be placed on preventative strategies**. Many of the chapters highlight the potential benefits of **extending immunisation schemes as this becomes appropriate**. Stopping HCAIs by implementing protocols of hygiene and antibiotic use to reduce risk of their occurrence is central to reducing overall HCAIs and **better antimicrobial stewardship** to preserve the effectiveness of antibiotics is a major mechanism for addressing antimicrobial resistance. Yet an intrinsic problem of the preventative approach is that the population does not see the impact of such work because disease is avoided rather than treated. Politicians need to publicly endorse the importance of this approach and **push for greater application of preventative measures around infection and infectious diseases**.

Throughout the subsequent chapters of this report the greatest potential opportunities for reducing the impact of infectious diseases lies in either adopting new approaches to diagnostics or in ensuring that existing best practice is rolled out across the country. **The education and continuing professional development of health, public health and care professionals is key to achieving this.** The responsibility to ensure this occurs sits firmly with the Royal Colleges and Health Education England. Yet with competing pressures, both timetable and economic, the importance of maintaining the skills of the workforce can be overlooked. Training in the prevention and management of infections must be given appropriate priority for all health and care professionals including managers from Chief Executive down.

Challenges for policy makers and clinicians are identified by the expert review

In the following section, I identify those areas that require specific consideration by policy makers and clinicians. The challenges identified should explicitly help to inform subsequent policy development. It is primarily aimed at those for whom a more in depth assessment is required of what I feel the key challenges are likely to be with regard to infection and infectious diseases. It also includes some specific recommendations around the actions necessary to address some of the more pressing aspects of the challenges discussed above.

Challenge 1: Health inequalities

Throughout history, infectious diseases have been a marker for social and economic disadvantage. Poor diet, housing and environmental conditions, exposure to pests and vectors, lack of access to good healthcare and low incomes are all features of low socioeconomic status that predispose to the acquisition and transmission of infectious diseases. Chapter 3 'Health inequalities and infectious diseases' demonstrates this remains true today.

The re-emergence of infections such as tuberculosis and the ongoing threat from influenza has reinforced the disparity in health between affluent and poor. The incidence of these diseases and the resulting health outcomes reflect a socioeconomic gradient with those who are worse off economically experiencing higher rates of disease and poorer outcomes.

Local Authorities are now charged with the duty to improve the health of their populations. The NHS Commissioning Board (NHSCB) and the new clinical commissioning groups (CCGs) also have a responsibility to reduce health inequalities. These members of the Health and Wellbeing Boards must ensure that individually and collectively they are bringing their resources to bear on the intractable problems of reducing health inequality. Health and Wellbeing Boards must recognise that effective tackling of infectious disease threats will be an integral part of their work in reducing health inequalities and improving the health of their populations. This must include ensuring that immunisation programmes are effectively commissioned, cover a high proportion of the target population, are delivered safely and effectively and are having a measurable impact on the prevalence of these diseases. We must also ensure that effective arrangements are in place to reduce the risk of outbreaks of infectious disease and to manage those outbreaks effectively and to learn from them when they occur.

Recommendation 1

Infectious disease issues (particularly immunisation, TB and Flu) need to be included as standard in JSNAs and Health and Wellbeing Boards should explicitly consider how they will address inequalities due to infectious diseases in their local Health and Wellbeing strategy.

Challenge 2: Healthcare Associated Infections (HCAIs)

Infections acquired as a consequence of healthcare are a serious problem. Every year in England hundreds of thousands of potentially preventable infections occur in people receiving healthcare services. In addition to the deaths and disease resulting directly from these infections, the consequences for patients are longer recovery times and poorer health outcomes. The consequences for the healthcare system are increased bed occupancy and length of stay in hospital, increased costs and the potential for transmission of the infection to other patients.

We have had much success in reducing mortality and morbidity from HCAIs over the last two decades with marked falls in the incidence of two bacteria responsible for many HCAIs *C. difficile* and MRSA, which have been part of the mandatory national surveillance programme. This has been due in part to initiatives such as better control of antibiotic prescribing, hand-washing and hygiene protocols and consistent, meticulous, intravenous central line care. There is now a body of evidence describing best practice and the challenge is to apply this knowledge consistently and in all settings, and to build upon it over time. Quality improvement requires the application of the most effective measures consistently every time.

Recommendation 2

Better management of process, such as standardisation of surgical practice, needs to occur. Consequently, NICE should be commissioned to produce evidence based guidance in this area. Surveillance systems must allow the monitoring of the effectiveness of such interventions.

Success in tackling MRSA and *C. difficile* has also been due to the increased focus of health care organisations on these two specific infections through mandatory surveillance and target-setting. Despite the success in reducing the impact of these infections, we must consider the wider range of infections that occur in healthcare settings. MRSA now accounts for only 1.6% of bacteraemias and we must focus on tackling other more prevalent causes. The focus should move to embrace emerging threats such as the Gram-negative organisms which now account for the majority of these bloodstream infections, particularly as we are seeing the emergence of antimicrobial resistance to some of these organisms. We must apply the learning from our battle with MRSA and *C. difficile* but accept that in some cases different measures will be needed. The evidence to guide our interventions must be properly established through the evaluation of practice.

Recommendation 3

There needs to be an expansion of our policy focus from a concentration on MRSA and *C. difficile* (though continued monitoring remains important), towards the inclusion of other significant infections.

The pattern of health and social care in England is changing. More care is being delivered in community settings including people's homes and less through long stays in acute hospitals. This has implications for both the transmission and for the management of infectious diseases. As this focus changes, our prevention and management strategies also have to change as the importance of infection control in home care and community care increases. This will mean a shift of resources deployed by commissioners of care, towards strengthening infection control in the community including the training of staff and carers, information technology and management and diagnostic and screening services.

It is particularly important that infection control in the home becomes a priority for patients with long term conditions. Many HCAIs are diagnosed in hospitals but are acquired prior to admission in patients' homes and in community care settings. This transmission must be addressed with the same vigour that is now being applied in hospitals in order to protect the patients themselves and to prevent the importation of infections into other healthcare settings, putting other patients at risk.

Recommendation 4

Infection control policies of organisations responsible for the care of individuals should explicitly address the settings of care, including a focus on the home and community.

The NHS in England is well placed to collect, collate, analyse and disseminate information in a consistent and comprehensive manner. New computer science methods for linking and federating databases from health and social care offer the opportunity for a much greater understanding of infection, not just for HCAIs. Integration of health care data from all sources will allow more real time detection of infection events and would allow much greater control of transmission. Particular focus needs to be placed on intravascular device associated infections, surgical site infections and antibiotic use. The emerging science of genomics will soon allow much faster routine identification of pathogens than is possible with conventional diagnostic microbiology but will also yield data for tracking pathogens and enhance the possibilities for routine surveillance at local and national level. The real challenge of this new technology will not be in the linking of data but in the analysis of this new information and its translation into effective action.

Recommendation 5

Information standards need to be developed that allow national surveillance of infections, incorporating the information from emerging technologies and which also promote the local use of information. Public Health England, the Health and Social Care Information Centre, and the NHS Commissioning Board will need to work together to develop and promulgate these information standards. This needs to be part of the work around inter-operatability standards for health information systems.

Recommendation 6

Public Health England and other organisations with a surveillance remit must invest in workforce skills around data mining and bio-informatics. Collaborations between these organisations and academic institutions must be explored. Ways need to be found that allow us to make data transparent and available so that the many communities interested in data can be encouraged to help solve some of the analytical challenges posed by infectious diseases.

Challenge 3: Antimicrobial resistance (AMR)

The dramatic fall in mortality and morbidity in the nineteenth and early twentieth centuries was due to public health measures to prevent and to reduce transmission of infectious diseases. The medical advances of the second half of the twentieth century including the transformation of modern surgery have been underpinned by the ability to successfully treat infections. Without this ability the mortality rates from infectious diseases in the very young and the very old would increase markedly and surgery would carry much greater risks.

Resistance to antimicrobial agents has been observed ever since the introduction of antibiotics in the 1930s and 40s. As resistance has increased, new classes of antibacterial, antiviral, antiprotozoal and antifungal agents have been developed in response but the development of antibacterials and antiprotozoals has now slowed and we must act decisively if we are to retain an effective armamentarium against the ever changing range of infectious pathogens. We need to do two things. First we need to preserve the effectiveness of our existing antimicrobial agents and secondly we need to encourage the development of new agents in the future.

The key to preserving the effectiveness of our existing antimicrobial agents in England is better stewardship. This means clear evidence based guidance on the use of antimicrobial agents based on sound research. At present there is variability in the criteria used for initiation of antibiotic therapy, particularly when the diagnosis is uncertain. The duration of antibiotic therapy for particular conditions is also variable and often not based on scientific evidence. The decision to stop or change antibiotic therapy when a diagnosis is made or microorganism sensitivities are known is sometimes not made quickly enough. All of these situations may cause antibiotics to be given inappropriately where they cannot benefit the patient, or for too long. This overuse of antibiotics increases the opportunity for the development of resistant strains. We must address this problem in both primary and secondary care settings.

The international nature of antimicrobial resistance means that global action is required to mount an effective response. The inappropriate use of antimicrobial agents in other countries, and the production of counterfeit medicines, pose risks to our population. It is important that we take an international view of this problem and work with other nations to ensure that effective measures to reduce the development of antimicrobial resistance are implemented as widely as possible.

Recommendation 7

Action is needed at the international, national and local level: antimicrobial resistance should be an issue that has the same level of political interest as MRSA and *C. difficile* in England. It should be placed on the national risk register (specifically, the 'National Security Risk Assessment') and the Government should campaign for it to be given higher priority internationally, including collaborations to ensure the development of new antimicrobials and vaccines such as Private Public Partnerships.

Antibiotic use is not limited to humans and a large quantity of antimicrobials are used every year in veterinary practice and the fishing and farming industries. While the current evidence suggests that this is not a major cause of resistance in bacteria that affect human health (at least in the UK), it does provide a further vehicle for the development of antimicrobial resistance. The work of the Department for Environment, Food and Rural Affairs (Defra) and other agencies in combating the emergence of resistance is considerable and important. Our approach to tackling the problem of antimicrobial resistance must bring together experts in human and animal health to develop joint and complementary initiatives in this field.

Recommendation 8

The national approach to tackling antimicrobial resistance should be managed jointly between DH and Defra to ensure that a comprehensive integrated programme is developed. The UK 2013-2018 cross government antimicrobial resistance strategy and action plan is welcome. It provides a base for future working but this needs to be built upon.

A focus on better stewardship of antibiotics in England and across the UK will help to conserve our treatment options by slowing the development of resistance but we must also be aware that antimicrobial resistance is a global problem. The increase in international travel and migration in the last few decades has led to an increase in the importation of resistant organisms. Many very infectious organisms such as influenza have always been transmitted

internationally in large epidemics. More recently, we have seen an increase in the importation of resistant strains of less infectious organisms such as tuberculosis and HIV. Port health surveillance and control measures have a role to play but many of these conditions do not cause symptoms in the early stages of infection and the affected individuals may be unaware of their disease at the time of arrival in the country. If routine surveillance does not identify these individuals, it is important to our society that new entrants to the country are given rapid access to primary care services to provide the opportunity for early diagnosis and appropriate treatment.

The supply of new classes of antimicrobial agents for future use has slowed over the last few decades in contrast to drug development for other conditions. This is in part due to the scientific challenge associated with the problem but is also partly due to the conditions of the market for new pharmaceuticals. Antimicrobial agents are used sparingly and for short duration. Over time, they are subject to diminished efficacy due to the development of antimicrobial resistance. Sometimes they are withheld for the future, limiting the profitability of a fixed term patent. Moreover trial requirements are onerous and costly. In short, there are fewer economic incentives to produce new antimicrobial agents than there are for other classes of drug – a market failure.

If we are to secure a 'pipeline' of new antimicrobial drugs for the future then we must align the private and societal risks, and the costs and benefits of research and development of these agents. There are many ways to incentivise innovation, engaging the private sector, public institutions and academia. The challenge is to alter the balance of these incentives so that we have a thriving, vibrant, sustainable and safe programme of research and development into new antimicrobials.

Recommendation 9

Rapid diagnostics enabling appropiate treatment and surveillance will be key to addressing the issues raised by imported infections. Identification of imported infections and carriage of organisms with antimicrobial resistance is critical. Once identified, effective infection control mechanisms exist for most infections. This should be a specific focus within the Public Health England surveillance strategy.

Challenges through the life stages of infectious disease

Life stage – Perinatal

Perinatal mortality, that is death before birth and in the first 7 days of life, has been declining in England for many years and is now 44% lower than in 1980. Infant mortality, that is death in the first year of life, has also declined. Although this is good news, the levels are still higher than many other EU countries and the rate of decline in infant mortality is less than the average of that seen in our most comparable EU counterparts, the EU15. These levels of mortality are therefore still unacceptably high. The mortality is also not evenly distributed. Higher rates of mortality are seen in those of lower socioeconomic status and those from minority ethnic backgrounds, in particular for children of mothers born in Pakistan, Bangladesh and Africa. Mortality in early life contributes significantly to the inequality in overall mortality in our society.

The role of infection in perinatal and infant deaths is complex. Infection is a major cause of premature birth which is associated with higher risks of mortality and morbidity. Premature babies are also at greater risk of acquiring infections. Despite this risk, premature babies are often undervaccinated. Infections may occur at any time, including in the womb during pregnancy but particular concerns are bacterial infection during the period of labour and delivery (early onset sepsis) or in the period just after birth (late onset sepsis).

Early onset sepsis, in the first 48 hours of life, occurs due to infection with bacteria such as Group B *Streptococcus* or *E. coli* acquired from the mothers genital tract. This infection has a very high mortality rate particularly in low birth weight infants, even with appropriate antibiotic treatment. Although intrapartum antibiotic treatment has shown some promise, the development of a specific vaccine against Group B *Streptococcus* is a focus of current research.

Late onset sepsis is due to infection acquired after birth and so by definition, many cases are HCAIs. Neonatal intensive care units have higher rates of HCAI than other intensive care facilities perhaps reflecting the particular vulnerability of premature babies but highlighting the critical importance of good infection control practice in these units. When infections are resistant strains the situation is particularly concerning. This once again emphasises the importance of addressing the challenges of HCAIs and antimicrobial resistance.

A major success in recent years has been the reduction in mother to baby transmission of HIV infection. If a mother is given appropriate antiretroviral medication and appropriate infection control measures are taken at the time of birth and afterwards, the risk of transmission of HIV from an infected mother to her baby can be reduced from 1 in 4 down to 1 in a hundred. This raises two important issues;

- a surveillance, detection and management system for patients with infection in pregnancy integrated into antenatal and postnatal care pathways can yield great benefits for mother and baby
- treatment of the mother with antimicrobial agents or vaccines during pregnancy can be the best way to protect the unborn child from infection.

With the introduction of influenza vaccination, immunisation during pregnancy is now becoming an established part of our national immunisation programme. This is an intervention that will grow in importance in future years and it is important that the dialogue with the public be maintained to share the understanding of the benefits of this approach.

Recommendation 10

Public Health England, both through the NHS Commissioning Board and as part of its health improvement strategy, needs to consider how it will promote the understanding of the benefits and encourage the informed uptake of immunisations during pregnancy.

Life stage – Child

The burden of infectious disease in childhood in England is much less than in the past. In part this is due to social and economic development and the consequent improvements in diet, living conditions, hygiene and education. It is also due to the hugely effective vaccination programmes that have vastly reduced the impact of many once-feared infections such as diphtheria and measles. Through international cooperation and systematic implementation of vaccination worldwide, we have also seen the global eradication of smallpox and we are close to the eradication of polio.

The maintenance and expansion of our world class vaccination programme is a key priority and a cornerstone of our child health programme. We must continue to ensure that our children are properly protected from vaccine-preventable disease.

Some important infections remain for which there is no effective vaccine such as Respiratory Syncytial Virus that are causes of serious disease in this age group. Until we are able to produce vaccines for these infections, surveillance, early diagnosis and high quality case management are essential.

One of the major challenges facing paediatricians today is the increasing number of children attending clinical services with a febrile illness that might be a serious bacterial infection, but is more likely to be a less serious viral infection. Short stay admission rates in children continue to rise. The proportion of these children with a serious bacterial infection is very small but in the absence of an accurate diagnostic test to distinguish these infections from much less serious viral infections, these children are subjected to a battery of screening tests that are usually negative. This is distressing and unpleasant for the child, concerning to parents, is costly and uses a large quantity of medical time.

A rapid test to distinguish serious bacterial infections from viral infections would reduce hospital admissions, prevent unnecessary clinical tests and reduce the use of intravenous antibiotics. This should be a priority for child health research.

Recommendation 11

Vaccination uptake rates are a key priority and need ongoing monitoring. This is likely to be the single most effective intervention for reducing disease burden due to infection. Within the commissioning of immunisation by Public Health England from the NHS Commissioning Board, and through schools, there should be a requirement to ensure improvement of vaccination coverage in those groups with traditionally low uptake.

Life stage – Adolescent and young adult

Adolescence is a time of great change and great opportunity. Many lifelong behaviours that fundamentally affect health are determined in this period. As young people begin to assume responsibility for their current and future health, there is a window of opportunity to enable them to make informed choices at this formative stage in their lives. With the increased focus on health behaviour as a determinant of mortality and health outcomes over the last few decades, it is surprising that this age group is the only life stage where large improvements in health have not been achieved over the last fifty years. In fact mortality rates in 15-24 year olds are now above the rate of those aged 1-4 years for the first time in recorded history.

The two main challenges for the prevention and control of infections in adolescence are to reduce the impact of risky behaviour on disease incidence and to ensure that preventive public health programmes such as immunisation and chlamydia screening are made easily available to people in this age group.

This will require the infrastructure to ensure appropriate services are in place. Also, education and health improvement campaigns covering risky behaviours, such as those around sexual health and relationships and substance use, are linked into these services. Services (particularly sexual health services) will need to be young person friendly. With different aspects of sexual health services coming under the remit of public health in Local Authorities and Clinical Commissioning Groups (CCGs), this is an important area in which new relationships between commissioners need to be built.

It is increasingly becoming apparent that adolescents are an age group where vaccines are likely to play a more important role. Experience from the HPV vaccine suggests that a similar approach to implementation is likely to be most effective.

Recommendation 12

Public Health England and the NHS Commissioning Board should provide joint guidance for the commissioning of preventative public health programmes and services aimed at adolescents. This is a priority for sexual health services where the need goes beyond adolescents to other groups, particularly men who have sex with men where the rising HIV prevalence requires a reassessment of current approaches. Joint Strategic Needs Assessment's (JNSAs) should include an assessment of the effectiveness of joint working in this area, with Health and Wellbeing boards holding local commissioners to account.

Recommendation 13

Directors of Public Health should ensure that the school nursing system they commission is fit for purpose for the implementation of new vaccination programmes.

Life stage – Adult

The majority of individuals in the adult life course stage are physically healthy and often more robust than other life stages to some infections e.g influenza. However, as this life stage represents the majority of the population, even as a low risk group it represents a substantial population that are likely to present with infectious disease related issues to health care services. It can also be a group that spreads infection to and between more vulnerable groups, hence the importance of frontline healthcare staff being immunised each year for influenza.

There are specific subgroups that are at higher risk of infection in adulthood, these include migrants, those with strong family links abroad and injecting drug users (both current and former).

Primary care practitioners play a vital role in early identification of infectious diseases such as hepatitis B & C and HIV. Early identification can substantially improve health outcomes. Consideration of patients' country of birth when evaluating their risk exposure will aid differential diagnosis of a person's presenting symptoms.

Offenders also represent a specific at risk population that is particularly challenging to treat effectively. While their detention represents an opportunity to engage, the level of movement of offenders between prisons is just one example of the many real challenges to continuity of care. Yet prison health services can offer diagnostic tests as part of screening or active case-finding programmes such as testing for blood-borne viruses and this needs to be encouraged.

Recommendation 14

Training and continuing professional development need to include a specific focus on infectious disease and risk groups, so that medical practitioners, healthcare professionals and managers are equipped with the right skills to deal with these challenges. The Royal Colleges responsible for CPD and Health Education England should ensure that this is incorporated effectively into current and future education initiatives.

UK residents travel ling to visit friends and relatives in their country of origin are the major risk group for UK reports of several important travel-associated diseases, including malaria and tuberculosis. One of the major routes of entry of antimicrobial resistant infections to the UK is via people accessing healthcare abroad. The reasons for people accessing care may be health tourism or simply due to spending extended time periods out of the country. There is a need for the general public to educate themselves about these risks.

Recommendation 15

Public Health England as part of its health improvement strategy should include a focus on improving people's knowledge and behaviour around infection risks abroad. This should include encouraging the public to seek travel health advice *before* travelling.

Life stage – Older adult

The population is getting older and more people are living longer. The average life expectancy in Britain exceeds 82 years in women and 78 in men. The burden presented by infection and infectious diseases in older adults is now only likely to grow. Three particular challenges for the older population are likely to come from healthcare-associated infections, urinary tract infections and influenza.

Many older people suffer with chronic illness and substantial disability in their later years and greater vulnerability to infections may result. In part this can be due to greater exposure to infectious disease through more frequent need for healthcare, greater vulnerability to the impact of having an infection or greater susceptibility to infection due to suppressed immune systems (i.e. when chemotherapy or other treatments suppress the immune system) and through living with other elderly with these risk factors in care homes. Aging itself also results in a decline in immunocompetence: the immune system begins to lose some of its functions and cannot respond as quickly or as efficiently to stimuli. However many of the infection problems in older people are preventable or are a result of heath care procedures that could be managed better in order to avoid further problems of the infections themselves.

There are already numerous initiatives to reduce the impact of HCAIs. The importance, however, of the challenges facing infection control as care moves into the community and the home, and care home settings cannot be underestimated. Specific issues will be both the knowledge of appropriate infection control actions in these new settings and responsibility for them.

Recommendation 16

There is good evidence of the effectiveness of improving staff knowledge and understanding of infection control in improving health outcomes. We need to extend and improve this expertise in health and care workers now, and continuing into the future. Making those organisations that are primarily responsible for care also responsible for infection control issues in care settings would be a key step in ensuring these issues are addressed.

Urinary tract infections (UTIs) are the second most common HCAI after respiratory tract infections, comprising 17.2% of the total. Urinary catheters are relatively frequently used in older patients as part of care and are often associated with UTIs. Simple interventions, such as reminders to review

the need for urinary catheters, with a view to removing them as soon as possible, can reduce the number of associated infections. Ensuring widespread adoption of these interventions remains key.

Protection by influenza immunisation in older people is lower than in younger adults and children, and may be very low in some years when the match between vaccine and circulating strains of influenza is poor. Strain mismatch may be more important for younger rather than older age groups. Despite this, improving vaccination rates (both in older people and in frontline workers who may spread the disease) remains central to reducing the impact of infectious diseases in older people. An opportunity to reduce the impact of influenza may be more widespread use of antivirals at the appropriate time. However, current evidence suggests this is rarely done and increasing the use of antivirals may also substantially reduce the impact of Influenza. More research is needed.

The long-term challenges and opportunities that need to be built into future policy development.

Chapter 11 is the horizon scanning chapter and identifies the future challenges and opportunities around infection over the long- term. It is clear from this work that many future challenges are already well characterised. Global outbreak data from 1940 to 2004 show that around 60% of emerging infectious human diseases are of zoonotic origin (i.e. emerging from animals) and further emphasise the need for collaborative working between veterinary and health services.

Most novel infections, including zoonoses as well as drug resistance, are likely to be imported rather than arise de novo in the UK. Early detection and response to contain threats are likely to be key to our ability to address new infectious disease challenges. The UK currently has concentrated expertise in centres in London and Liverpool specialising in the clinical diagnosis of imported infections and it is important this is maintained as a national strategic asset. Fit for purpose surveillence, across both humans and animals, that triggers and informs action to novel infections is also key. As our knowledge and understanding of the risks, mechanisms and risk groups for imported infections grows, and as these factors change, we will need to constantly ask whether we are striking the right balance of surveillence intensity between geographical coverage and risk profile. This also reinforces the importance of the WHO role and the need for global surveillance to achieve early identification and risk assessment, and to enable the timely setting up of control measures, particularly for diseases of zoonotic origin.[5]

Three of the main drivers of future emerging and re-emerging diseases in the UK are:

(a) climate change,

(b) urbanisation affecting humans' relationship with animals and

(c) antibiotic usage leading to growing rates of antimicrobial resistance.

The continuing increase in organisms that are resistant to multiple antimicrobial drugs is one of the greatest health threats faced today. Antibiotic resistance is currently our main concern. With increased use of antivirals and other antimicrobials, resistance will become a wider problem.

These threats need to be at the heart of future planning for infections and infectious diseases, but the exciting potential opportunities are from the impact of developing technologies, particularly those that the advances in genomic medicine make possible.

Whole-genome sequencing of infectious agents gives the ultimate in resolution between two related pathogens. Rapid technological advances in DNA sequencing have led to the availability of benchtop sequencers that are drastically reduced in cost and likely to become cheaper. These can sequence multiple bacterial or viral genomes in less than a day. The use of these methods will almost certainly become the standard diagnostic approach and have the potential to be the impetus for a step change in the effectiveness of surveillance. Specified pathogens isolated in diagnostic laboratories can be sequenced and this information fed into current surveillance systems to track disease trends. Such a system could also be used to monitor the emergence and spread of clinically important bacterial drug resistance. Already there is growing evidence that whole-genome sequencing can be used to map the spread of MRSA within or between hospitals, or between the hospital and community. *Mycobacterium tuberculosis* is currently routinely genotyped in the UK, and sequence data generated to define drug resistance could be used at no extra cost.

The short term advantages of data linkage and making better use of information already collected is discussed above. To realise these benefits in a sustainable manner Public Health England, the Health and Social Care Information Centre and the NHS Commissioning Board will need to develop and promulgate clear information standards for surveillance, and interoperability standards for health information systems that will enable data from different sources to be linked efficiently and effectively. It is only if this is in place that the advances in diagnostic technology, particularly those in genomics, can be harnessed to improve population health.

Recommendation 17

Any national strategy that encompasses the development and roll-out of genomic diagnostic testing for infections should include the delivery of real surveillance data as an integral part.

Within vaccines there are two separate areas where change is likely to present opportunities. The development of new and more effective vaccines and the potential for improvement in the efficiency of the administration of immunisation programmes.

The application of 'systems biology' is already allowing the prediction of immune responses to vaccines through gene signatures. In effect, this means the future efficacy may

be assumed without such extensive and expensive formal trials and could lead to a much faster development of new vaccines. There will need to be the flexibility within the regulatory and health and care systems to respond to the development of new vaccines and implement them where appropriate. However, the experience of the 2009 influenza pandemic shows that the development of an influenza vaccine that is cross-protective against all strains, and thus generated long-lasting immunity, remains the most important vaccine development priority.

To improve the efficiency of immunisation programmes we need a system that can identify every individual, every vaccine that they need and when they need it; schedules immunisations; identifies defaulters; audits refrigerators' stocks and orders vaccines. GP databases that hold email addresses or mobile phone numbers should already be capable of scheduling these vaccinations and the challenge will be to move from this to greater joined up functionality. Developments in information technology make this feasible and it could potentially be done through national, single web-based system.

Such a system would need to be an easily interrogable so that the performance of immunisation programmes as a whole can be assessed and improved upon.

Meanwhile, our armatorium is weakened by patchy uptake of vaccines. This must be addressed at every level, across the country. Research, from basic discovery through to evaluative and applied, will continue to be essential for underpinning future action.

Finally, I must highlight that infection is everyone's business. There has often been too little focus from individuals. All those with responsibility in health and care need to increase their focus on infection and infection control, this includes politicians, CEOs, managers, clinicians, academics and also the public. Antimicrobial resistance must not be allowed to worsen and patients need to be treated effectively and promptly.

To address the challenges being faced due to antimicrobial resistance we will require the concerted effort of many people. A collaborative approach which welcomes everyones input is needed, action such as the recent jointly hosted Royal United Services Institute and Science and Technology Facilities Council event to identify gaps in the research knowledge around antimicrobial resistance is a good example of this.

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Chapter 2

Epidemiological overview of infectious disease in England

Chapter authors
Mike Catchpole[1], Sarah Tomkins[2], Paul Cleary[3]

1 Director of Infectious Disease Surveillance and Control, Health Protection Agency
2 Senior Scientist (Epidemiology), Health Protection Services Colindale, Health Protection Agency
3 Regional Consultant Epidemiologist, Health Protection Agency North West

Overview

The aim of this chapter is to provide an overview of the epidemiology of infectious diseases across all life stages, and to highlight some of the factors that determine the different patterns of infectious disease at different stages of life. The epidemiology of infectious disease results from the interplay between infectious microorganisms, human beings and the environment (see Figure 2.1). Differences in the epidemiology of infectious disease at different stages of the life course are determined by differences in these interactions:

- In the earliest stages of life, the immune system has not yet developed protective responses to many infections. Children are particularly prone to infections spread by close contact in settings such as nurseries or schools, but may be protected against some diseases by vaccines.
- In adolescence and adulthood, behavioural factors such as sexual activity or injecting drug use have a significant influence on the epidemiology of infectious diseases such as sexually transmitted diseases or hepatitis C.
- In the elderly, the pattern of infectious disease reflects environmental factors such as hospital admission and host factors such as impaired immunity from disease or medical intervention (such as antibiotic or immunosuppressive therapy), resulting in infections such as *C. difficile* or invasive fungal infections, or infections which are resistant to treatment.

Host and environmental factors also drive inequalities in disease burden between different socio-economic and demographic groups. Crowded living conditions are a risk factor for respiratory tract infections,[1] while homelessness or imprisonment increases the risk of tuberculosis.[2] Larger-scale geopolitical environmental factors can also have a significant effect on disease epidemiology. Financial constraints on HIV prevention activities in Eastern Europe coincided with rises in HIV incidence among injecting drug users, although this was also driven by changes in individual behaviour (greater use of higher-risk injectable amphetamine-based drugs). Climate also plays an important role. Heavy rainfall and run-off from agricultural land may overwhelm water filtration systems, causing *Cryptosporidium* outbreaks.[3] Long-term climate change could lead to the establishment of *Aedes albopictus* – an insect vector for viral infections such as West Nile virus and Chikungunya fever – in most of Europe, including England.

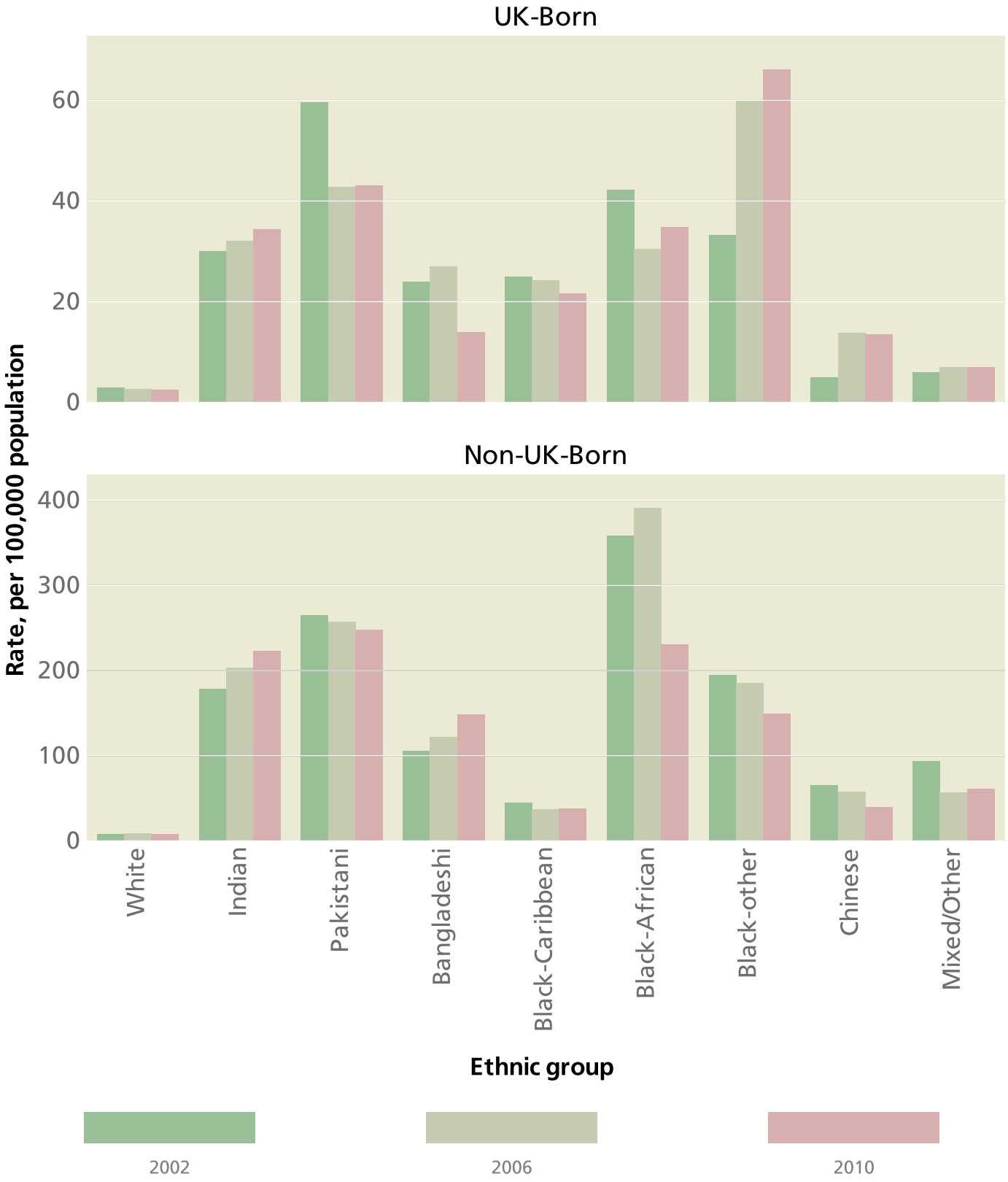
Figure 2.1: The determinants of infectious disease epidemiology

AGENT
- Infectivity
- Pathogenicity
- Virulence
- Immunogenicity
- Antigenic stability
- Survival/Resistance

ENVIRONMENT
- Weather
- Housing
- Geography
- Occupational setting
- Air quality
- Food

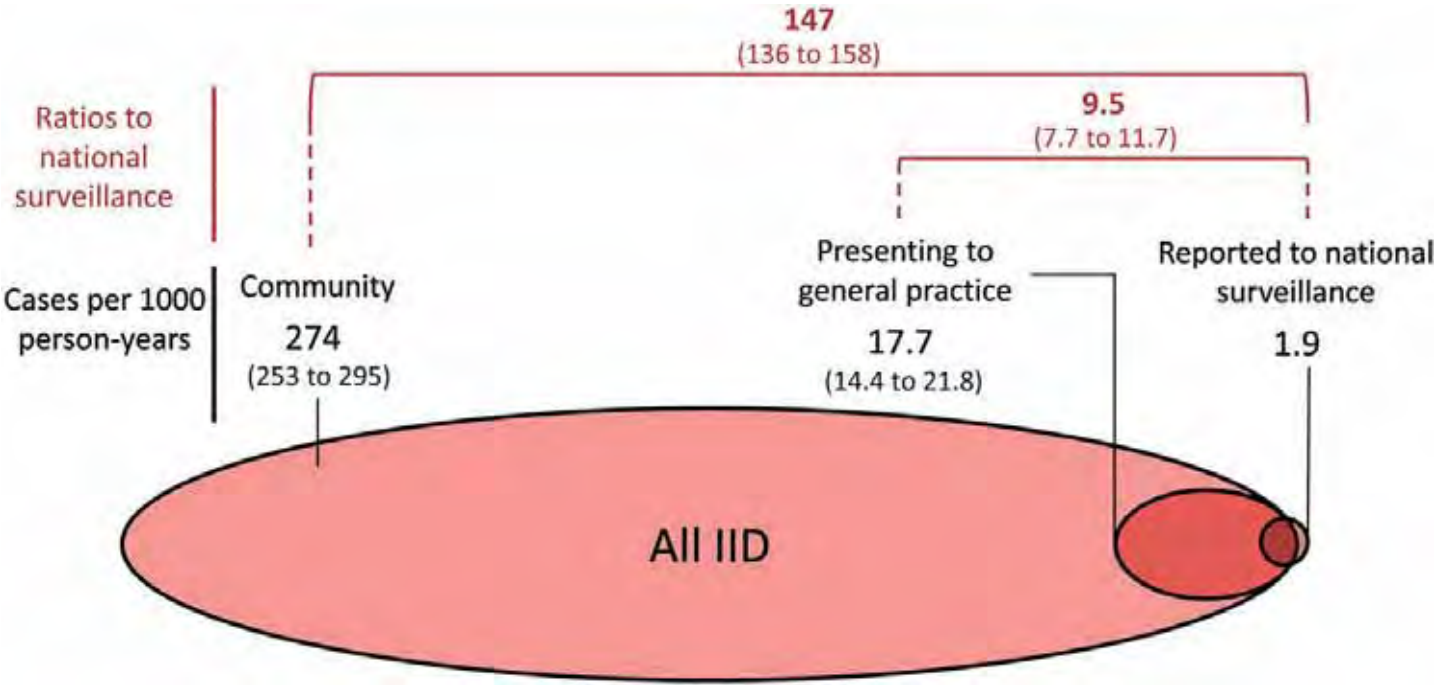
HOST
- Age
- Sex
- Genotype
- Behaviour
- Nutritional status
- Health status
- Immunity

Figure 2.2: Tuberculosis case rates by place of birth and ethnic group, United Kingdom, 2002, 2006, 2010



Source: Enhanced Tuberculosis Surveillance, HPA. 2010/06/02 population estimates, ONS. (Analysis by HPA)

Figure 2.3: Total, diagnosed and reported incidence of infectious intestinal disease, UK (from Longitudinal study of infectious intestinal disease in the UK (IID2 study))



The current burden

The greatest burden of morbidity for most infectious diseases, except for those transmitted primarily through sexual contact or injecting drug use, falls on the very young or old. The economic burden from infectious diseases in England, including costs to the health service, to the labour market and to individuals themselves, is estimated at £30 billion each year, with a large proportion of these costs incurred because of respiratory or gastrointestinal infections[i].

Respiratory infections

Respiratory infections, in particular pneumonia and exacerbations of chronic bronchitis, are the leading cause of infectious disease mortality and morbidity, particularly among the elderly and those with underlying chronic disease, such as chronic bronchitis, cancer or heart disease. A number of these cases are caused by bacteria that are very infrequently the cause of illness in the healthy population, and they represent an important inequality in disease experience among those at risk of the predisposing chronic diseases.

Consultation rates in general practice for respiratory tract infections have fallen modestly over the past decade. In recent years the highest rates have been seen in young children and the elderly. In 2010, the highest rates of consultation for influenza-like illness were observed among adolescents and young adults, reflecting that these age groups were most susceptible to the pandemic H1N1 strain of influenza A. In non-pandemic years, seasonal influenza is a major cause of morbidity and mortality, with on average approximately 4,400,000 symptomatic cases of flu per year between 2005 and 2008 and over 12,000 deaths each year, albeit with marked year-to-year fluctuations, disproportionately affecting the elderly, those with chronic heart or lung disease, diabetics and pregnant women.

Respiratory syncytial virus (RSV) is the commonest cause of severe respiratory illness and hospital admissions due to acute respiratory illness in young children. RSV is also an under-recognised cause of severe or fatal respiratory illness in elderly people. RSV activity peaks in December and January but varies from winter to winter.

Rates of tuberculosis have increased moderately over the past decade. Most of this rise has been associated with cases among individuals not born in the UK; in 2010 the proportion of cases among those born outside the UK rose to 73% and the rate of tuberculosis among the non-UK-born population was 20 times the rate among those born in the UK. Most non-UK-born cases originate from South Asia or sub-Saharan Africa (see Figure 2.2). Other groups particularly affected include the homeless, drug or alcohol users and prisoners. London and the West Midlands have been the most affected regions over the last decade, and the highest rates have been seen among men and the 15 to 44 age group.

Gastrointestinal infections

Gastrointestinal infections are a major cause of potentially preventable illness, and they cause explosive outbreaks in both community and healthcare settings. Laboratory surveillance of infection provides valuable information on trends and possible outbreaks but only detects the tip of a much larger 'iceberg' of infection (see Figure 2.3).

i Analysis commissioned for this report from the Health Protection Analytical Team, Department of Health (unpublished).

For each reported case of gastrointestinal infection there are an estimated 147 unreported cases. Every year in the UK there are an estimated 17 million cases, affecting around 25% of the population, leading to about a million GP consultations and nearly 19 million days lost from school or work. Gastrointestinal infection due to verocytotoxin-producing *E. coli* (VTEC) can be fatal, particularly in young children or the elderly, and is the commonest cause of acute kidney failure in children, complicating approximately 10% of reported infections each year. Every year, particularly in the winter months, outbreaks of norovirus infection result in closures of hospital wards, with a significant impact on the healthcare system.

The highest rates of gastrointestinal infectious disease are seen among young children, but gastrointestinal infections also remain an important cause of morbidity among adults (see Figure 2.4). Rates of diagnosis of campylobacter, norovirus and shigella infection have risen since 2003/4. Increases in campylobacter and shigella infection have occurred particularly among the elderly, but also among younger age groups. Diagnoses of norovirus have risen sixfold, partly due to more sensitive laboratory diagnostics. In contrast, salmonella infections have been falling for a decade. Rates of other major bacterial and protozoal causes of gastrointestinal infection, including VTEC and *Cryptosporidium*, have remained stable over the past decade.

Campylobacter is the commonest bacterial cause of gastroenteritis (diarrhoea and vomiting), with almost 60,000 cases reported in 2010, a 43% rise since 2004. The highest rates of infection occur in the young and the old. Campylobacter infections are often associated with the consumption of undercooked meat (especially poultry, including chicken liver products), unpasteurised milk or untreated water, but most infections remain unexplained.

Viral causes of gastroenteritis are particularly common in the very young and the elderly. Rotavirus is the major cause of gastrointestinal infections in infants, resulting in an estimated 18,000 paediatric admissions annually in England and Wales. Among the elderly, norovirus infections are an important cause of illness and a cause of outbreaks in care homes and hospitals.

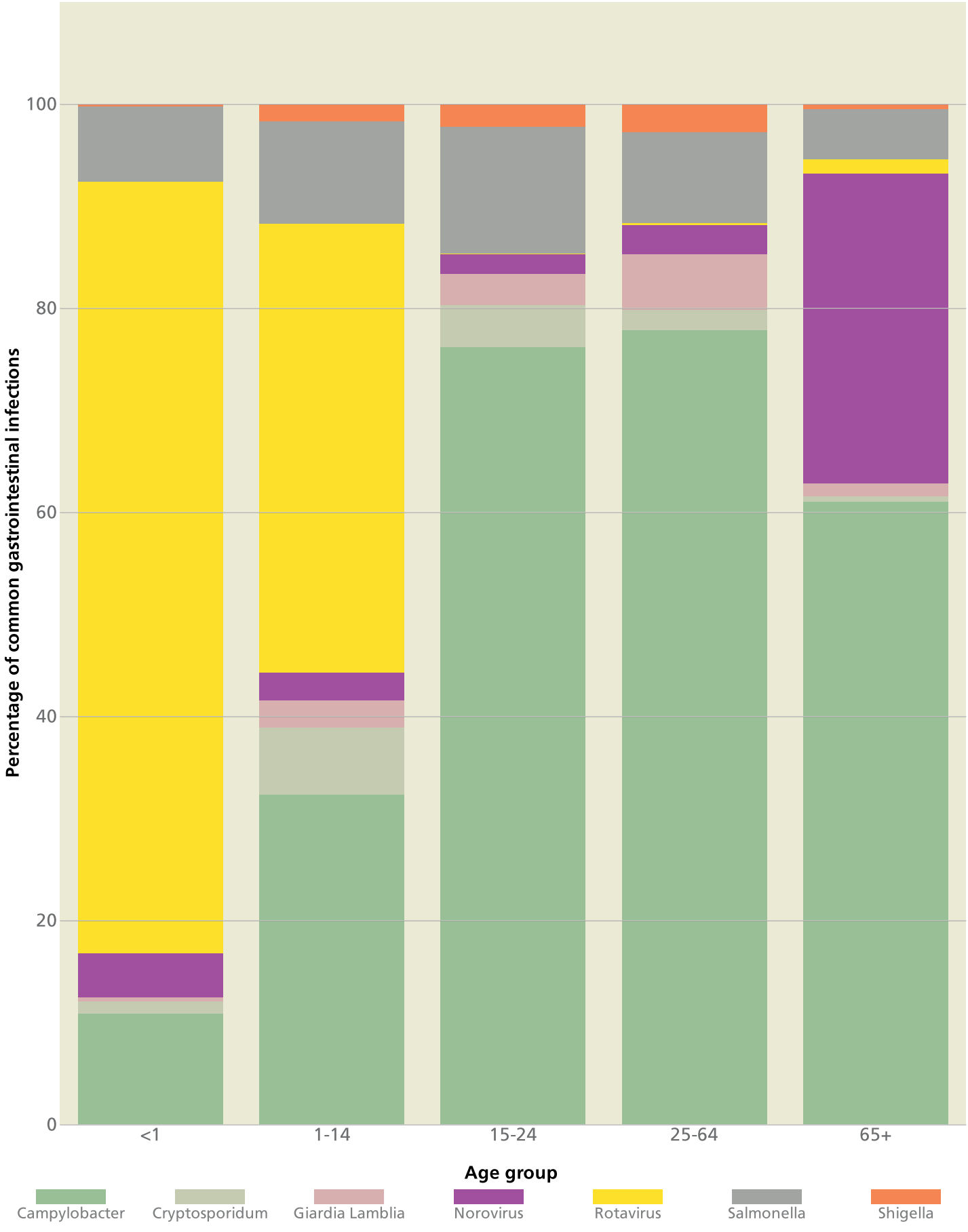
Vaccine-preventable and invasive bacterial infections

Safe, effective vaccination programmes have a profound impact on the epidemiology of infectious disease. Diseases such as polio, diphtheria and tetanus are no longer a significant cause of disease in England because of high levels of vaccine coverage.

Some diseases remain a threat despite the availability of effective vaccines. Indigenous measles transmission returned to the UK between 2006 and 2009 after a 10-year absence, resulting in large outbreaks of measles – particularly in populations with low vaccine coverage, such as the Orthodox Jewish population in London and Irish travelling communities across England. There was also some transmission in the wider community, mostly among children of preschool and primary-school age. A further increase was seen in early 2011, related to infections imported from other parts of Europe, most notably France, with older children and young adults affected. Cases of mumps have also increased recently, particularly among adolescents and older children, and particularly in educational settings. This is partly due to waning immunity in individuals vaccinated earlier in life.[4]

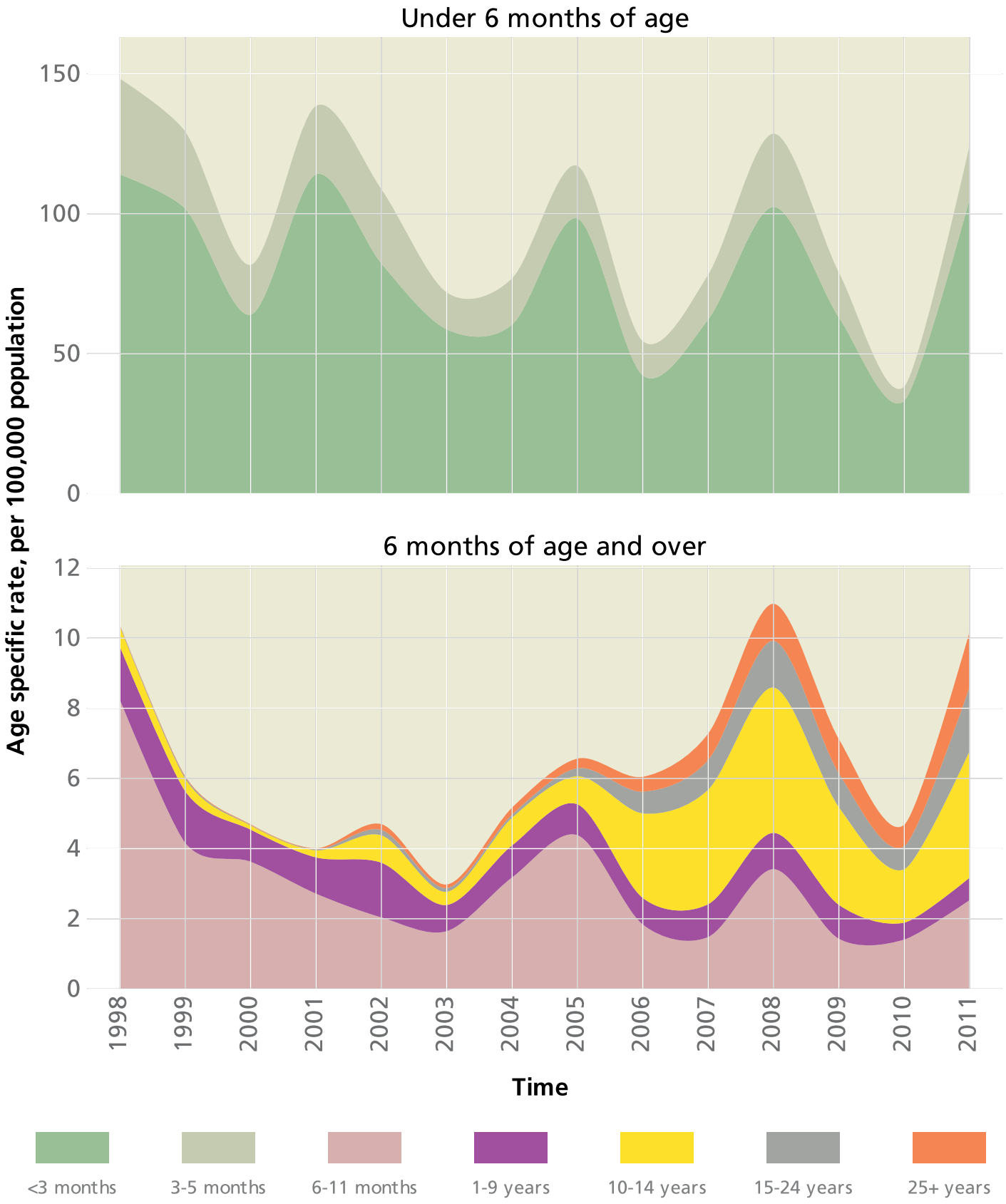
Pertussis (whooping cough) diagnoses have increased significantly since late 2011, and by the second half of 2012 the national outbreak of pertussis was the largest seen in England in over two decades (see Figure 2.5). The increase at first mostly affected those aged 15 or older but has extended to infants under 3 months, who are below the age of vaccination and have the highest risk of complications (with nine deaths in England in the first nine months of 2012). In response to this, a temporary programme of offering pertussis vaccine to all pregnant women was introduced in late 2012, to boost antibodies in vaccinated women in late pregnancy so that pertussis antibodies are passed from the mother to her baby.

Figure 2.4: Common gastrointestinal infections by age and infection, England, 2011



Source: LabBase2, HPA. (Analysis by HPA)

Figure 2.5: Trend in confirmed cases of pertussis infection by age, England and Wales, 1998 to 2011



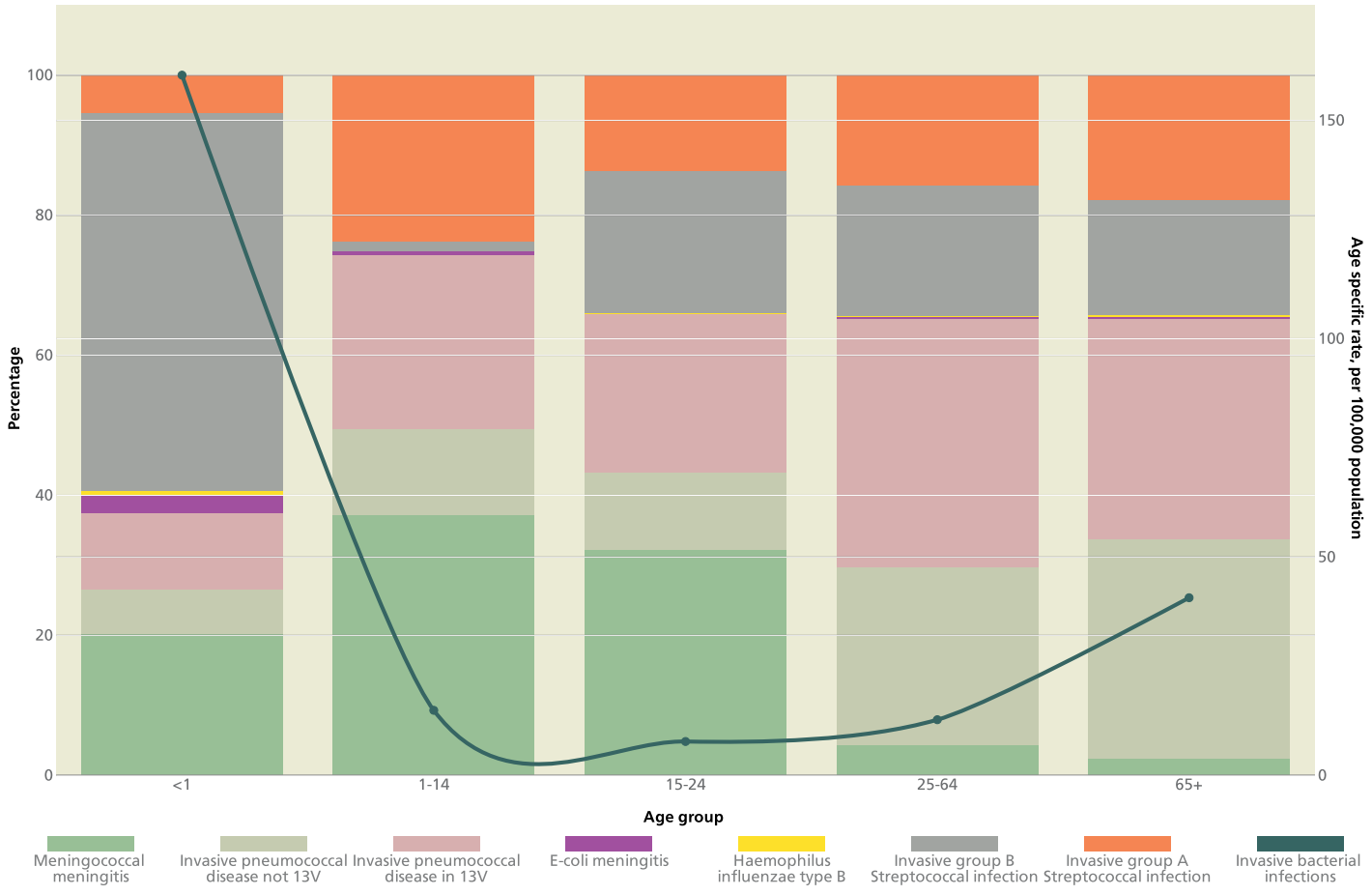
Source: LabBase2 and MOLIS, HPA. 1998 to 2010 population estimates, ONS. (Analysis by HPA)

Invasive disease from streptococcal, meningococcal or other bacterial infections may still be serious or fatal despite antibiotic therapy, particularly at the extremes of age (see Figure 2.6). Group B streptococcal infections, and to a lesser extent *E.coli* infections, cause significant morbidity such as meningitis (inflammation of the protective membranes (meninges) covering the brain and spinal cord), particularly in the first few weeks of life. Almost 20% of people with invasive group A streptococcal infections, most of which occur in the very young or the elderly, are admitted to an intensive-care or high-dependency unit and more than one in five die within seven days of diagnosis.[5]

Invasive pneumococcal disease commonly causes illness in children, the elderly, individuals without a spleen and patients with impaired immune systems. Pneumococcal infection causes community-acquired pneumonia, bloodstream infections and meningitis, and otitis media in children.[6] Each year an estimated one in every thousand adults is affected, and 10% to 20% die. Following the addition to routine childhood vaccinations of a vaccine against seven common types of pneumococcal infection in 2006, the incidence of invasive pneumococcal disease fell by a third; greater reductions were seen among those aged under 2 years. However, as disease from vaccinated types fell, disease from other types rose, so in 2010 the vaccine was extended to protect against a further six types of pneumococcal infection (see Figure 2.7).

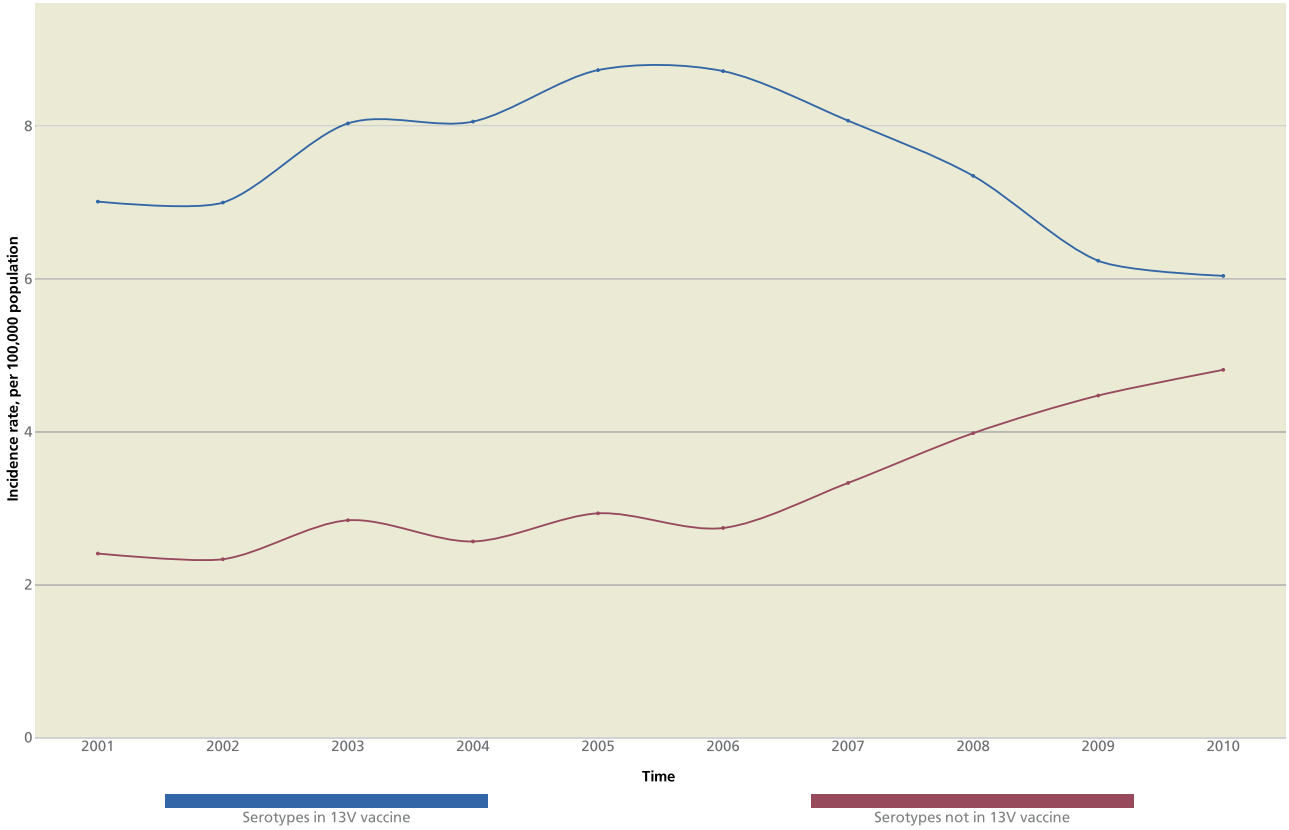
Invasive meningococcal disease still causes substantial morbidity and mortality, mostly affecting infants and young children, with a smaller peak of incidence among adolescents. Meningococcal disease has declined in all age groups in recent years, due partly to the success of routine immunisation against group C meningococcal infection (see Figure 2.8). The incidence of group B meningococcal disease has remained stable since 2007, while incidence of the less common group Y disease has increased. The proportion of cases that die remains low across all age groups except those aged over 65 years, whom, despite the disease being relatively uncommon, have higher fatality rates in affected individuals.

Figure 2.6: Cases of selected invasive bacterial infections by age, England, 2011



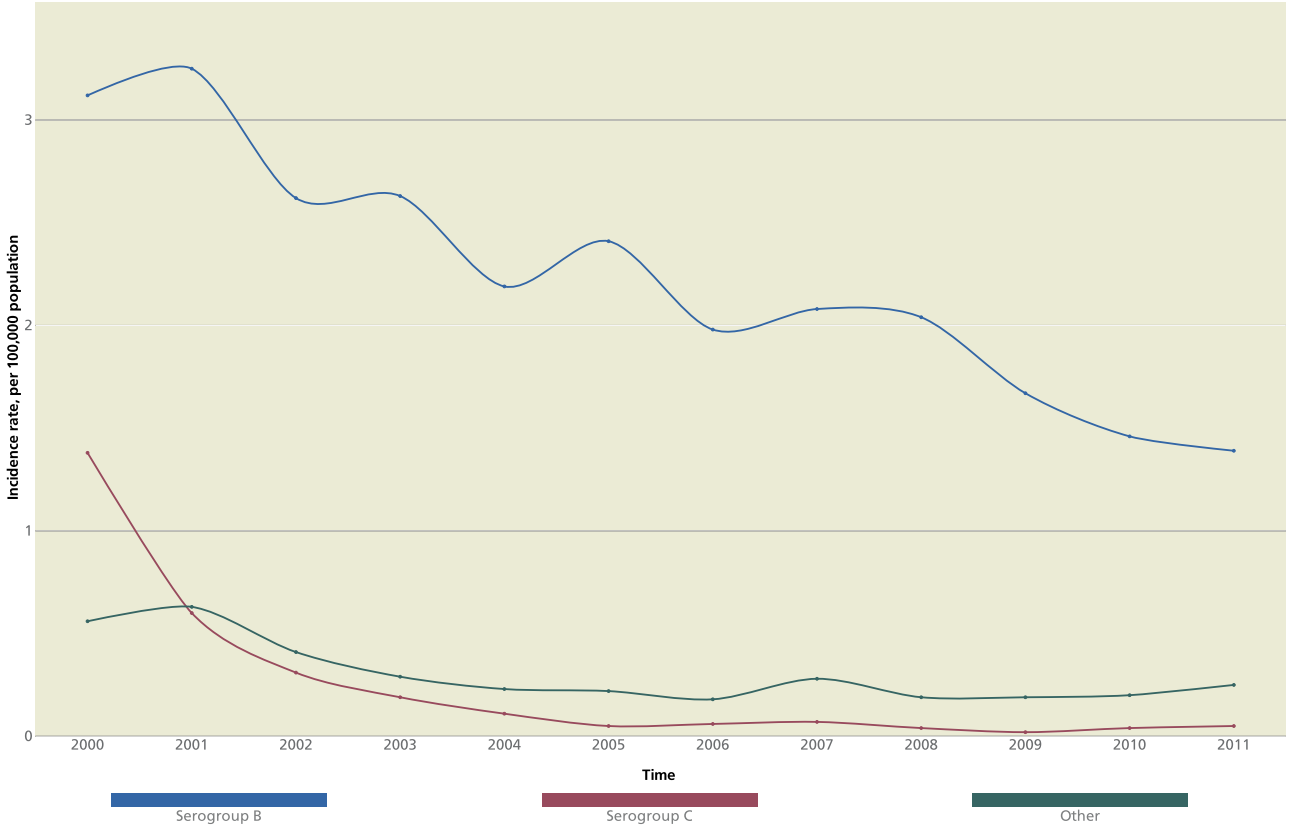
Source: LabBase2 and HPA Enhanced Surveillance, HPA. 2010 population estimates, ONS. (Analysis by HPA)

Figure 2.7: Trend in incidence of invasive pneumococcal disease by serotypes in/not in the vaccine, England, 2001 to 2010



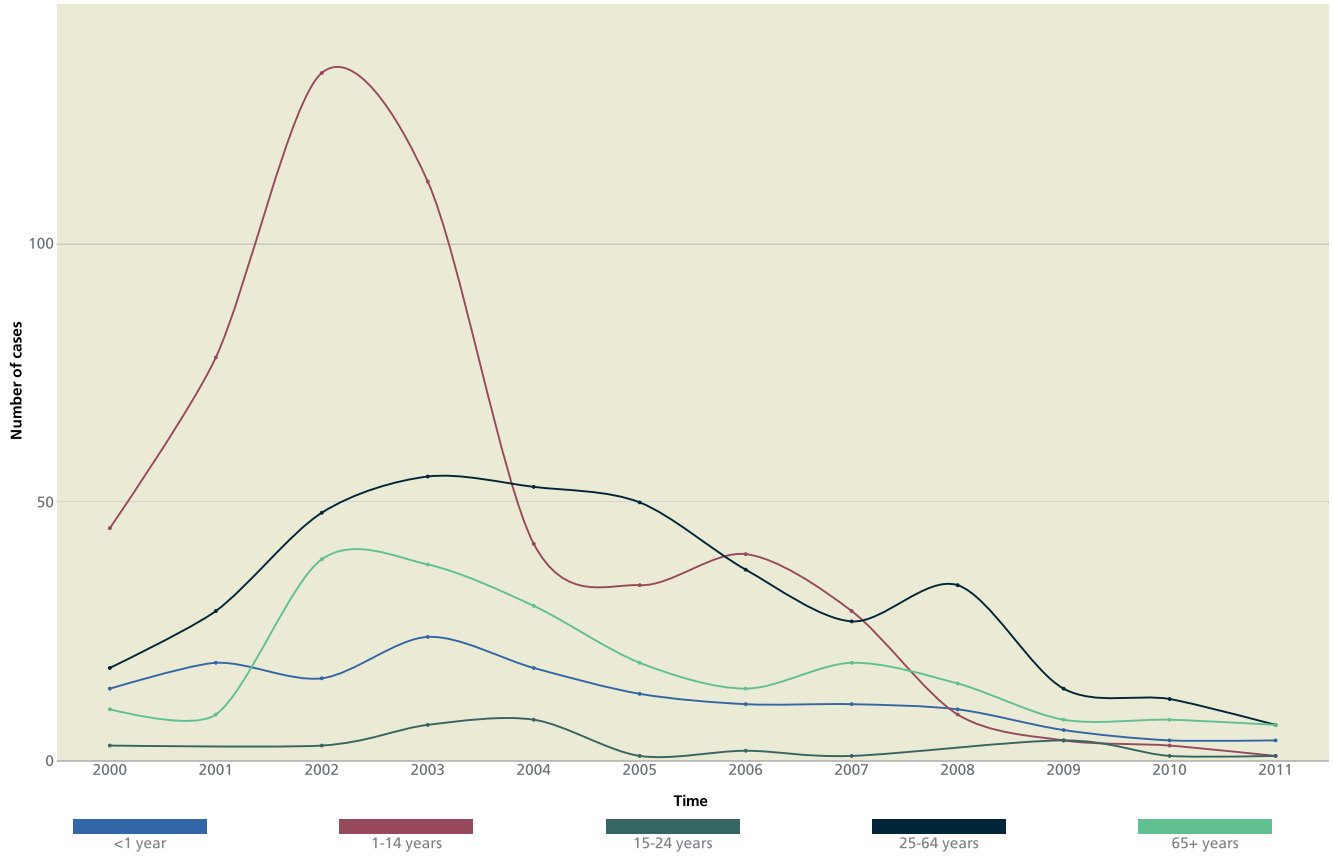
Source: Respiratory & Systemic Infection Laboratory, HPA. 2001 to 2010 population estimates, ONS. (Analysis by HPA)

Figure 2.8: Trend in incidence of invasive meningococcal disease by serotype, England, 2000 to 2011



Source: Meningococcal Reference Unit, HPA. 2000 to 2010 population estimates, ONS. (Analysis by HPA)

Figure 2.9: Trend in confirmed cases of invasive H.influenzae type B by age, England, 2000 to 2011



Source: LabBase2 and MOLIS, HPA. 2000 to 2010 population estimates, ONS. (Analysis by HPA)

Before the introduction of the *Haemophilus influenzae* type b (Hib) vaccine in 1992, *H. influenzae* was a significant cause of meningitis, pneumonia and epiglottitis, particularly in children under 5 years, but it is now rarely seen (see Figure 2.9).

Sexually transmitted infections

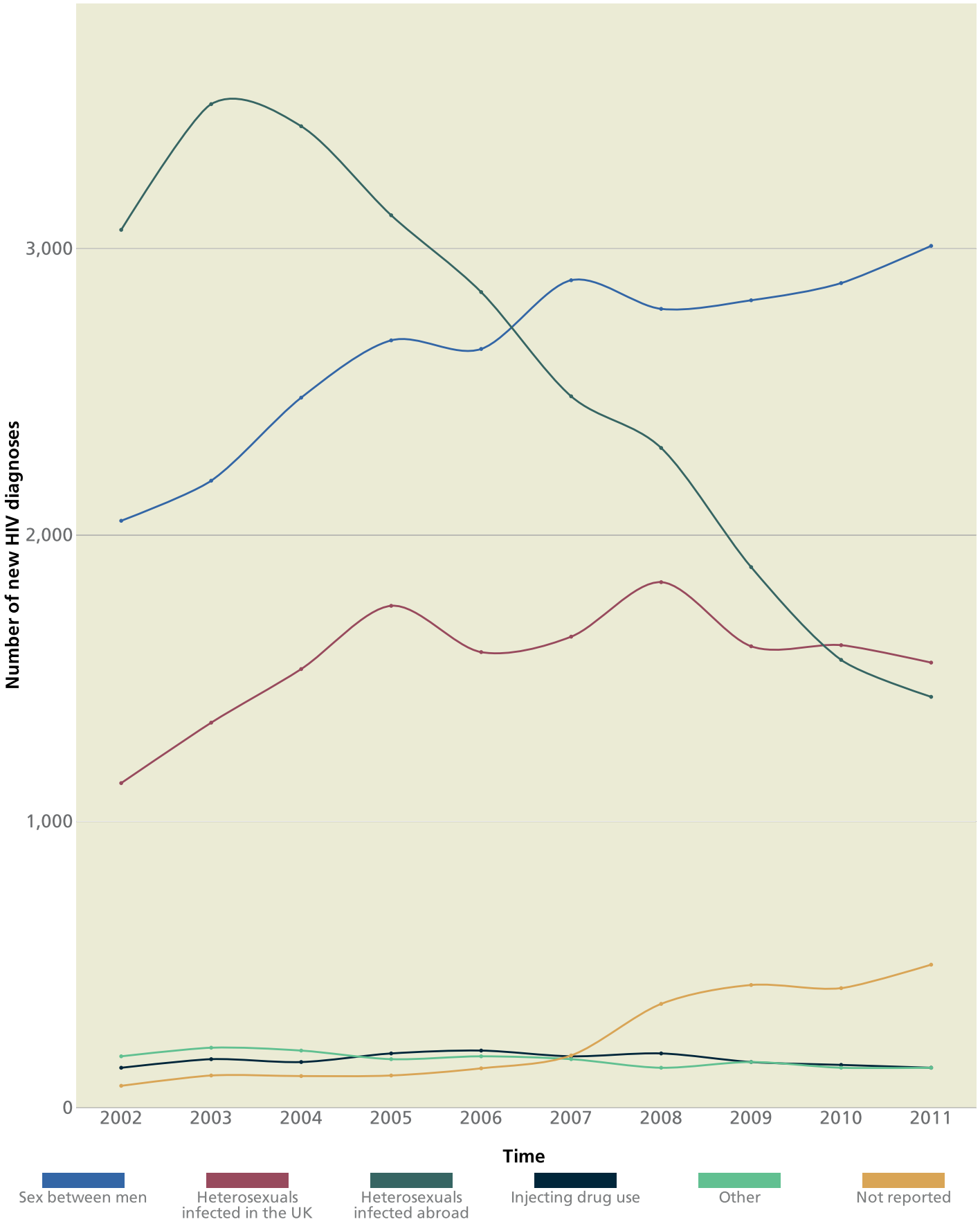
The overall number of new HIV diagnoses each year has fallen since 2006, mainly due to the halving in the number of HIV diagnoses among heterosexuals who were probably infected abroad (many in sub-Saharan Africa). New cases have continued to rise, however, among men who have sex with men (MSM): in 2011, for the first time since 1998, the number of new diagnoses in MSM was greater than the combined number of new diagnoses in heterosexuals infected abroad and in the UK. The trend in new diagnoses among heterosexuals infected within the UK is relatively stable (see Figure 2.10).

The highest rates and largest numbers of sexually transmitted infections (STIs) are generally seen in adolescents (particularly females) and adults below the age of 25 years (see Figures 2.11 and 2.12). Over 10% of 16 to 19 year-olds and approximately 14% of 13 to 15 year-old girls diagnosed with an acute STI will become reinfected within a year. STIs that disproportionately affect MSM, such as HIV, syphilis and lymphogranuloma venereum (LGV), show a peak in incidence at a higher age than those infections that are more commonly seen among heterosexual males and females.

STI rates vary considerably across England with the highest rates seen in large urban conurbations. Diagnoses of STIs have risen over the past decade, reflecting high levels of unsafe sexual behaviour, more sexual health screening in genitourinary medicine (GUM) clinics or through the National Chlamydia Screening Programme, and more sensitive molecular diagnostic tests.

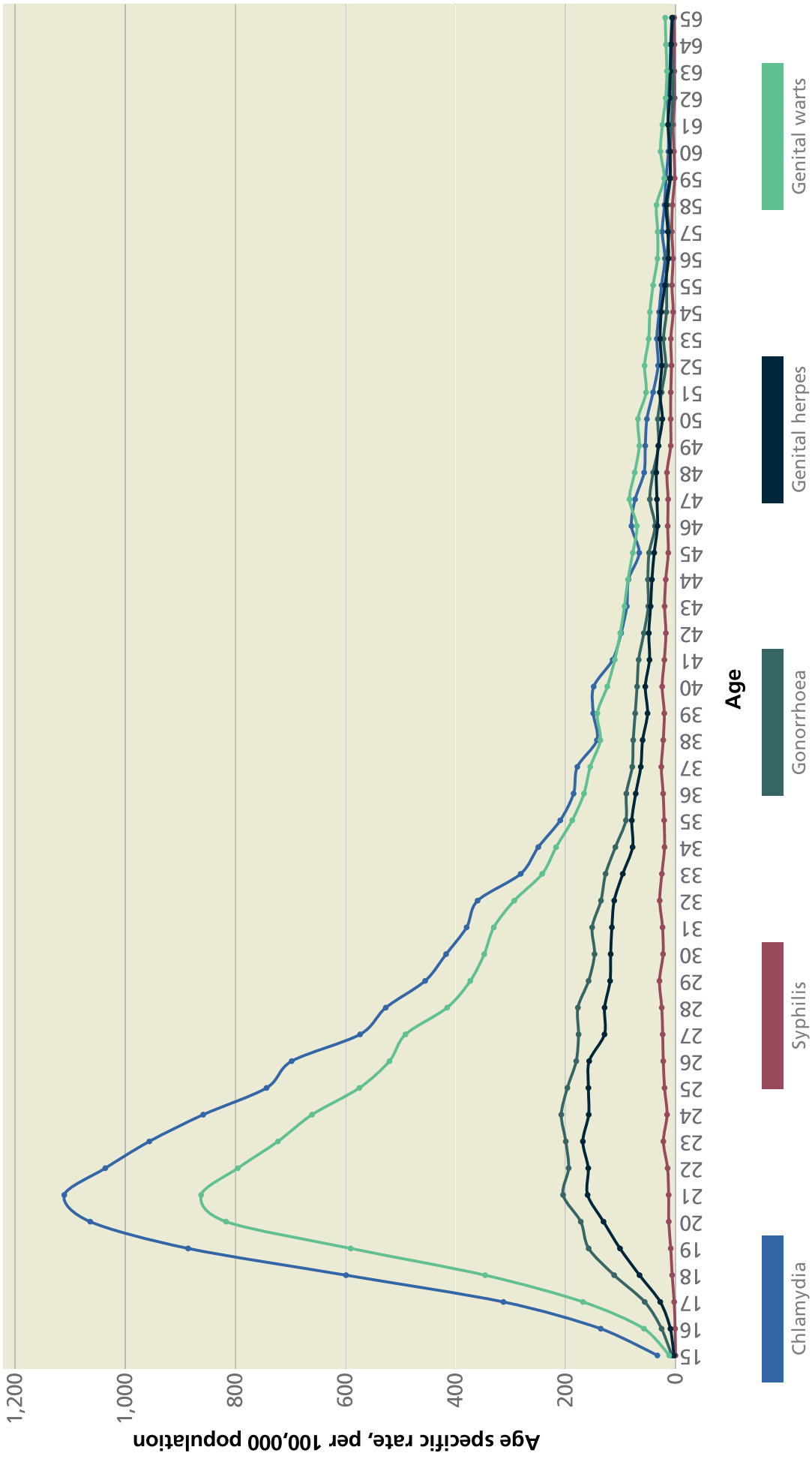
Among MSM, a large increase in diagnoses of gonorrhoea, chlamydia, non-specific urethritis and genital warts cases, as well as an ongoing LGV epidemic in older HIV-positive MSM, outbreaks of other STIs such as those caused by *Shigella flexneri* and *Shigella sonnei*, and increasing new diagnoses of HIV, indicate ongoing high levels of unsafe sex in this population (see Figure 2.13).

Figure 2.10: Trend in the number of new HIV diagnoses by exposure group, UK, 2002 to 2011



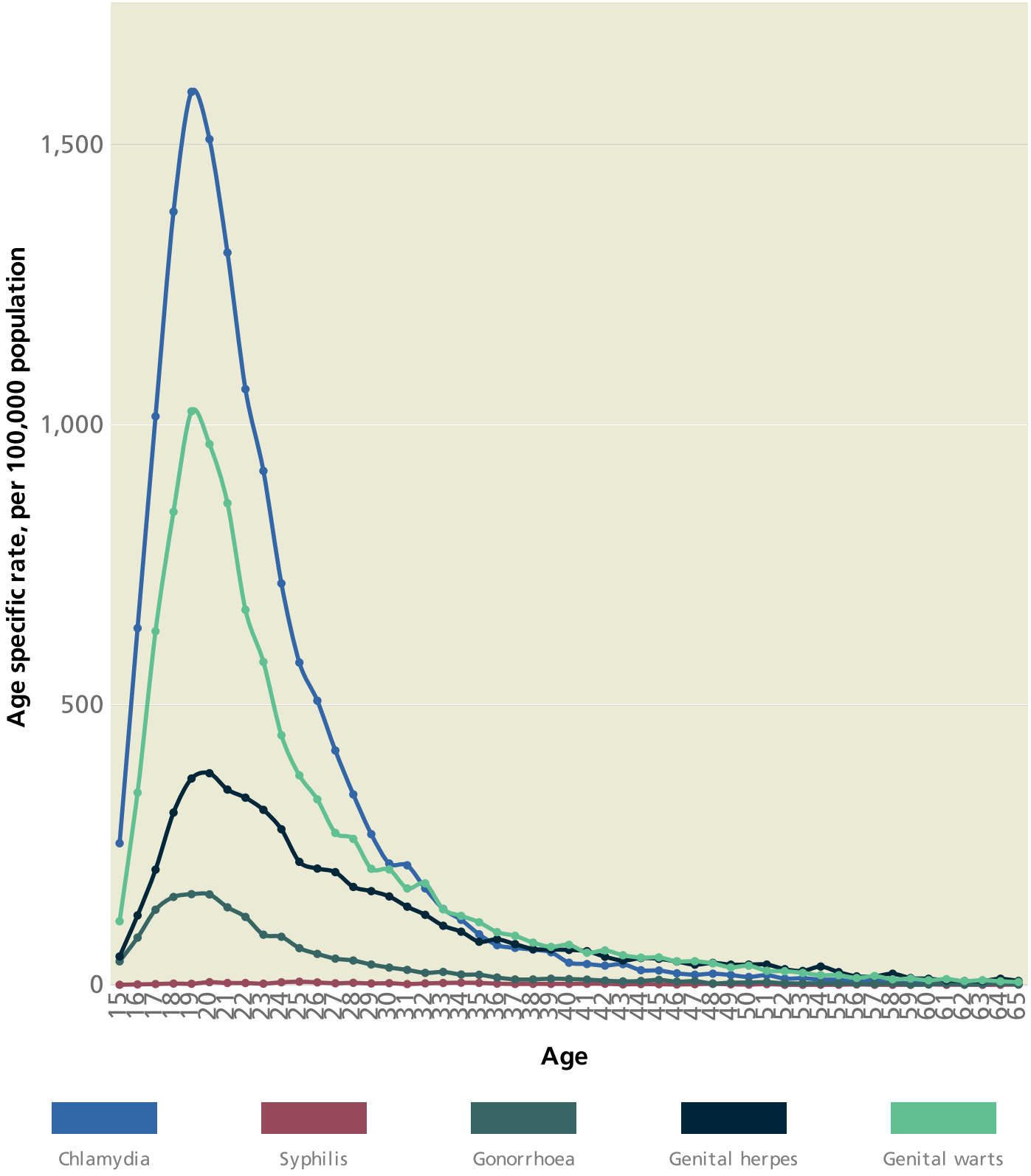
Source: HIV and AIDS New Diagnoses and Deaths Surveillance, HPA and Health Protection Scotland and Paediatric data complied at University College London, Institute of Child Health.

Figure 2.11: Rates of selected STIs diagnosed in genito-urinary medicine clinics in men aged 15+ years by age, England, 2011



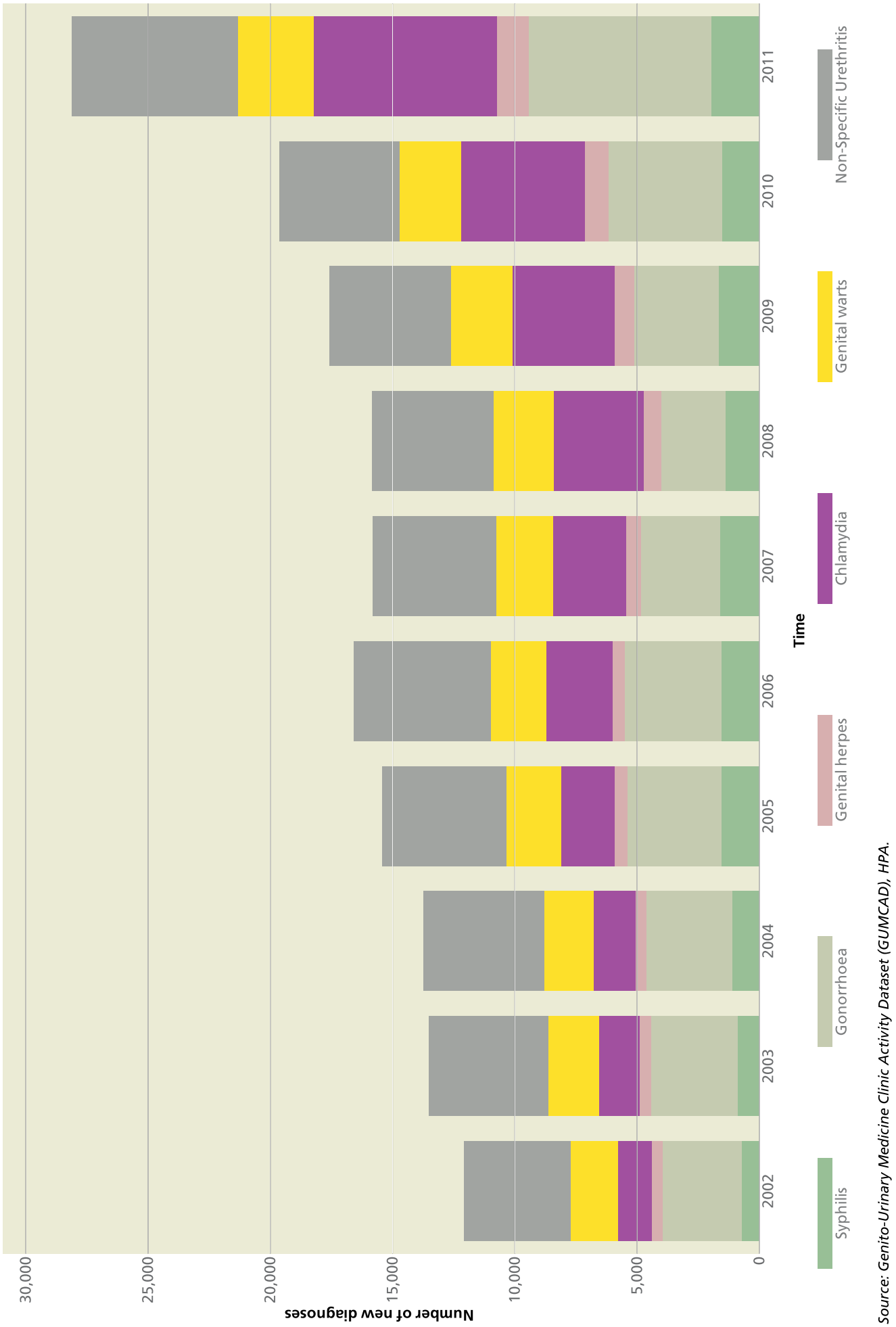
Source: Genito-Urinary Medicine Clinic Activity Dataset (GUMCAD),HPA. 2010 population estimates, ONS. (Analysis by HPA)

Figure 2.12: Rates of selected STIs diagnosed in genito-urinary medicine clinics in females aged 15+ by age, England, 2011



Source: Genito-Urinary Medicine Clinic Activity Dataset (GUMCAD), 2010 population estimates, ONS. (Analysis by HPA)

Figure 2.13: Trend in the number of new diagnoses of selected STIs among men who have sex with men, England, 2002 to 2011



Source: Genito-Urinary Medicine Clinic Activity Dataset (GUMCAD), HPA.

Blood-borne virus infections

Following efforts to increase awareness and detection of undiagnosed hepatitis C infection, laboratory reports of hepatitis C have risen each year since 2004, particularly after the introduction of statutory laboratory reporting in 2011. In the UK, an estimated 216,000 individuals have chronic hepatitis C infection. In 2010 most new diagnoses of hepatitis C were in men, and half were in individuals aged between 25 and 39 years (see Figure 2.14). The predominant risk factor for infection is current or previous injecting drug use (accounting for an estimated 44% of infections among hepatitis C infected 15–59 year-olds in England).

The proportion of hepatitis B cases linked to injecting drug use has fallen from nearly half to a small percentage. Unprotected sex is the leading risk factor for infection with hepatitis B. Infection is twice as common in males, especially those aged 35–44 years. The rate in London is higher than in any other region of England.

Healthcare-associated infections

A healthcare-associated infection (HCAI) is an infection occurring in a patient receiving care in a hospital or other healthcare facility (or apparent after discharge) that was not present at the time of admission. There are many different types of HCAI, such as bacteraemia (infection of the blood) caused by meticillin-resistant (MRSA) or sensitive (MSSA) *S. aureus* or *E. coli*, diarrhoea caused by *C. difficile* infection or infections following surgery. The World Health Organization has noted that HCAI represents the most frequent adverse event during care delivery and that no institution or country can yet claim to have solved this problem.

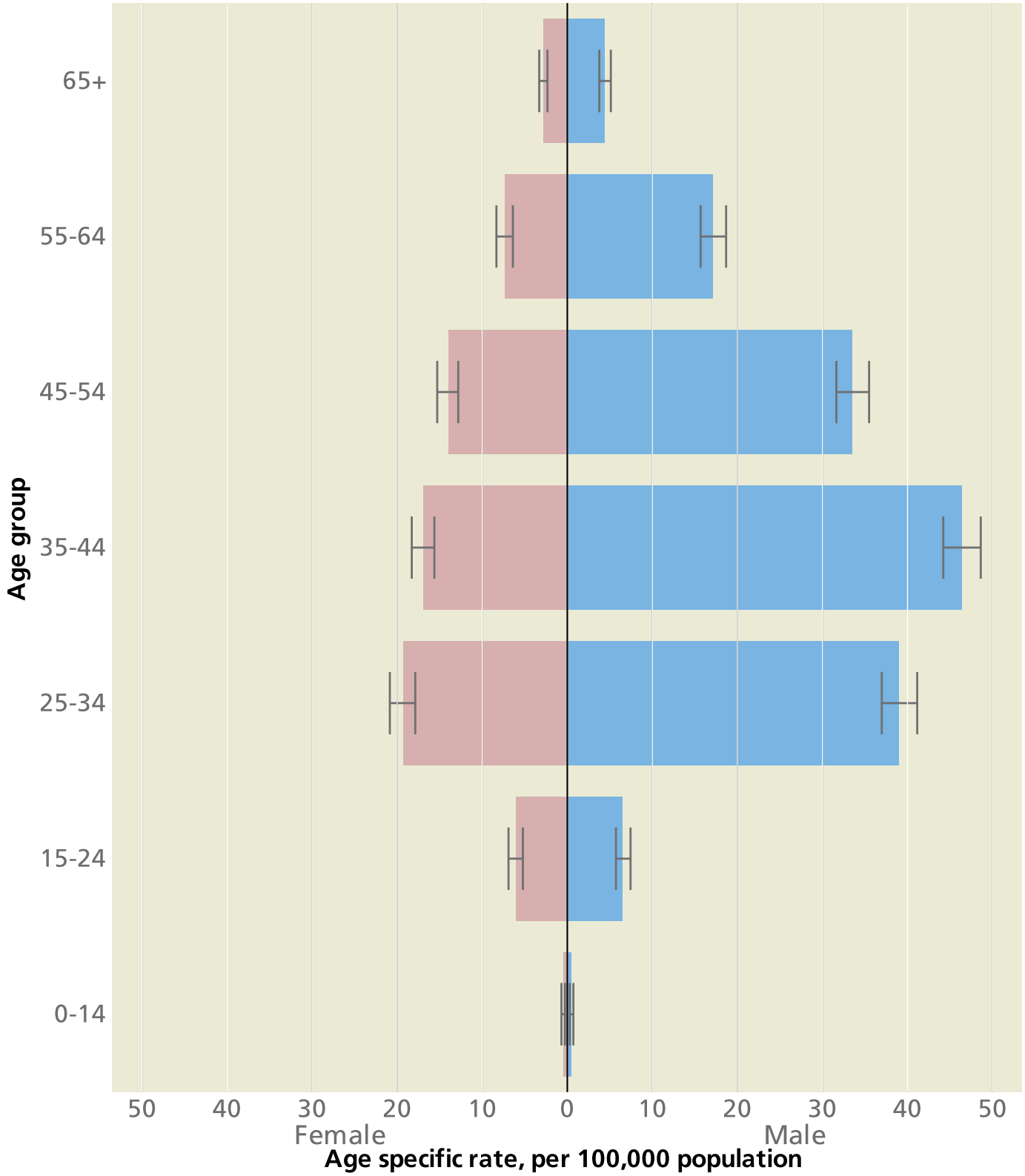
Rates of *C. difficile* have fallen consistently in all English regions in recent years. MRSA has fallen markedly and is now very low in many areas. Rates for MSSA bacteraemia remain several times higher than those for MRSA bacteraemia and voluntary surveillance data suggest rates have only begun to show a slight downward trend from 2008[1].

Reports of *E. coli* bacteraemia rose by a third between 2007 and 2011, despite a small fall in other bacteraemias, reaching 30,000 in 2011, when almost a third of bacteraemia reports were *E. coli*. The highest rates were seen in patients aged 65 years and over and in those aged under 1 year.

The J-shaped age profile of HCAI cases mirrors that of the population receiving inpatient healthcare or institutional social care with high levels of input from healthcare. Rates fall in the early years of life but rise exponentially in adulthood, with the highest rates being seen in the elderly (see Figures 2.15 and 2.16). This reflects not only greater exposure to health or social care settings, but also greater susceptibility to infection due to underlying poor health.

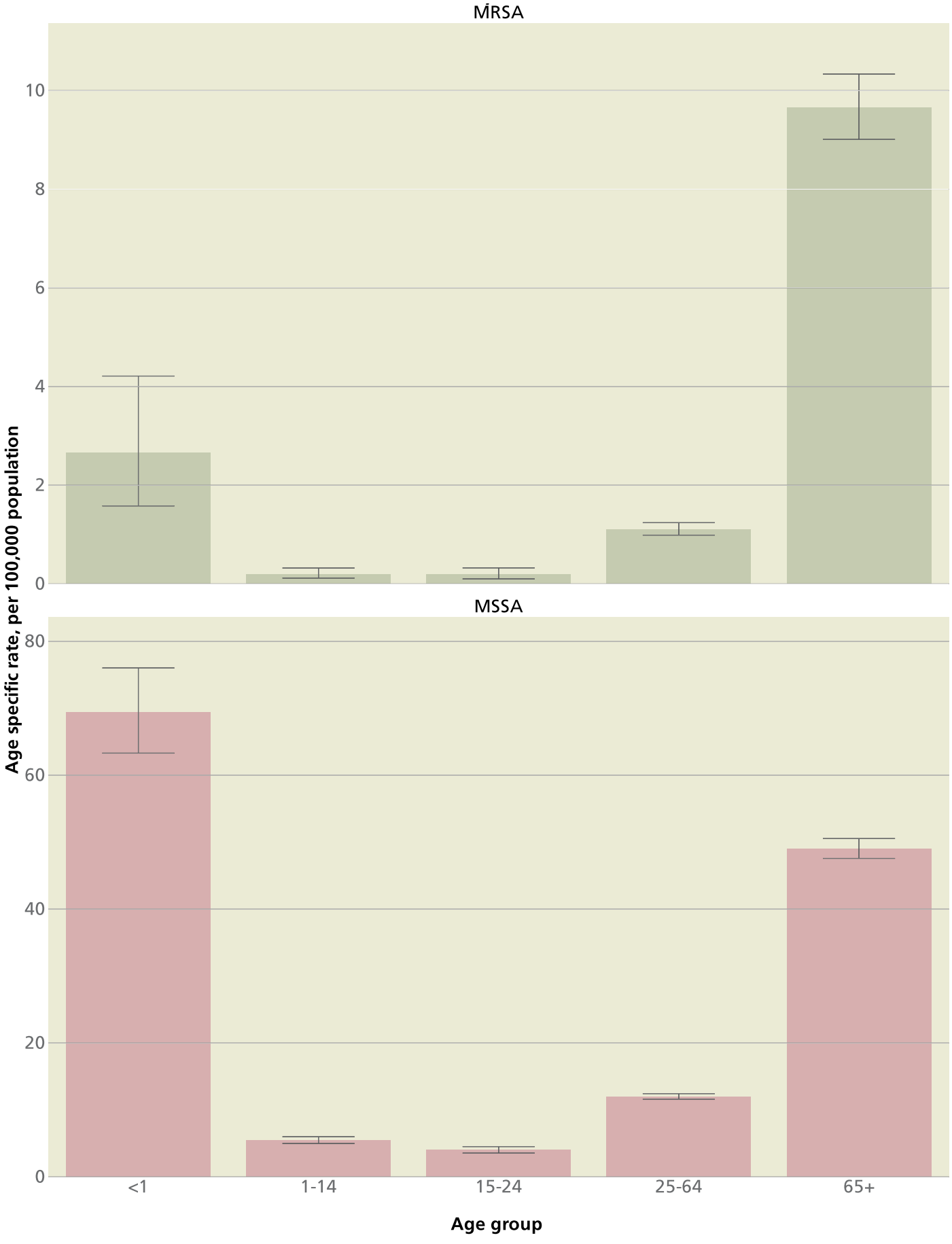
Norovirus is the most common viral cause of infectious gastroenteritis in England and Wales. It is generally mild and short-lived but may cause outbreaks which have a significant impact on schools, healthcare and social settings, particularly in winter. In England and Wales, 2,822 hospital outbreaks of gastrointestinal infection were notified to the Health Protection Agency norovirus outbreak reporting scheme during the 2010–2011 and 2011-2012 reporting period (July to June, reflecting the winter peak in activity). Most of these were confirmed as being caused by norovirus and most of them resulted in bed closures or restrictions to admissions (see Figure 2.19).

Figure 2.14: Hepatitis C laboratory report rate by age and sex, England, 2010



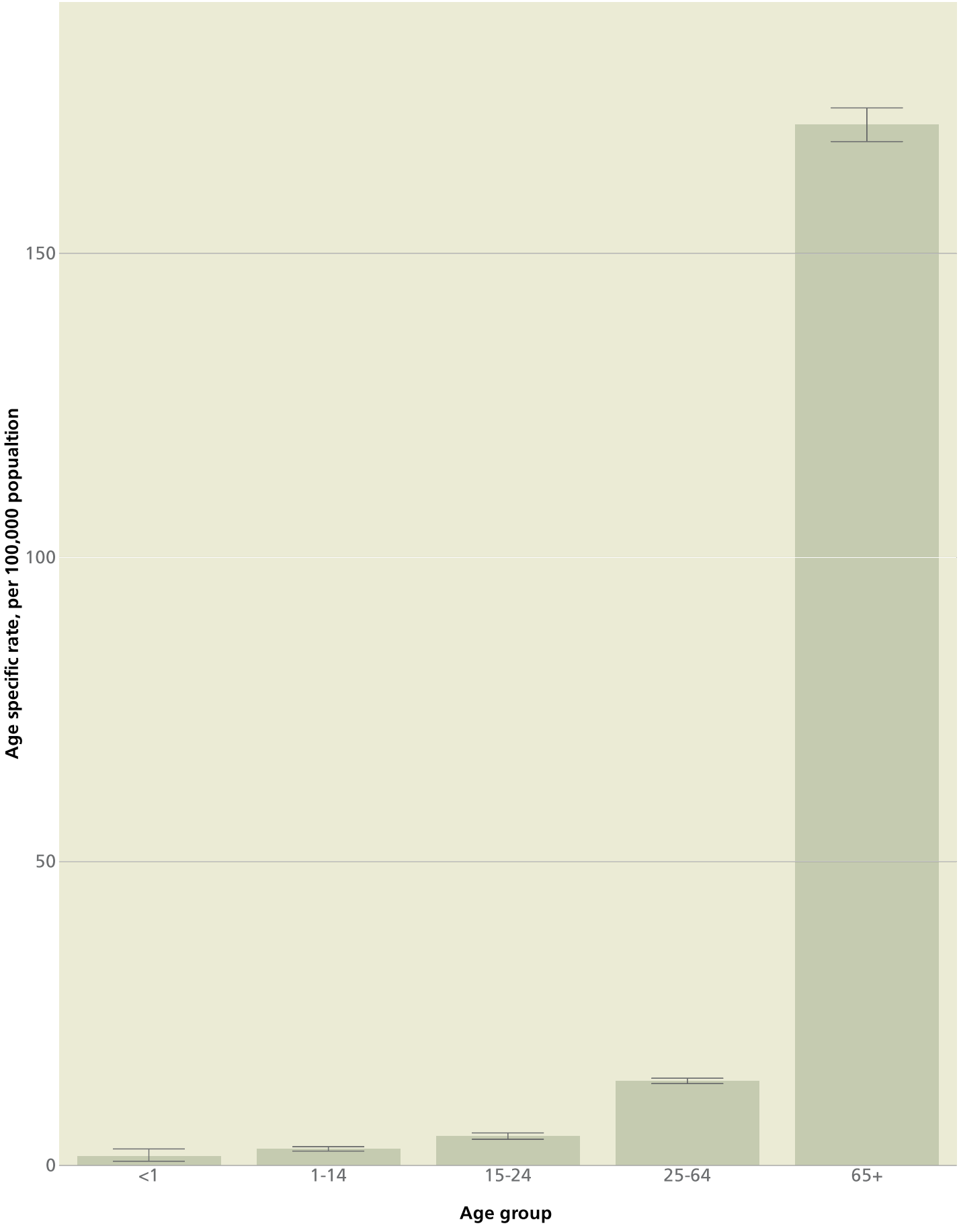
Source: Centre for Infections laboratory data, HPA. 2010 population estimates, ONS. (Analysis by HPA)

Figure 2.15: Meticillin-resistant and sensitive Staphylococcus aureus (MRSA and MSSA) bacteraemia rates by age, England, 2011



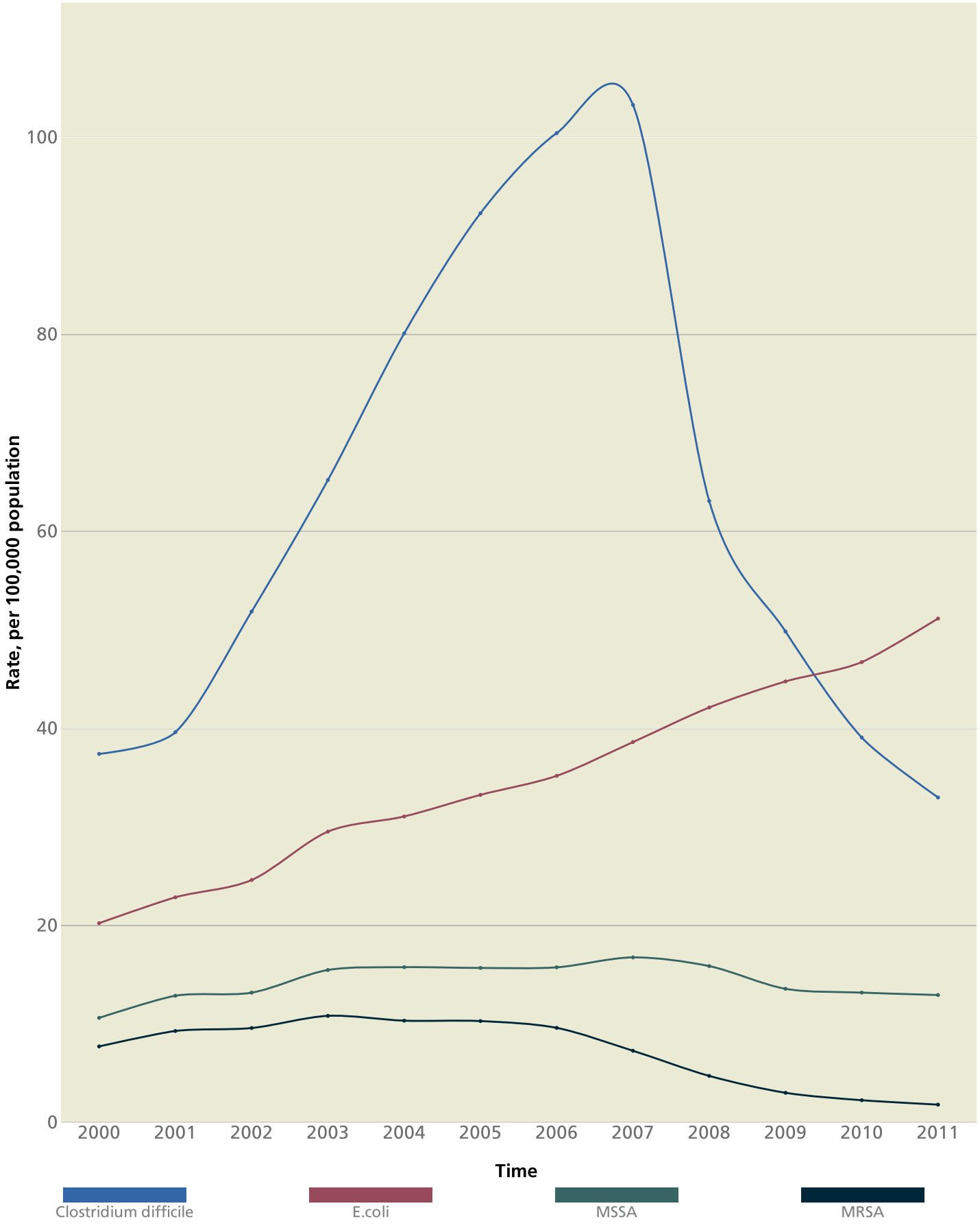
Source: Healthcare Associated Infections (HCAI) Data Capture System, HPA. 2010 population estimates, ONS. (Analysis by HPA)

Figure 2.16: Rate of Clostridium difficile infection rates by age, England, 2011



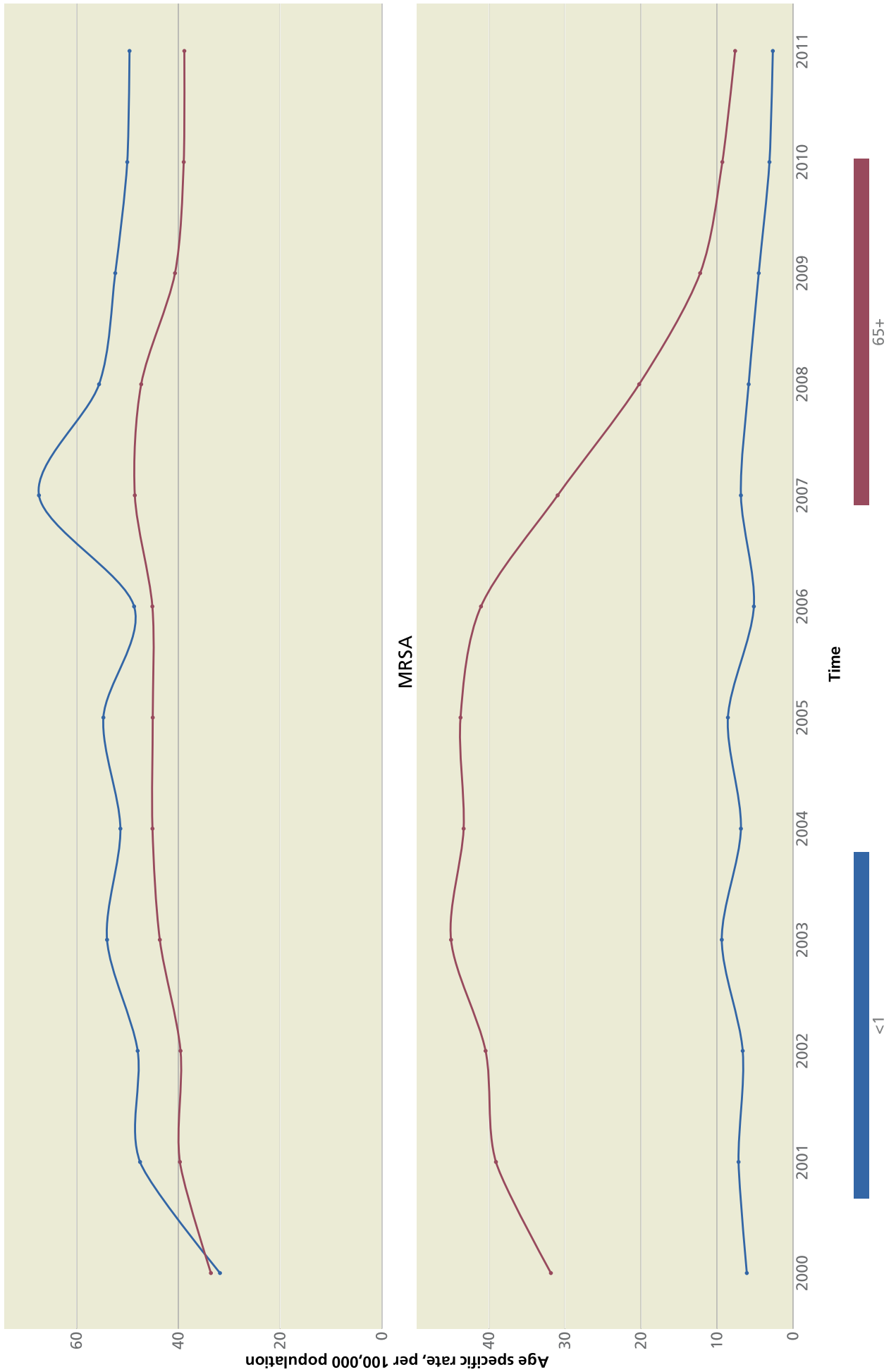
Source: Healthcare Associated Infections (HCAI) Data Capture System, HPA. 2010 population estimates, ONS. (Analysis by HPA)

Figure 2.17: Trend in C. difficile infection, Meticillin-resistant and sensitive Staphylococcus aureus (MRSA and MSSA) and E. coli bacteraemias, England 2000 to 2010



Source: Healthcare Associated Infections (HCAI) Data Capture System and LabBase2, HPA. 2000 to 2010 population estimates, ONS. (Analysis by HPA)

Figure 2.18: Trend in meticillin-resistant and sensitive Staphylococcus aureus (MRSA and MSSA) bacteraemia diagnoses rates by age (less than 1 year and 65+), England, 2000 to 2011



Source: Healthcare Associated Infections (HCAI) Data Capture System, HPA. 2000 to 2010 population estimates, ONS. (Analysis by HPA)

Challenges in infectious disease control

Among the challenges of containing infectious disease are the inapparent nature of infection in asymptomatic individuals, the adaptability of microorganisms, the rapidity with which infections can spread around the globe, the ubiquity of certain organisms in the environment, and the disproportionate burden on marginalised or hard-to-reach groups.

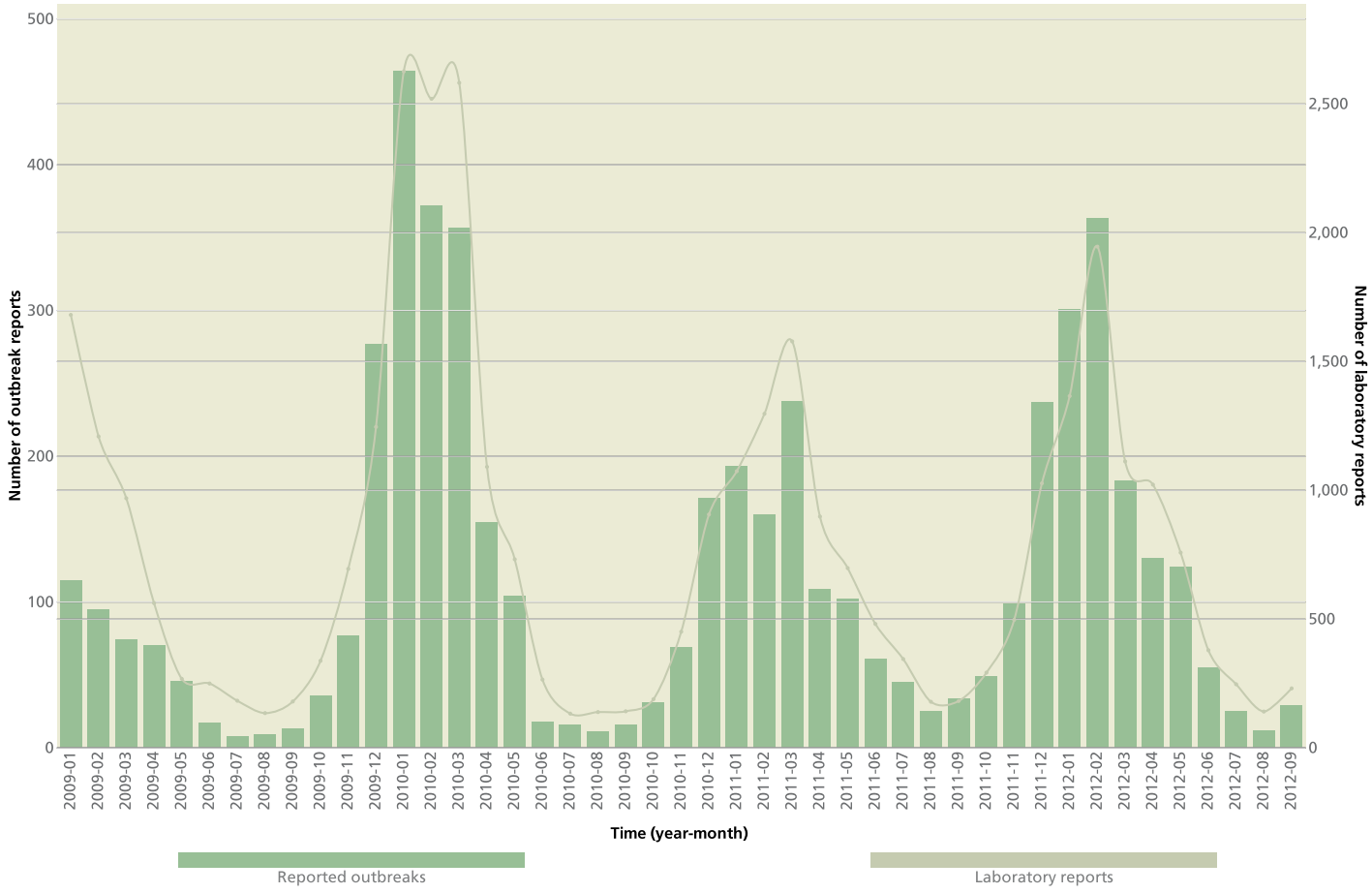
Asymptomatic infection is a particular challenge in the fight against sexually transmitted infections. Many people with infections such as chlamydia or HIV are unaware; they can infect others and miss opportunities for treatment that would prevent complications such as pelvic inflammatory disease (or infertility in the case of chlamydia, or severe immune suppression in the case of HIV). Such treatment would also reduce the risks of transmission to others.

Many microorganisms can undergo rapid changes, giving rise to new forms that are resistant to the antimicrobial drugs used to treat infections, or are able to escape the protection provided by immunisation, or become adapted to new environments**. The continuing increase in organisms resistant to antimicrobial drugs is one of the greatest threats that we face today.** Resistance can be transferred between different species of bacteria, resulting in organisms that are resistant to many or all available drugs, causing major problems in some parts of the world and with the potential to spread quickly to other areas. This is particularly true for infections that are associated with healthcare settings, such as Enterobacteriaceae, but also for infections such as tuberculosis or gonorrhoea.

The ability of microorganisms to exchange genetic material between strains or species is an important factor in the emergence of new infectious diseases and the re-emergence of infections that had previously been controlled by immunisation or other means. A good example of this is the influenza virus, which can give rise to worldwide epidemics (pandemics) when new strains arise that can escape the protection offered by natural immunity or vaccination.

Many existing human infections are zoonotic, and **experience shows us that the majority of new and emerging diseases are also likely to be of zoonotic origin.** It is vital, therefore, that the medical and veterinary sectors work together to share epidemiological expertise and surveillance data in a co-ordinated way to most effectively identify and mitigate risk to public health.

Figure 2.19: Laboratory reports of norovirus infections and norovirus outbreak reports by month of report, England and Wales, January 2009 to September 2012



Source: LabBase2, Hospital Norovirus Outbreak Reporting Scheme, HPA.

It is now possible for a person to travel around the globe in less time than it takes for symptoms to appear following an infection. The impact of international tourism and travel on infectious disease epidemiology was seen in 2009 with the rapid spread of pandemic H1N1 influenza from Mexico to Spain and the UK, and also in 2003 with the rapid spread of SARS from SE Asia to Australia, Europe, Africa, and North and South America.

The impact of international migration is seen when infections that occurred in the country of origin cause illness in the destination country, such as with tuberculosis in England, where most cases are among those born outside the UK and the highest rates of disease are seen in London and the West Midlands, where there are large migrant populations. HIV infection acquired in countries with high HIV prevalence was the most common source of infection among cases in the UK before recent changes in migration patterns.

The recent exponential growth in international trade presents new challenges for infectious disease control, particularly related to the global trade in foods: importation of contaminated food can cause significant outbreaks. About half the food eaten in the UK is imported. In Germany in 2011 an outbreak of a severe strain of *E.coli* caused by contaminated Egyptian fenugreek seeds resulted in 2,987 cases of acute gastroenteritis, 855 cases of haemolytic uraemic syndrome (HUS) and 53 deaths. **Complex international food distribution networks make the investigation and control of such outbreaks difficult, requiring collaboration between national and international agencies.**

Infectious disease surveillance and prevention activities are also made difficult by the fact that the highest prevalence of many infections of public health importance, such as tuberculosis, hepatitis C and many sexually transmitted infections, is frequently to be found within population groups that are relatively hard for health services to reach, such as new migrants, the homeless and injecting drug users.

As we have seen here and will be shown in more detail in subsequent chapters, infectious diseases remain an important cause of illness, but patterns of infectious disease are different at each stage of the life course, as are the measures we need to take to protect human health.

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Chapter 3

Health inequalities and infectious diseases

Chapter authors

Anthony Kessel[1], James Wilson[2], Ibrahim Abubakar[3], John Watson[4], Richard Pebody[5], Maria Zambon[6], Gayatri Amirthalingam[7], Aileen Kitching[8], Mary Ramsay[9], Gwenda Hughes[10], Valerie Delpech[11], Emma Savage[12], Sarika Desai[13], Ellen Bloomer[14], Peter Goldblatt[15]

1 Director Public Health Strategy and Medical Director, Health Protection Agency
2 Lecturer in Philosophy and Health, Director, Centre for Philosophy, Justice and Health, University College London
3 Professor in Infectious Disease Epidemiology, Research Department of Infection and Population Health, University College London and Tuberculosis Section, Respiratory Diseases Department, Health Protection Agency
4 Head, Respiratory Diseases, Health Protection Agency
5 Consultant Epidemiologist, Head of Influenza and Acute Respiratory Virus Surveillance section, Health Protection Agency
6 Director of Reference Microbiology, Health Protection Agency
7 Consultant Epidemiologist, Immunisation, Hepatitis & Blood Safety Department, Health Protection Agency
8 Speciality Registrar (Public Health Medicine), Health Protection Agency
9 Consultant Epidemiologist, Health Protection Agency
10 Consultant Scientist (Epidemiology), Health Protection Agency
11 Consultant Epidemiologist, Health Protection Agency
12 Principal Scientist STI Surveillance, Health Protection Agency
13 Senior Scientist (Epidemiology), Health Protection Agency
14 Research Fellow, Department of Epidemiology and Public Health, University College London
15 Deputy Director, UCL Institute of Health Equity, University College London

Overview

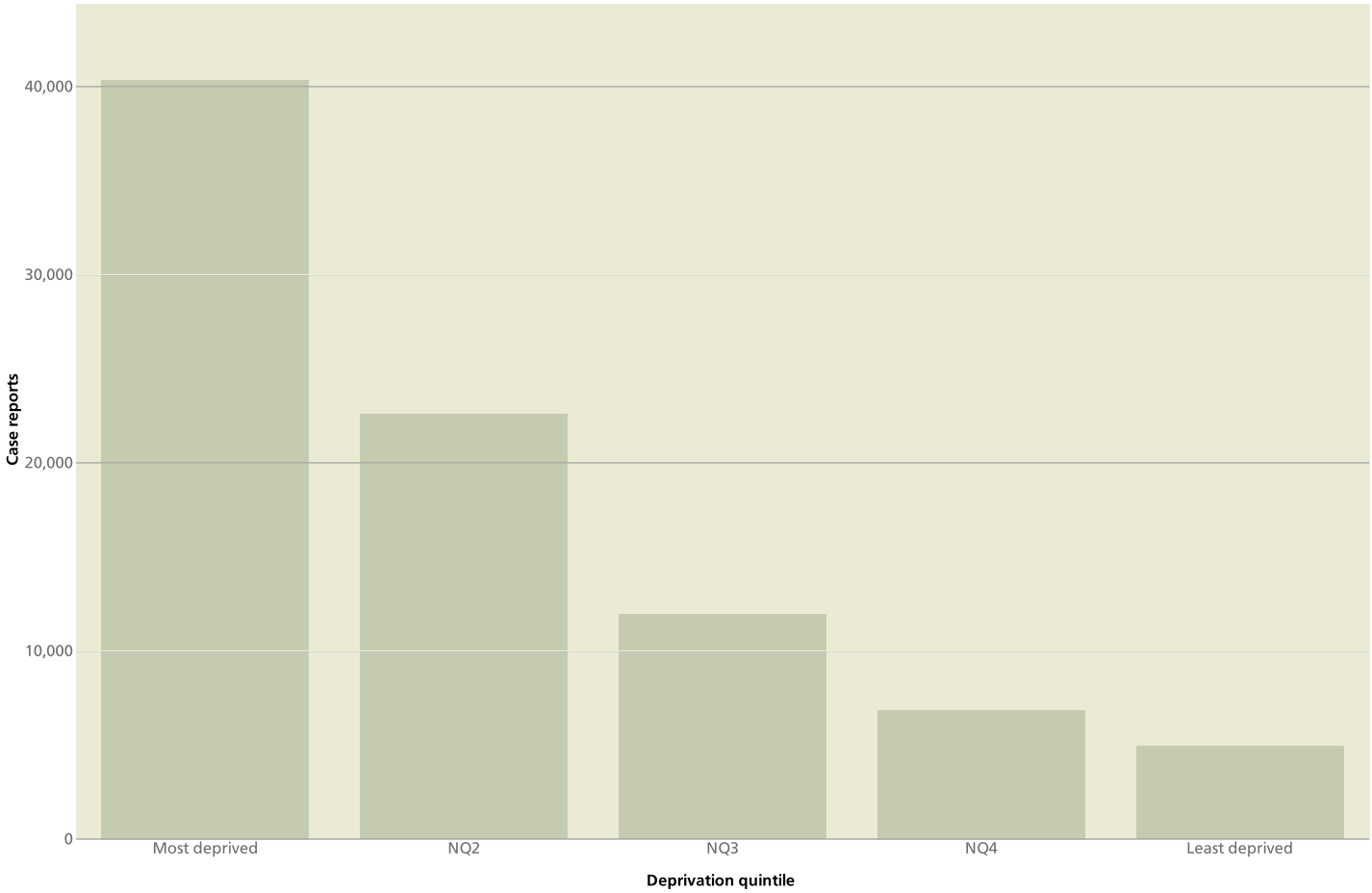
The *Black Report* of 1980 showed that an individual from the lowest social class is likely to have worse health throughout his or her life, and die younger, than someone who is better off.[1] The findings of the *Black Report* were replicated in 1992 in the *Health Divide*,[2] followed by an independent inquiry,[3] new government policy[4] and specific strategies aimed at reducing health inequalities.[5, 6] Following the recent wide-ranging World Health Organization review, the importance of health inequalities is now well established.[7]

The term 'inequalities in health' is essentially descriptive – referring to a range of socially determined differences in both health experience and health status between countries, regions and socio-economic groups. However, "in industrialised countries such as the United Kingdom, the term 'inequalities in health' has tended to refer to differences in health status between regions and population subgroups that are regarded as inequitable."[8] In other words, the underlying notion is that there is something inherently unfair – and wrong – about the gap between the health experiences of different social groups, and that a fairer picture of overall population health entails a commitment to narrower distribution of health experiences in social groups that make up the population.[9, 10, 11, 12]

Health is a prerequisite for the pursuit of the kinds of life that citizens have reason to value,[13] as well as often being thought important for its own sake.[14, 15, 16, 17] Groups who suffer from health inequities suffer a health shortfall both in comparison with better-off groups and in comparison with the life that they themselves could have enjoyed under more favourable circumstances. The latter shortfall provides the primary reason for the unfairness of health inequities.[18, 19] Action on the social determinants of health thus has the goal of creating the conditions in which each individual can live a long and healthy life.

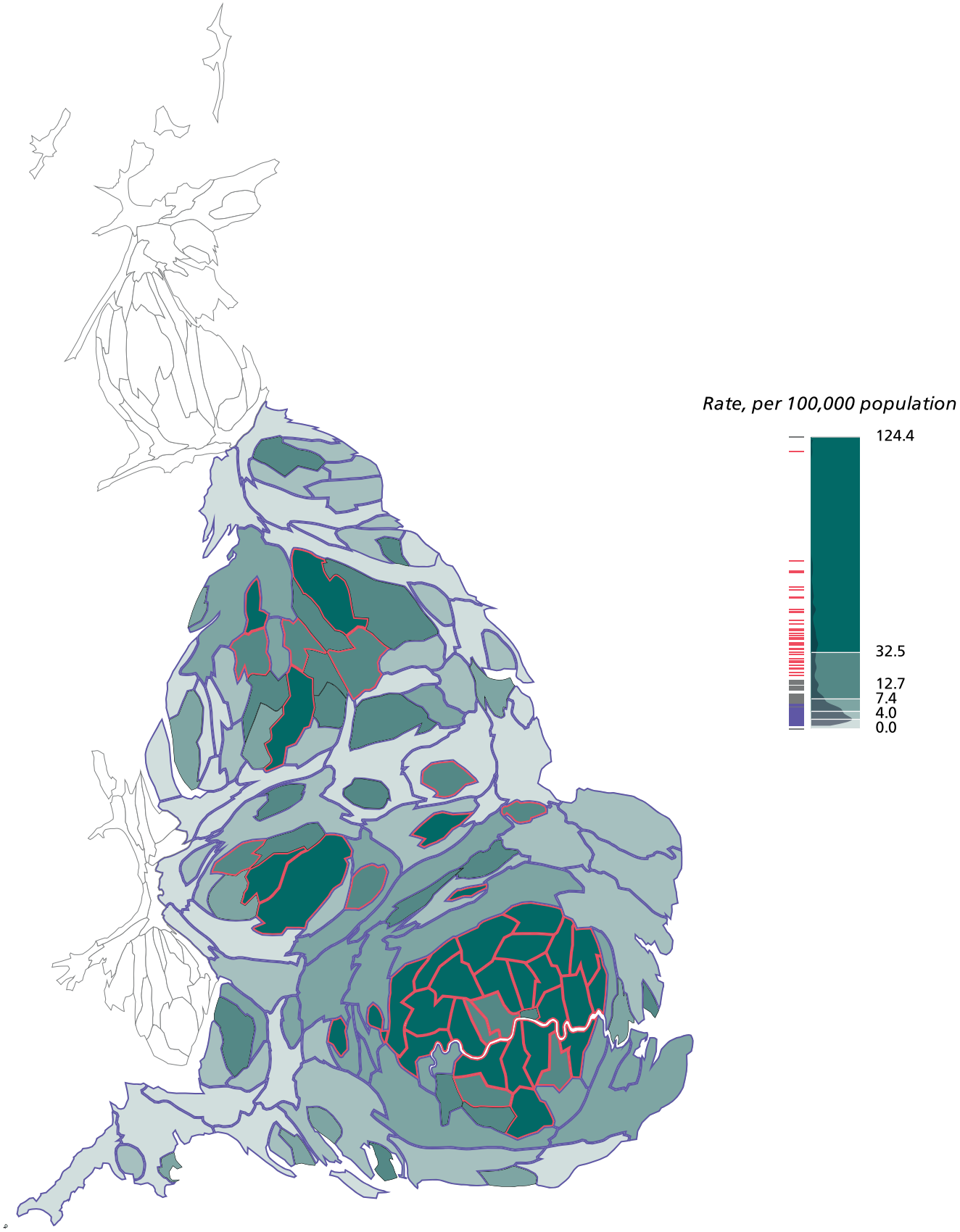
In this chapter we use four examples – tuberculosis, influenza, immunisation and sexually transmitted infections – to illustrate the relationship between health inequalities and infection.

Figure 3.1 Number of tuberculosis case reports by deprivation, United Kingdom, 2001-2011



Source: Enhanced Tuberculosis Surveillance, HPA.

Figure 3.2 Average annual tuberculosis case rate by upper tier local authority, England, 2008-10



Source: Enhanced Tuberculosis Surveillance, HPA. 2008-09 population estimates, ONS. (Analysis by HPA)

Tuberculosis and health inequalities

Tuberculosis was a major cause of morbidity and mortality in the UK throughout the 18th and 19th centuries. Levels declined, however, during the 20th century, reaching a nadir in the late 1980s. Since then, the incidence of tuberculosis in the UK has consistently increased, with considerable inequalities in the geographical and socio-economic distribution of cases. The rise in UK cases of tuberculosis has predominantly affected deprived groups, especially those with social risk factors such as homelessness, a history of imprisonment or migration from high-burden countries.

Between 2000 and 2011, over 86,000 individuals were diagnosed with tuberculosis in the UK. Figure 3.1 shows that more than 70% of cases were diagnosed in the most deprived 40% of the UK population. Not only do deprived groups have higher rates of tuberculosis; there is also evidence of a significant association between levels of deprivation and diagnostic delays, often due to problems among these groups in engaging with healthcare, increasing the probability of transmission.[20]

The geographical distribution of cases also starkly illustrates the inequalities in the populations affected by tuberculosis (see Figure 3.2). Urban areas with high levels of socio-economic deprivation and ethnic minority populations, often associated with a high population density and poor-quality housing, have high rates of tuberculosis.

Most cases are diagnosed in individuals with risk factors for tuberculosis, such as being non-UK born, with the highest burden in the most deprived migrant groups. Among cases with a known place of birth reported in 2011, 74% were born outside the UK, with the majority of these individuals originating from South Asia (59%) and sub-Saharan Africa (24%).

Other socio-economically deprived groups, such as those with a history of drug use, homelessness and/or a history of imprisonment, also have a higher risk of tuberculosis. Between 2009 and 2011, about 10% of tuberculosis cases in the UK had at least one such risk factor. The importance of these risk groups lies in the fact that they have the highest risk of transmission in the UK,[21] the highest risk of acquiring drug resistance strains and are least likely to complete treatment.[22]

The successful control of tuberculosis in our major cities depends on our ability to target interventions at these deprived groups. The Find and Treat Service in London (shown to be cost-effective in identifying and ensuring the management of tuberculosis in deprived urban groups with social risk factors for tuberculosis)[23] needs to be continued, alongside national implementation of National Institute for Health and Clinical Excellence (NICE) guidelines[24, 25] and successful delivery of the recently announced pre-entry tuberculosis-screening programme.[26]

Influenza and health inequalities

There are both theoretical reasons and growing empirical evidence for a substantially higher burden of ill health due to influenza among socially disadvantaged groups. A better understanding of the causes of these differences is needed to help direct more effective approaches to planning control and prevention, and reducing health inequalities.

Some groups of the population may be at increased risk of exposure to influenza and other respiratory viral infections – notably children, parents caring for children, teachers and healthcare workers. Overcrowding is likely to be associated with increased risk of exposure to influenza infection, and the prevalence of overcrowding in the home increases with decreasing socio-economic status. One study conducted in London during the 2009 influenza pandemic indicated that, although influenza was initially concentrated in affluent areas following introduction through transmission in private secondary schools, subsequent transmission was more intense in the most deprived areas.[27]

Once exposed to infection, there may be differences in the population in terms of the risk of becoming infected. The most important influence on this is whether or not an individual has been recently immunised against influenza, and with a vaccine that provides effective protection. A recent UK study[28] demonstrated that males, patients from deprived areas and those from areas with a higher proportion of non-white residents had lower flu vaccination rates overall. In another study,[29] higher rates of vaccination were found among older people, those who were married and those who made greater use of hospital and community services. Homeless adults are also at greater risk of other vaccine-preventable respiratory infections.[30]

Only a proportion of those infected with influenza virus develop a clinical illness. However, the severity of that illness, and the likelihood of complications, is related to a number of factors in the individual – including age, smoking history and the presence of underlying chronic health problems (the prevalence of which increases with decreasing socio-economic status, as does smoking). Canadian and British studies have shown increased likelihood of adverse morbidity (hospitalisation) and mortality in the 2009 pandemic associated with deprivation and minority ethnic group status, respectively.[31, 32]

In another study of the 2009 influenza pandemic in England, people in the most deprived fifth of the population were three times more likely to die from pandemic influenza than those in the least deprived fifth of the population,[33] leading the authors to conclude that socio-economic disparities should be considered in future pandemic influenza planning in order to try and narrow inequalities in health outcomes. This recommendation has recently been echoed by researchers from the United States.[34]

Immunisation and health inequalities

Vaccination programmes have been shown to reduce health inequality worldwide.[35] However, differences in vaccine uptake persist in England and are associated with a range of social, demographic, maternal- and infant-related factors.[36]

The 2009 NICE guidance[37] on reducing the differences in immunisation uptake identified a number of groups at increased risk of not completing routine immunisations in England and Wales. These included: those who have missed previous vaccinations;[38] looked-after children; those with physical or learning disabilities; children of teenage or lone parents; younger children from large families; and those from some minority ethnic groups or non-English-speaking families. Findings from the UK Millennium Cohort Study indicated that mothers of unimmunised infants differ in terms of age and education from those of partially immunised infants.[39] Different strategies may be required to increase full vaccination coverage in these different groups.

Factors influencing vaccine uptake have changed over time.[39] Prior to 1998, lower MMR uptake was associated with single parenthood, area deprivation, high birth order and large family size.[40] Since 1998, however, there is some evidence that uptake of MMR has declined at a greater rate among children of more highly educated parents and among those living in more affluent areas,[41] in response to unfounded concerns over safety. Nevertheless, this faster decline has not been sufficient to eliminate the unequal social distribution of uptake.[40]

Underserved minorities have repeatedly been involved in vaccine-preventable disease outbreaks within the UK and across Europe. While many of these groups are culturally closed communities (e.g. Orthodox Jews,[42, 43] Roma[44, 45]), they are not a homogenous group.[46] As an example, a measles outbreak in 2007[47] was thought to have been associated with a gathering of Irish Travellers in south-east London and was subsequently linked to a measles outbreak in Norway,[48] the Norwegian authorities reported that the Traveller community responded favourably to interventions, with many non-vaccinated contacts being given MMR vaccine.[48]

The importance of three factors (recognising differences between population groups, realising that different approaches are needed to meet the needs of different groups, and targeting the groups with more barriers to vaccination) has been urged previously.[39, 49] The report Fair Society, Healthy Lives,[50] led by Sir Michael Marmot, advocates 'proportionate universalism' – to reduce the steepness of the social gradient in health, actions must be universal, but with a scale and intensity that is proportionate to the level of disadvantage. Indiscriminate population-based interventions that aim to improve overall uptake of vaccination are unlikely to reduce social inequalities in uptake,[51] and specific approaches to improve coverage in hard-to-reach groups should remain a priority in the NHS.

Sexually transmitted infections and health inequalities

Sexually transmitted infections (STIs) are a major cause of ill health globally and can lead to longer-term morbidity, including pelvic inflammatory disease, ectopic pregnancy, tubal infertility and neonatal disease.[52] The most common STIs in the UK are genital chlamydial infection, genital warts, gonorrhoea, genital herpes and syphilis.[53]

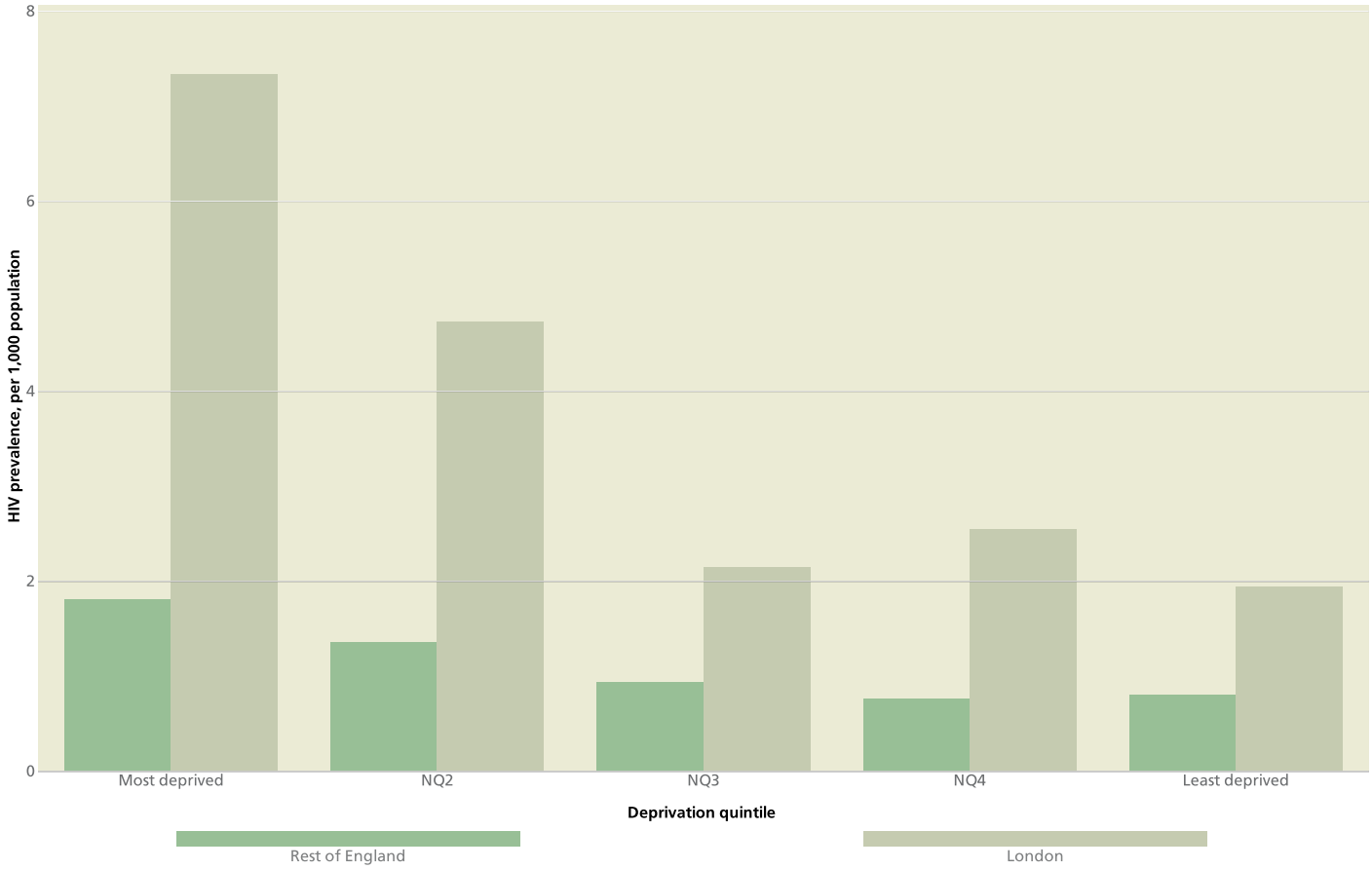
In the UK, STIs disproportionately affect young adults, black ethnic minorities (especially black Caribbeans) and men who have sex with men (MSM).[54, 55, 56] These groups are concentrated in urban areas and for many groups deprived urban areas, particularly London. Disparities in STI rates across ethnic groups are particularly acute for gonococcal infection, where rates are six times higher in black population groups than in white population groups.[53] The inequitable distribution of STIs across the population is probably driven by a complex interplay of health-service provision and access, educational levels, health awareness, healthcare-seeking behaviour and sexual behaviour.[57, 58, 59] Those living in deprived areas are also more likely to become reinfected with an STI, which may fuel a vicious cycle of increased health-service workload, delayed service access and treatment, and infection persistence.[60, 61]

HIV is an infection that disproportionately affects two key populations: black Africans and MSM. In 2010, 32% of the estimated 86,100 people living with HIV in England were African-born heterosexuals and 44% were MSM. HIV prevalence was approximately 30 times higher for these groups than for the English general population. Black Africans are more likely to be diagnosed at a late stage of infection (66%) than MSM (39%). Many factors contribute to this disparity, including acquiring the infection abroad[62] and HIV-related stigma and discrimination.[63]

The most deprived areas in England also have the highest HIV prevalence; this is particularly evident in London, where diagnosed HIV prevalence ranges from 7.3 per 1,000 in the most deprived areas to 1.9 per 1,000 in the least deprived areas (see Figures 3.3 and 3.4). Living with HIV can be associated with an individual's ability to work, financial difficulties[64] and social challenges such as immigration status.[65]

In terms of reducing health inequalities, improving STI screening coverage among high-risk populations and ensuring sufficient capacity for prompt access to sexual health services are vital for infection control.[66] In England, the National Chlamydia Screening Programme (NCSP) offers opportunistic chlamydia testing to all young adults aged 15–24 through local community-based settings, including GPs, pharmacies, outreach and remote testing, and has successfully reached more deprived populations.[67, 68, 69] Specific guidance has been published for increasing HIV testing among MSM and black Africans, as well as to normalise testing (and hence reduce stigma) in primary and secondary care services in high-prevalence areas.[70, 71, 72, 73, 74, 75]

Figure 3.3 Diagnosed HIV prevalence in persons aged 15 to 59 years by deprivation, England, 2010



Source: The Survey of Prevalent HIV Infections Diagnosed (SOPHID), HPA and Health Protection Scotland and Paediatric data complied at University College London, Institute of Child Health. 2010 population estimates, ONS. Note: data has been adjusted for missing exposure group information.

Opportunities

Social determinants clearly have an important influence on the burden of infectious disease. Any action to reduce the impact of infectious diseases needs to be placed in the context of wider activity to reduce health inequalities. Following from this, a priority for reducing infectious diseases is implementation of the cross-government recommendations from *Fair Society, Healthy Lives*,[50] namely to:

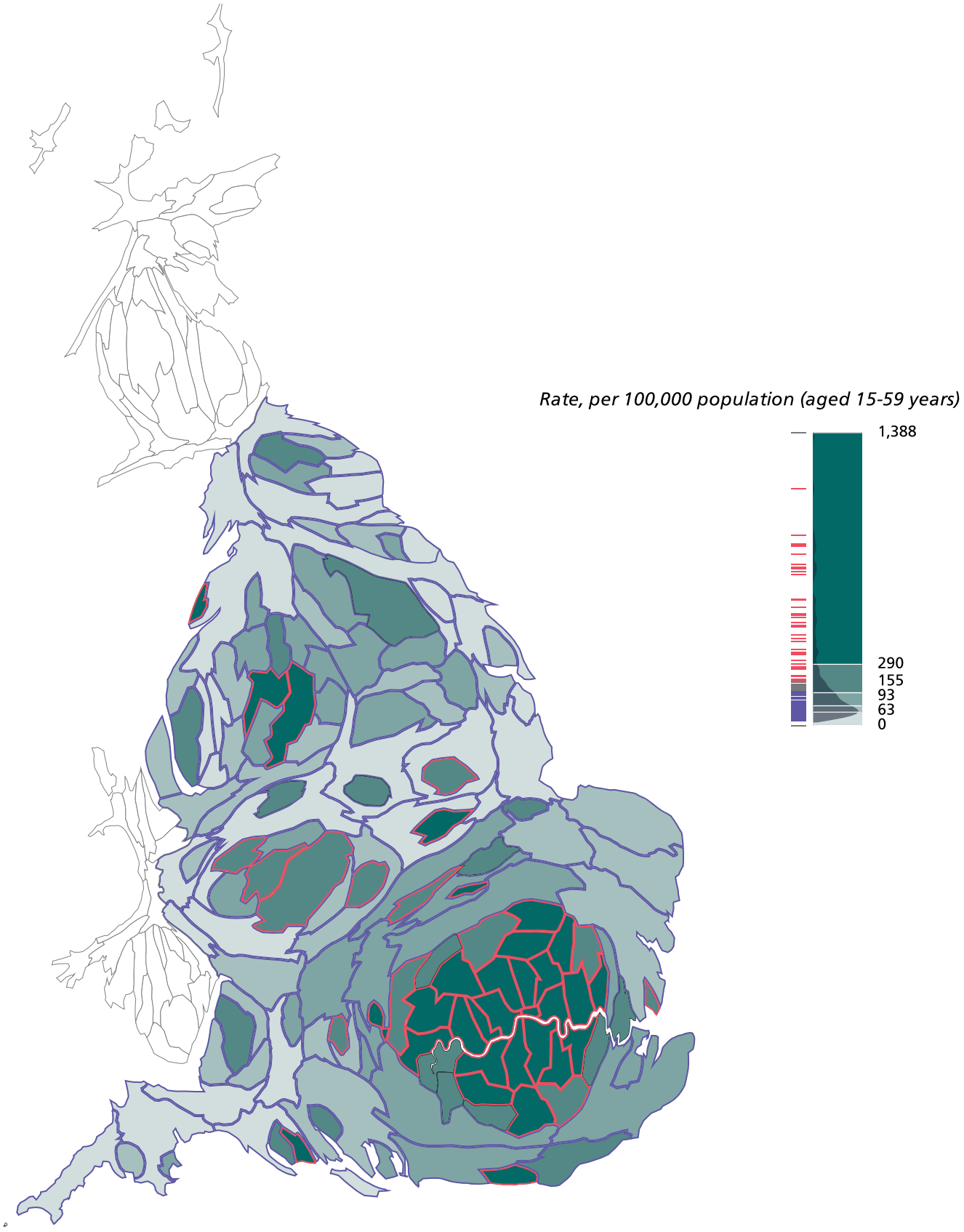
- Give every child the best start in life
- Enable all children, young people and adults to maximise their capabilities and have control over their lives
- Create fair employment and good work for all
- Ensure a healthy standard of living for all
- Create and develop healthy and sustainable places and communities
- Strengthen the role and impact of ill-health prevention.

A major lever to achieve this will be for the Directors of Public Health (DPH) of Local Authorities, and their teams, in the new public health system to embed local reduction of inequalities. The DPH will be well positioned in the council architecture to ensure that health inequalities remain at the top of the agenda, using the important vehicles of the Joint Strategic Needs Assessment (JSNA) and the new Health and Wellbeing Boards. It is important that within these forums there is explicit recognition of health inequalities in infectious diseases, as well as other health and wellbeing issues. The DPH and local authorities should be charged with reducing health inequalities, and monitored against their progress.

Both Public Health England and the NHS should also play central roles in the reduction of health inequalities. Public Health England will be key, and should be tasked with marshalling evidence and guidance around reducing health inequalities, supporting local action, and evaluating the effectiveness of local health-inequality reduction plans. The inequalities in infectious diseases highlighted in this chapter provide a starting point. The new NHS commissioning organisations (NHS Commissioning Board and Clinical Commissioning Groups), as well as Acute Trusts, should be required to develop health-inequality reduction plans and should be evaluated against their delivery.

There is a need to inform the evidence base around what works to reduce inequalities in health protection. New research calls addressing interventions in health protection should include the requirement for researchers to assess or demonstrate reductions in health inequalities.

Figure 3.4 Diagnosed HIV prevalence in persons aged 15 to 59 years by upper tier local authority, England, 2010



Source: Survey of Prevalent HIV Infections Diagnosed (SOPHID), HPA. 2010 population estimates, ONS. (Analysis by HPA)

Conclusions

Action on health inequalities, including those seen for infectious diseases, requires action across all the social determinants of health and throughout the life course.[76] In 2010, *Fair Society, Healthy Lives* [50] confirmed that health inequalities in England continued to be a problem and made recommendations to address the social determinants of health in order to reduce these inequalities. The examples of infectious diseases presented in this chapter illustrate that health inequalities persist in these areas of health protection, and that much remains to be done to create a fairer society.

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Chapter 4

Healthcare-associated infections

Chapter authors
David Wyllie[1], Lily O'Connor[2,3], Sarah Walker[2,3], Jim Davies[3], Elizabeth Sheridan[1], Susan Hopkins[1,4], Tim Peto[2,3], Derrick Crook[2,3]

1 Public Health England
2 Oxford University Hospitals NHS Trust
3 University of Oxford
4 Royal Free London NHS Foundation Trust

Overview

Healthcare is a risk factor for severe infection such as bacteraemia.[1] Healthcare-associated infection (HCAI) affected over 300,000 patients in England in 2007; *Staphylococcus aureus* or *C. difficile* infections alone were recorded as causing 9,000 deaths.[2] The cost to the NHS is in excess of £1 billion each year.[2] There have been many attempts to reduce the risk of infection, and some significant progress has been made. Much more, however, remains to be done.

There are two distinct modes of developing infection:

- **Transmission-dependent infections** (such as person to person, exposure to contaminated environments/equipment/devices) involve the acquisition of the pathogen from healthcare, principally in hospitals. This is illustrated by the work of Semmelweis concerning the acquisition of group A streptococcus,[3] and the recent media attention upon *C. difficile*[4, 5] and meticillin-resistant *Staphylococcus aureus* (MRSA).[5, 6] The approach to prevention involves both the interruption of spread and acquisition and the adoption of protective measures such as vaccination (e.g. for hepatitis B virus[7]) and antimicrobial prophylaxis (e.g. for post-exposure HIV[8]).
- **Infections arising from the patient's own microbial flora** take advantage of opportunities created by healthcare procedures. Examples include early infection following surgery, and infection following the insertion of an intravascular catheter. The most prominent pathogen causing such infections is *S. aureus*.[9, 10] Approaches to prevention are focused upon interrupting the progression from harmless colonisation to infection: for example, through decontamination of the skin before surgery,[11] prophylactic antibiotics prior to skin incision,[12] or careful insertion and aftercare for placement of devices such as intravascular catheters.[13, 14]

Some pathogens can play a role in either of these settings. *S. aureus,* which causes infection after surgery, can also spread epidemically from patient to patient or even from staff to patients.[5, 6]

Key challenges

Key challenges in preventing HCAIs apply to both routes of transmission and can be considered in terms of the host (the patient), their environment and the pathogens.

The host

There are many factors intrinsic to the host that increase vulnerability to HCAIs. Some of these factors are becoming more prevalent due to changing demography, success of medicine in prolonging life, and substantial lifestyle changes.

Extremes of age are becoming more pronounced, both with the survival of pre-term neonates, some as young as 24 weeks at birth, and with a larger proportion of people surviving to old age – sometimes with multiple and severe co-morbidities. This changing demography is enlarging the population that is at higher risk of infection and particularly HCAI. Lifestyle-related health risks, some of which are becoming more prevalent, are also associated with the risk of developing HCAIs such as surgical-site infection. These life style risks include smoking, excessive consumption of alcohol, and obesity.[15]

Increasing numbers of patients have risk factors acquired by the host as a consequence of healthcare: for example, drug treatments which suppress the immune system and prosthetic/medical devices which provide a potential locus for infection.

Environment (including building and staff working arrangements)

The design, construction and maintenance of healthcare facilities have a substantial bearing on the risk of developing HCAI.[16] Overcrowding, design that limits cleaning, poor ventilation (particularly in operating theatres) and poor water-supply management (risk of *Legionella* species and *Pseudomonas aeruginosa*) all play a role in contributing to the risk of HCAI and are domains referred to under the Health and Social Care Act 2008: Code of Practice for health and adult social care on the prevention and control of infections and related guidance.[17] This is particularly a consideration for older hospital facilities and may be an increasing factor with the growing proportion of people cared for in community settings where the construction of facilities may be less formally regulated.

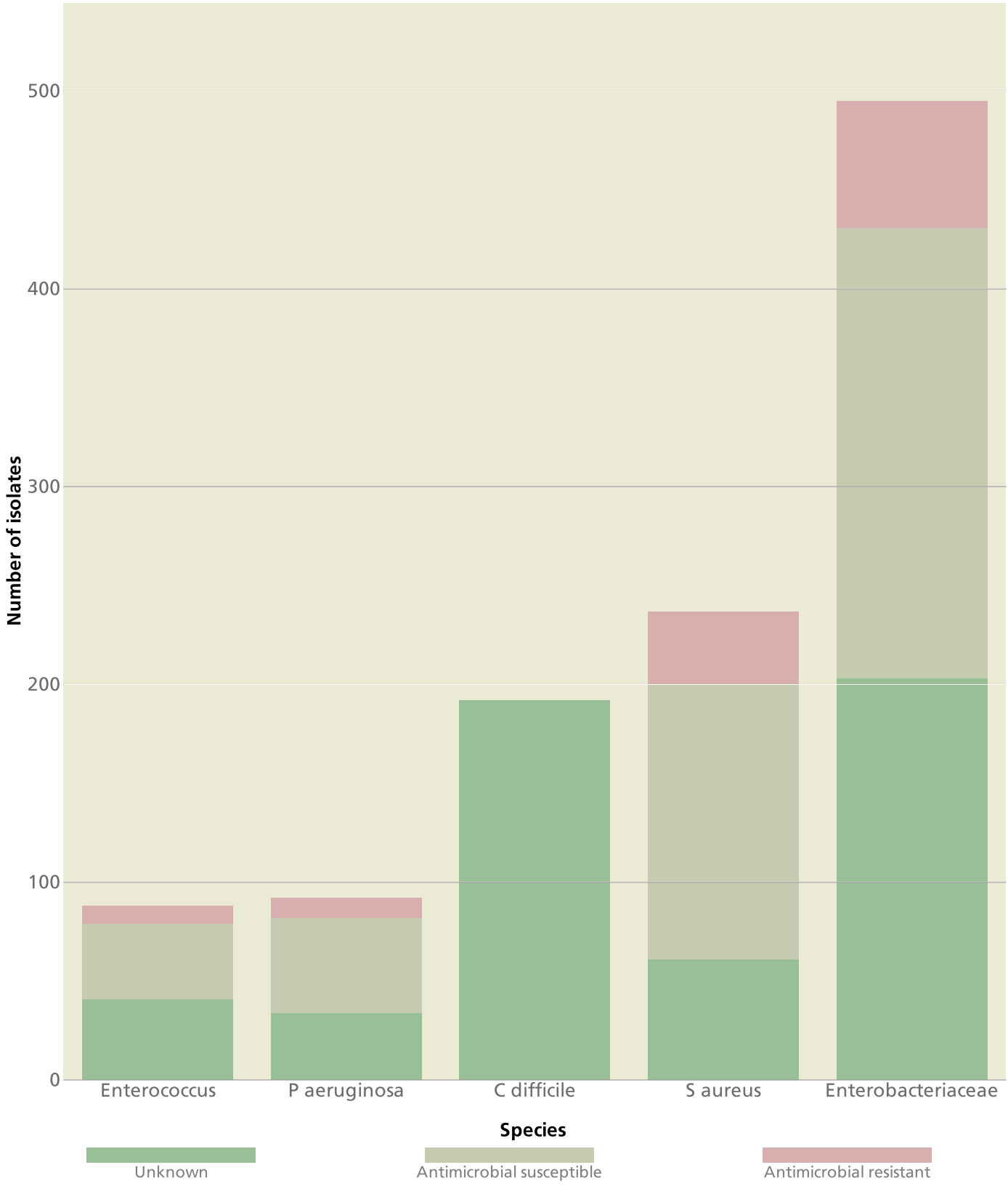
The staff providing healthcare play a major contributory role in exposing patients to the risk of developing infection. The staff's attention to optimal hygiene practices, known to reduce infection risk, is crucial to sustaining a safe environment. **Hand hygiene in general, and particularly no-touch or aseptic techniques when handling vascular catheters[11] and urinary catheters respectively, is important in reducing infection risk**. It is important that these good practices are adopted by the community-based workforce which is increasingly delivering care in out-of-hospital settings.

Pathogens

The major pathogens encountered in the latest cross-sectional study of HCAI in England for 2011/12 from patients with bacteraemia[18] are listed in Figure 4.1. Other pathogens reported as causing substantial epidemics or outbreaks of HCAI not highlighted by the survey are: norovirus, Acinetobacter species, *Klebsiella* species, respiratory syncytial virus (paediatric units), enterovirus (neonatal intensive care), group A streptococcus, *Legionella* species, *Aspergillus* species (building works and transplant patients) and *Nocardia* (transplant patients). A wide range of other pathogens can very rarely be implicated in HCAI.

One significant issue is the proportion of pathogens that are resistant to first-line antimicrobial treatments. This represents a particular challenge to reducing the burden of HCAIs.

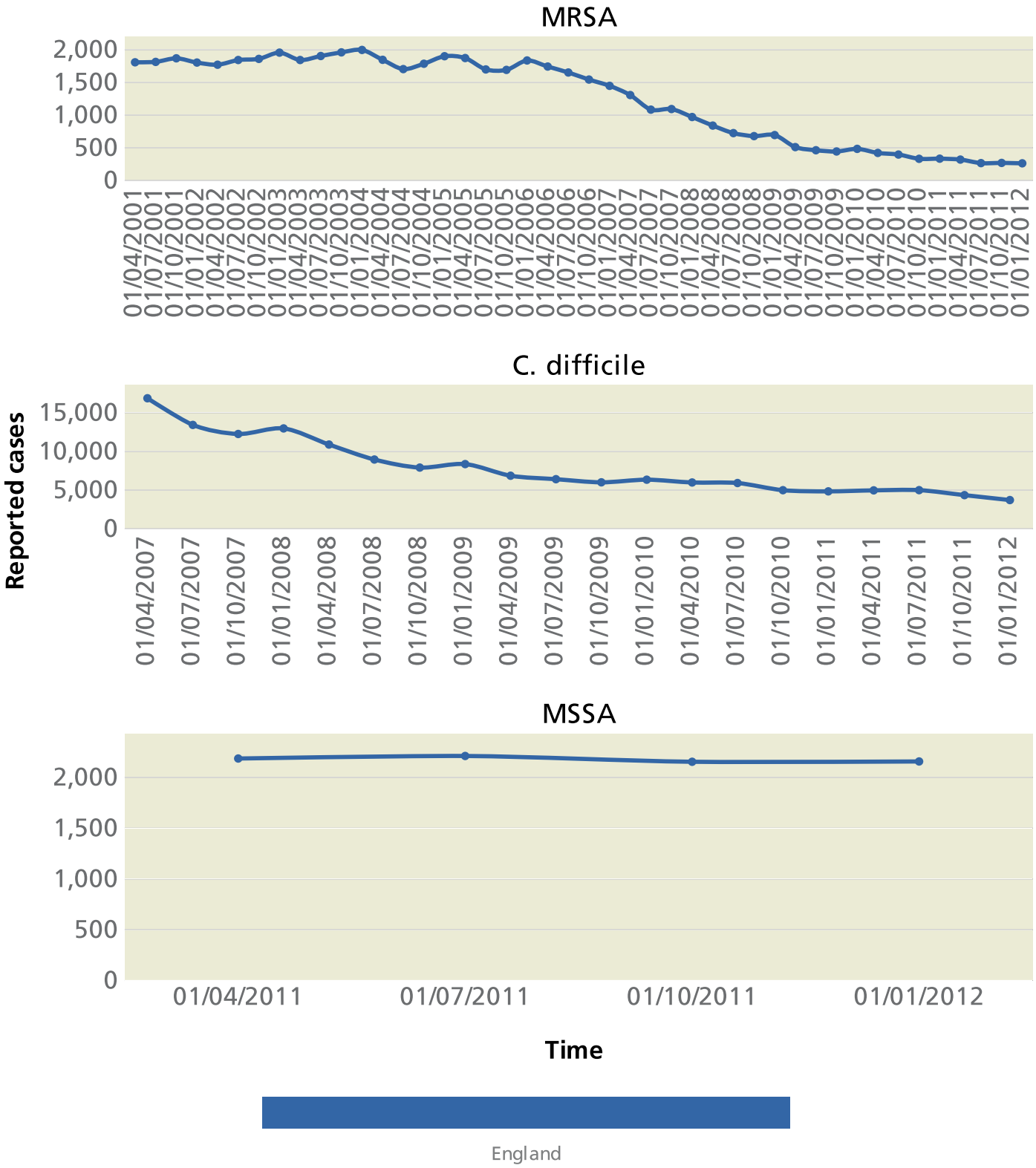
Figure 4.1: Leading pathogens in hospital patients by antimicrobial resistance, England, 2011



Source: English National Point Prevalence Survey on Healthcare Associated Infections and Antimicrobial Use, 2011: Health Protection Agency, England; 2012. (Dr Susan Hopkins, personal communication)

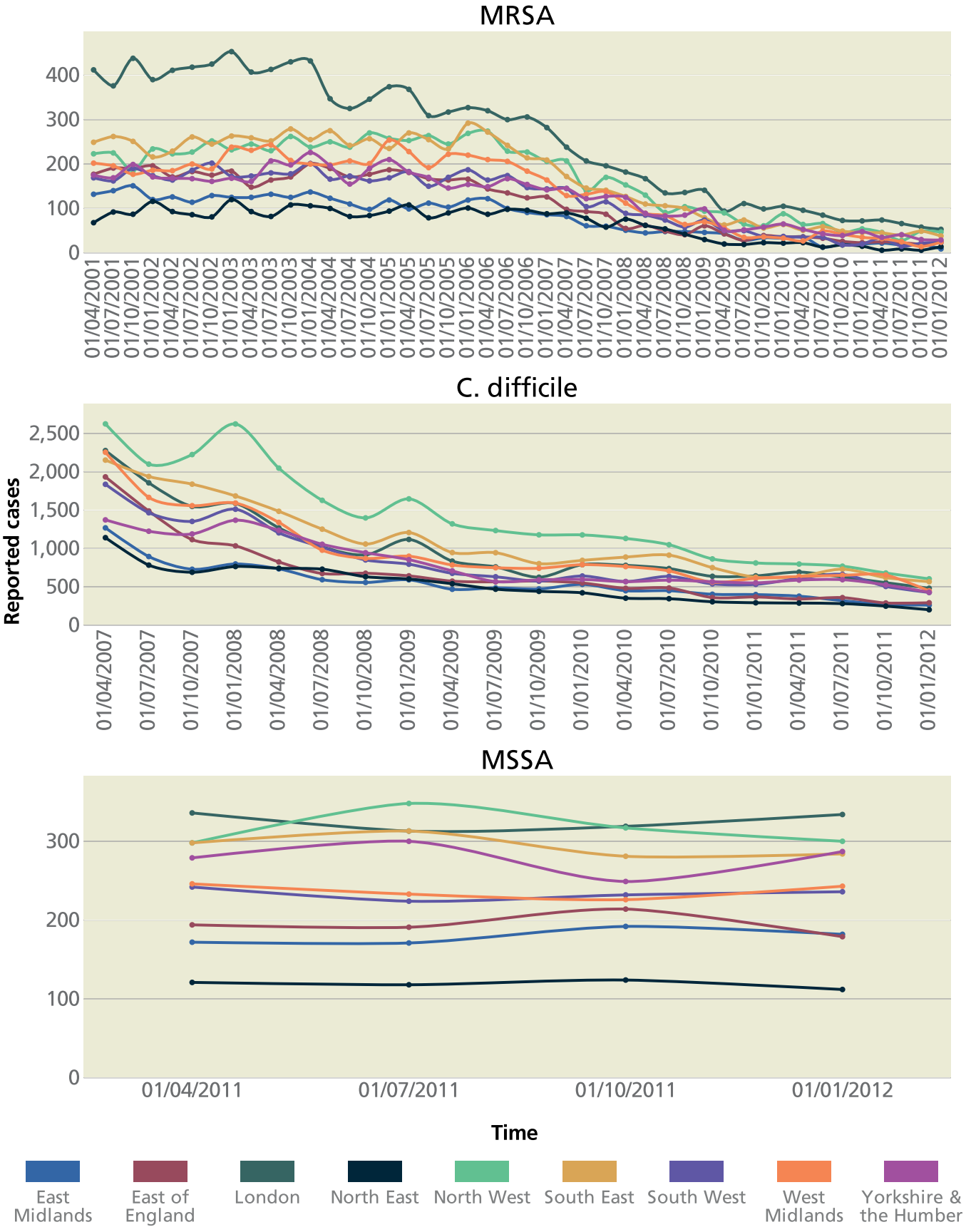
Depicted are the five leading pathogen categories identified among the 52,443 patients surveyed in 2011. Of the 1,526 pathogens identified, these five groups accounted for 1,104 (72%). In total 52,443 patients were surveyed of which 3,509 (6.7%) were diagnosed with HCAI. In the case of S. aureus, resistant refers to MRSA; for Enterobacteriaceae (mostly Escherichia coli) resistant refers to those encoding extended spectrum β-lactamases. Susceptibility testing is not undertaken for C. difficile as a routine.

Figure 4.2: National decline in reported cases of C.difficile and meticillin-resistant and sensitive Staphylococcus aureus (MRSA & MSSA), England, 2001 to 2011



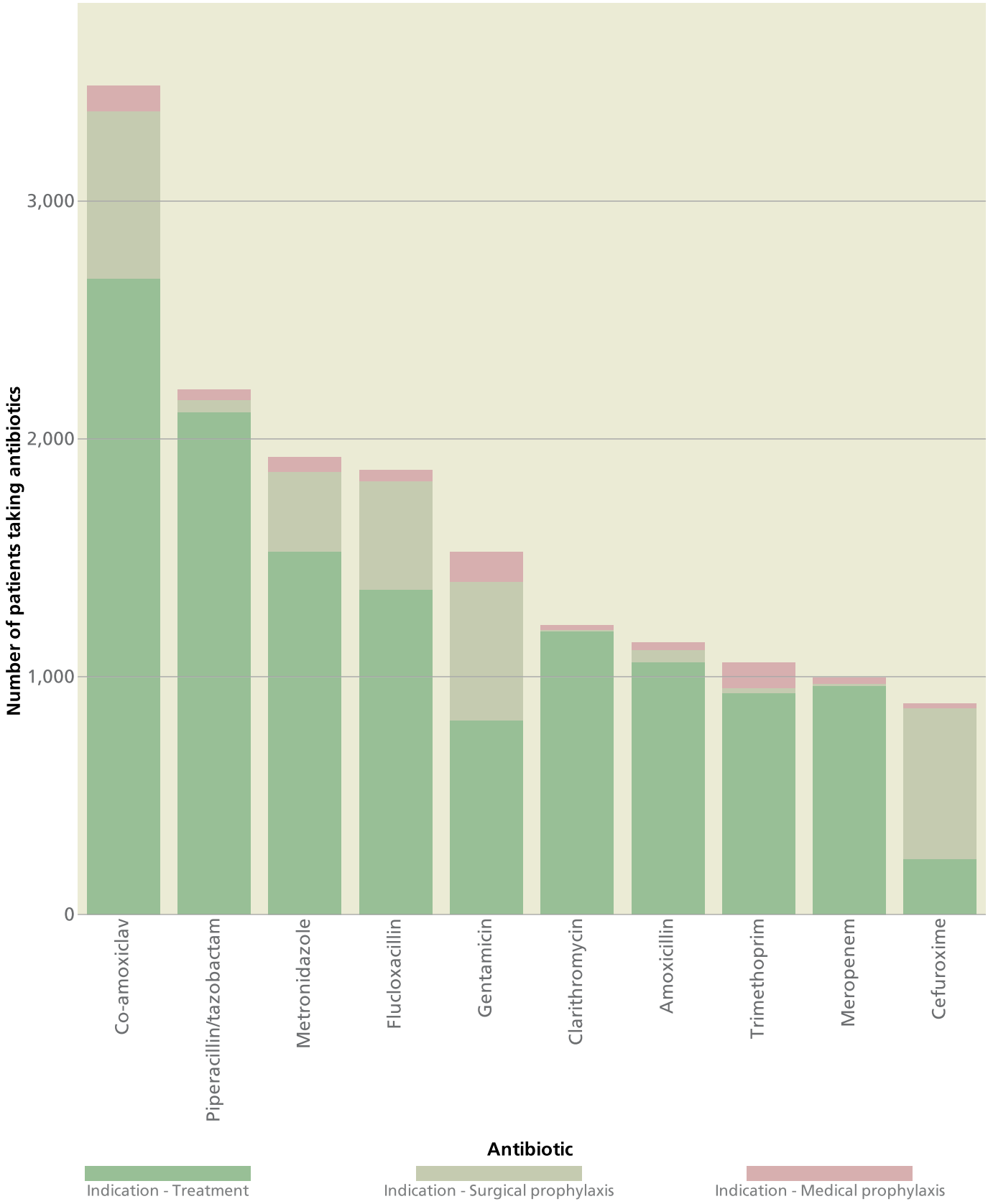
Source: Mandatory Surveillance Data, HPA. - Depicted is monitoring by manually collected mandatory reporting. C. difficile and MSSA mandatory reporting started in 2007 and 2011 respectively. TThe decline in reports for both C.difficile and MRSA from the mid-2000s shows a reduction in numbers to approximately 10% of their peak levels across England.

Figure 4.3: Regional decline in reported cases of C.difficile and meticillin-resistant and sensitive Staphylococcus aureus (MRSA & MSSA), England, 2001 to 2011



Source: Mandatory Surveillance Data, HPA. - Depicted is monitoring by manually collected mandatory reporting. C. difficile and MSSA mandatory reporting started in 2007 and 2011 respectively. The decline in reports for both C.difficile and MRSA from the mid-2000s shows a reduction in numbers to approximately 10% of their peak levels across England.

Figure 4.4: Antibiotic use in hospital inpatients, England, 2011



Source: HPA. English National Point Prevalence Survey on Healthcare Associated Infections and Antimicrobial Use, 2011: Health Protection Agency, England; 2012. (Dr Susan Hopkins, personal communication). NB: The lesser relative use of meropenem vs. piperacillin-tazobactam than apparent in Figure 5.4 of this report reflects the different denominators, common use of 3g meropenem per day, vs. 2g as the DDD, and, possibly, shorter treatment durations.

Prevalence and current trends

Prevalence of HCAI in England has been measured by national cross-sectional studies. There has been a major decline in HCAI, from 9.2% of patients in 1980 to 6.7% in 2011. This has been driven, in part, by substantial declines in both MRSA bloodstream infection and *C. difficile* infection in all parts of England in the last five years, as documented by mandatory surveillance (see Figures 4.2 and 4.3). Our understanding of what led to the epidemic rise and then fall in infections caused by these two organisms is incomplete. However, major changes in the type of antimicrobial exposure of hospitalised patients have occurred over the past seven years. Before 2006, quinolones and cephalosporins were leading antibiotics prescribed to hospital patients. The latest cross-sectional survey[18] demonstrates that quinolone use has nearly been discontinued, while cephalosporins are used in a minority of hospitalised patients . A recent study of MRSA at St George's Hospital, London suggests that antibiotic selection, particularly due to use of quinolones (ciprofloxacin), may have led to the epidemic rise of MRSA. The subsequent decline in MRSA being associated with reduced use of quinolones.[19]

Currently, for high-quality national surveillance, data collection and analysis is dependent on manual collection and is therefore restricted to a limited number of organisms. At a local level, it can be shown that integration between different hospital data sources can yield enhanced information for surveillance of a wide range of threats.

The work undertaken in Oxford hospitals provides an example of the effectiveness of local analysis of data from integrated information systems linking haematology and biochemistry. The hospitals monitored the rise and fall of *C. difficile* infection[20] and MRSA[21, 22] over a 12-year period (1998 to 2010), using automated systems that were free of biases arising from passive reporting. This approach also provided clear evidence of a near-50% decline in HCAI non-MRSA *S. aureus* (MSSA). This decline coincided with and may be due to the programmes to reduce line-associated bacteraemia analogous to Matching Michigan,[14] which was incrementally implemented in the Oxford hospitals from 2004.

The integrated-data approach used in Oxford hospitals also enabled the monitoring of pathogen severity. This represents one approach to early detection of virulent pathogens[20] which can require a concerted local public health and clinical response. The potential of this kind of approach is described in the section 'Opportunities to improve response to challenges', later in this chapter.

Examples of good practice

There have been several notable successes in the control of HCAI:

- **Central line care** This has improved dramatically over the past five years in both intensive-care units and renal dialysis units. The Matching Michigan programme was implemented in 2009 to enhance central venous line management in intensive-care units across England. This programme has demonstrated a highly significant reduction in line-associated infection among adult intensive-care units over 20 months of observation, from 3.7 to 1.48 central venous catheter-bloodstream infections per 1,000 central venous catheter-patient days ($p < 0.0001$) – a 50% reduction.[14]
- **Consistent, end-to-end good practice to reduce viral transmission** Near elimination of blood-borne virus acquisition from hospitals and blood transfusion has been achieved over the past 40 years[23, 24] through improvements in measures to prevent the spread of blood-borne viruses. These include testing of blood for transfusing and other blood safety measures, segregation of affected cases from unaffected cases, and comprehensive vaccination for hepatitis B virus.[25]
- **Antimicrobial control** Massive reduction in quinolone and cephalosporin use has been achieved over the past five years.[18] This was instigated by the Department of Health and was implemented by Hospital Trusts nationally. The change may have played a major role in the very substantial reductions in MRSA bacteraemia and *C. difficile* infection that have occurred over the same period.

Opportunities to improve response to challenges

There are key areas for further action in the future, in addition to continuing the good practice detailed in the previous section.

Better management of processes, such as standardisation of the surgical pathway to ensure that evidence-based practice is followed, could yield a reduction in wound infections. Arguably, the most likely way to achieve this would be to use approaches similar to those target-based approaches that have successfully reduced *C. difficile* and MRSA. This requires a firmly process-managed approach to the surgical pathway that ensures adherence to a well-established evidence base for each step.

Similarly, procedures for safely minimising antibiotic usage (as a different and additional approach to antibiotic stewardship) could plausibly lead to substantial reductions in antibiotic use in practice. Measures for improving infection control in the use of all intravascular devices (not just central lines) and urinary catheter management, as implemented in the Matching Michigan programme, should achieve a substantial reduction in line-associated bacteraemia and urosepsis.

Better use of emerging technologies could drive early, proportionate targeting of threats. Integration of healthcare data from all sources (NHS and other healthcare providers) for near real-time detection of infection events, and implementation of systematic surveillance of key HCAIs (such as intravascular device-associated infections, surgical-

site infections and individual patient antibiotic usage) would create the framework for developing process control points for key outcomes or thresholds for activities (e.g. antibiotic usage). **These data sources could be linked to new pathogen genomics data to unambiguously identify pathogen transmission locally,[5, 6] as recently shown for *C. difficile* infection.[4, 5]** This would underpin more informative regional and national surveillance. **Availability and analysis of individual patient prescribing data would open the way to data-driven improvements in antibiotic prescribing.** A national mandate to implement electronic prescribing to better monitor usage, with reported targets for usage, would be the most effective approach to driving this forward.

As opportunities for new linkage of data occur, the skill set required in those undertaking the surveillance function is likely to develop. There will be a need for translation of new computer-science methods for federating and linking healthcare and social services data. This would improve the data quality and quantity over the current models for linkage employed by organisations such as the Health Protection Agency and Dr Foster. Translating the data into meaningful action will call for people to use new database-mining and analytical approaches. **This will require the development, using new mathematical and statistical methods, of threat-detection approaches for these datasets.** These new methods could also be adapted to routine surveillance including all infection events.

In the future, cheaper and faster pathogen sequencing (bacteria and viruses) will replace much of diagnostic microbiology and yield data for tracking pathogens. The genomics data on DNA sequence relatedness will allow assessments of whether disease occurrences are linked, i.e. have the same source, and in some cases the direction in which infection spread. When linked to integrated clinical data this has the potential to provide spatial, temporal and outcome data that will revolutionise detection of transmission events and local, regional and national surveillance for both HCAI and all infection events.

A key feature of HCAI is the emergence of new threats. A recent example is the appearance of hyper-transmissible and virulent *C. difficile* to cause a national epidemic. This phenomenon will recur for other pathogens in unexpected ways, as the processes leading to the emergence of new strains and novel variants are stochastic. The focus is reasonably on influenza A virus, which is likely to be mostly community based rather than HCAI, although this is not the only major threat of an epidemic problem. This phenomenon needs to be incorporated into any surveillance programme and acute response plans must be developed to deal with the unexpected.

Steps must be taken to monitor the changes in HCAI arising from the alteration in balance between care in acute hospital, community hospital, care home and 'hospital at home'. There may be major shifts in where the impact of HCAI is seen and, more importantly, a rising burden of unrecognised HCAI. In many ways, the changing setting for healthcare provision highlights the need for the general public to learn and participate in taking responsibility for their personal hygiene measures. This will be increasingly important in delivering 'hospital at home' and is likely to require a programme to provide training and follow-up to ensure maintenance of adherence to these hygiene measures.

There remains the issue of the ageing hospital estate. Guidance to ensure more uniform standards for the entire built environment, particularly operating theatres and very old wards, is needed to ensure minimum standards. **To effectively reduce the risk of HCAIs there should be an expectation that standards in the existing NHS estate and care homes are similar to those of new build NHS**.

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Chapter 5

Antimicrobial resistance

Chapter authors

Keith W Ridge[1], Kieran Hand[2], Mike Sharland[3], Ibrahim Abubakar[4], David M Livermore[5]

1 Chief Pharmaceutical Officer, Department of Health, London

2 Consultant Pharmacist, Anti Infectives, University Hospital Southampton NHS Foundation Trust

3 Professor of Paediatric Infectious Diseases, Paediatric Infectious Diseases Unit, St George's Healthcare NHS Trust

4 Professor in Infectious Disease Epidemiology, Research Department of Infection and Population Health, University College London and Tuberculosis Section, Respiratory Diseases Department, Health Protection Agency

5 Professor of Medical Microbiology, Norwich Medical School, University of East Anglia, Norwich

Overview

Effective treatment of infection is an essential component of 21st-Century medicine. Modern surgery would be unacceptably dangerous if infections were likely to be untreatable, and cancer chemotherapy and organ transplatation – which suppresses the patient's immune system – would no longer be viable. As a result, microbes would win a major battle in their long fight with humans. This is now a real risk, as bacteria continue to develop resistance while the flow of new antibiotics has diminished.

This chapter examines:

- The nature of the resistance threat
- How to preserve the effectiveness of existing antibiotics
- Steps to ensure sufficient new antimicrobials for future generations.

The nature of resistance

Resistant microorganisms are those that are not inhibited by antibiotics or antimicrobials (these words will be used interchangeably). Infections caused by resistant microorganisms often fail to respond to treatment, extending illness and raising mortality. Resistance has steadily increased since systemic antibiotics were introduced in the 1930s and 1940s. What is new is the breadth of resistance and the dearth of new antibiotics being licensed.

The origins and accumulation of resistance

Resistance arises through mutations – chance errors as DNA is replicated – or via the transfer of DNA among bacteria, often as independent loops of DNA called plasmids. The use of antimicrobials then through natural selection favours resistant organisms, allowing them to proliferate while sensitive ones are killed. Over time, resistant bacteria come to dominate and treatments are lost.

Unlike the initial emergence of resistance, which involves random genetic events, the extent of this antibiotic-driven selection lies within human control for it reflects the extent of antibiotic use, the 'quality' of use, and the effectiveness of infection control. Moreover, advances elsewhere in medicine continue to expand the pool of vulnerable patients – mostly very young or very old – with underlying disease, as well as bringing them together in specialist units or socialised care. Such patients are prone to infection by many 'opportunistic' bacterial species which, although harmless to people in good health, are adept at developing resistance.

In addition, resistance is emerging in classical pathogens, threatening hard-won successes in their control. *Mycobacterium tuberculosis* – which caused many deaths in England in the 18th and 19th centuries – remains a major public health problem across Europe. Worryingly, the continent has a disproportionate burden of strains resistant to two key antibiotics, isoniazid and rifampicin: these are known as known as multi-drug resistant TB (MDR-TB).[1] Even more disturbingly, the Baltic States and parts of Eastern Europe have a major problem with 'extensively drug-resistant tuberculosis' (XDR TB) – i.e. resistant to the fluoroquinolones and at least one of amikacin, kanamycin or capreomycin. Another classical disease with disturbingly increasing resistance is gonorrhoea. Past decades saw the loss of sulphonamides, penicillins and ciprofloxacin as treatments. Cephalosporins are now part of the standard regimen but are being eroded by reductions in susceptibility, with no obvious 'next' drug.[2]

International travel spreads resistant bacteria from regions where they are frequent -particularly newly prosperous countries, where antibiotic use is generally heavy and infection control relatively weak- to the UK. Across Europe, around 25,000 people die each year as a result of hospital infections caused by resistant bacteria, adding €1.5 billion to hospital, treatment and societal costs.[3]

The UK: successes and new challenges

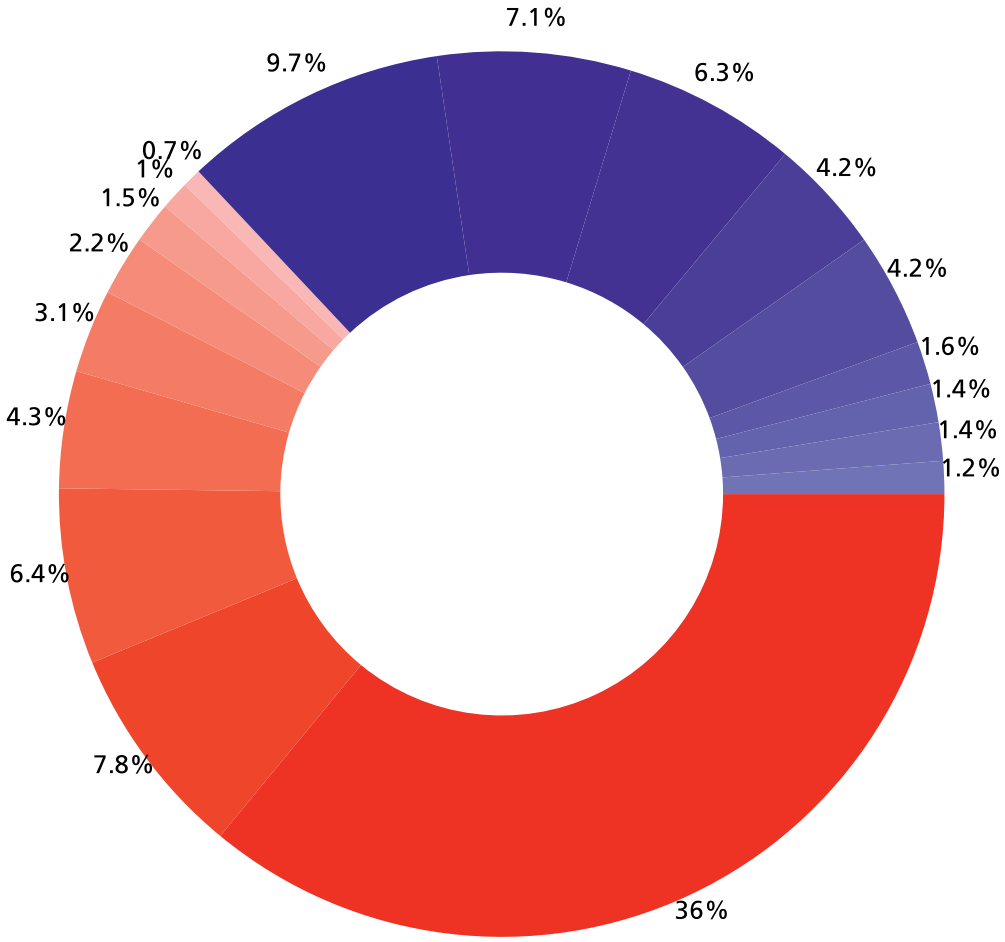
Healthcare-associated infections became headline news in the 1990s, with concern about meticillin-resistant *Staphylococcus aureus* (MRSA) and *C. difficile*. Public and political pressure expedited radical reform, especially in hospital infection control (see Chapter 4). Key changes included mandatory reporting, infection reduction targets and a requirement for the Senior Trust Executive of NHS Trusts to manage, report and audit infection rates. These requirements were underpinned by legislation (Health Act 2006 and Health and Social Care Act 2008) and were implemented in rapid succession. Although the effects of individual policy changes are hard to identify, the collective effect is impressive. In 2011, a total of 1,185 MRSA bacteraemias were reported in England – an 84.7% reduction from the 2003/4 peak of 7,700. For *C. difficile*, case numbers decreased by 53% between 2008 (40,705 reports) and 2011 (19,130 reports).[4]

Another success has been against *Streptococcus pneumoniae*. A 7-valent conjugate vaccine was added to the UK childhood schedule in 2006, and was replaced by a related 13-valent vaccine in 2010. These protect against invasive infection by those pneumococcal serotypes where resistance is most frequent. Very high vaccine uptake has been followed by both a significant reduction in invasive pneumococcal infections and in erythromycin-resistance, which was associated with a vaccine-covered serotype.[5, 6]

Nevertheless, new challenges are emerging, especially with the Gram-negative bacteria Enterobacteriaceae (including *E. coli, Klebsiella* and related species).[7] These are now the most frequent cause of hospital-acquired infection, as shown by the fourth national Health Protection Agency/European

Centre for Disease Control Point Prevalence Survey.[8] In the UK (excluding Scotland) 99,000 cases of bloodstream infection were reported to the Health Protection Agency in the fiscal year 2011/12. *E. coli* alone accounted for around 36% of the bacteraemias reported to the Health Protection Agency, compared with 11% for *Staphylococcus aureus* (of which just 1.6% were due to MRSA), the second commonest (see Figure 5.1). Recent European data[9] suggest a 30% mortality for patients with septicaemia due to multi-resistant *E. coli*, compared with 15% for those with susceptible *E. coli*. Extrapolating these proportions to Health Protection Agency data, with 50,000 bacteraemias per annum due to *E. coli* and other Gram-negative pathogens, a resistance rate of around 15% implies up to 5,000 patients die of Gram-negative sepsis each year, half with a resistant organism. This greatly exceeds current mortality due to MRSA and *C. difficile*.

Figure 5.1: Organisms causing Blood Stream Infections in adults in England, Wales and Northern Ireland, April 2011-March 2012



Gram negative
- Eschericha coli - 36%
- Klebsiella spp. - 7.8%
- Other Gram-negative - 6.4%
- Pseudomonas spp. - 4.3%
- Proteus spp. -3.1%
- Enterobacter spp. - 2.2%
- Bacteroides spp. - 1.5%
- Serratia spp. - 1.0%
- Acinetobacter spp. - 0.7%

Gram positive
- Staphylococcus aureus (MSSA) - 9.7%
- Non-pyogenic streptococci - 7.1%
- Enterococcus spp. - 6.3%
- Streptococcus pneumoniae - 4.2%
- Other Gram-positive - 4.2%
- Staphylococcus aureus (MRSA) - 1.6%
- Group B Streptococci - 1.4%
- Group A Streptococci - 1.4%
- Diptheroids - 1.2%

Source: HPA. English National Point Prevalence Survey on Healthcare Associated Infections and Antimicrobial Use, 2011: Health Protection Agency, England; 2012. Note: excludes 13,206 episodes of bacteraemia with coagulase negative staphylococci.

Critically, multi drug resistance is now accumulating in these Gram-negative species. Europe-wide surveillance from 2005 to 2010 indicates growing resistance to the cephalosporin, fluoroquinolone and aminoglycoside antibiotics among *E. coli* and other Enterobacteriaceae.[10] India and China are more extreme, with 50–80% cephalosporin resistance in *E. coli*.[11] This cephalosporin resistance drives use of carbapenems, which previously were 'reserved' (i.e. only used in the very sick, immune compromised, or as a last resort antibiotic). This, in turn, is selecting for carbapenem-destroying enzymes, called carbapenemases.[12] Very few antibiotics remain active against carbapenemase producers, and those that do have toxicity or limited efficacy.

Almost uniquely in Europe, cephalosporin resistance among *E. coli* and *Klebsiella* species in the UK stabilised or fell slightly from 2008, after a sharp rise from 2003 to 2007 (see 'Outcomes of antimicrobial stewardship'). This may reflect shifts in hospital antibiotic prescribing, based upon concern about *C. difficile*. Whilst this stabilisation is welcome, the proportion of multi-resistant *E. coli* and *Klebsiella* remains around 10–15% in bacteraemia, and since the total number of *E. coli* bacteraemias continues to rise, the overall burden of disease due to AMR remains a major concern.

Worse, growing numbers of carbapenemase producers are referred to the Health Protection Agency (see Figure 5.2). These are diverse, with (i) plasmid-mediated spread of the VIM and KPC enzymes among *Klebsiella* in NW England, (ii) repeated import of NDM enzymes from the Indian sub-continent[13] and (iii) import of OXA-48 from the Middle East, including via conflict casualties. This diversity complicates control and presents a hugely more complex challenge than MRSA, where the issue largely was the spread of two MRSA strains among many hospitals.[14] There are only five new antibiotics in the potential drug pipeline (Phase II or III) that will help to combat multiresistant Gram-negative bacteria, and none of these is a new type or class of antibiotic.[15]

Turning to classical infectious disease, the UK incidence of tuberculosis increased steadily from 1990, with emerging numbers of resistant cases. Isoniazid resistance links to an outbreak centred in London and, more recently, to cases infected abroad. Cases with multi-resistance increased from 30 in 2000 to over 80 in 2011 and, to date, there have been 24 cases with 'extreme' drug resistance. When considering gonorrhoea, isolates with reduced susceptibility to cefixime (which became the standard treatment after the earlier 'loss' of penicillin and ciprofloxacin) have proliferated since 2006. By 2010/11, numerous cefixime treatment failures were reported, driving a treatment switch to high-dose ceftriaxone plus azithromycin.[16] This, however, is just buying time: high-level ceftriaxone resistance has emerged in Japan, France and Spain.

Responses to resistance

There are three key responses to these challenges and all need to be actively pursued:

- Better stewardship of antibiotics
- Development and deployment of rapid diagnostics for infection and resistance
- Re-invigoration of antibiotic development.

Making the most of existing antimicrobials

It is critical that existing antimicrobials are preserved and targeted appropriately. This is achieved through guidance and 'stewardship', as described below. In the future, stewardship may be improved by faster and more precise diagnosis and detection of infections, pathogens and resistances. Such stewardship should be applied across all antimicrobial use, including use in animals. This holistic approach is addressed in UK 2013–2018 antimicrobial resistance strategy, led by the Department of Health.

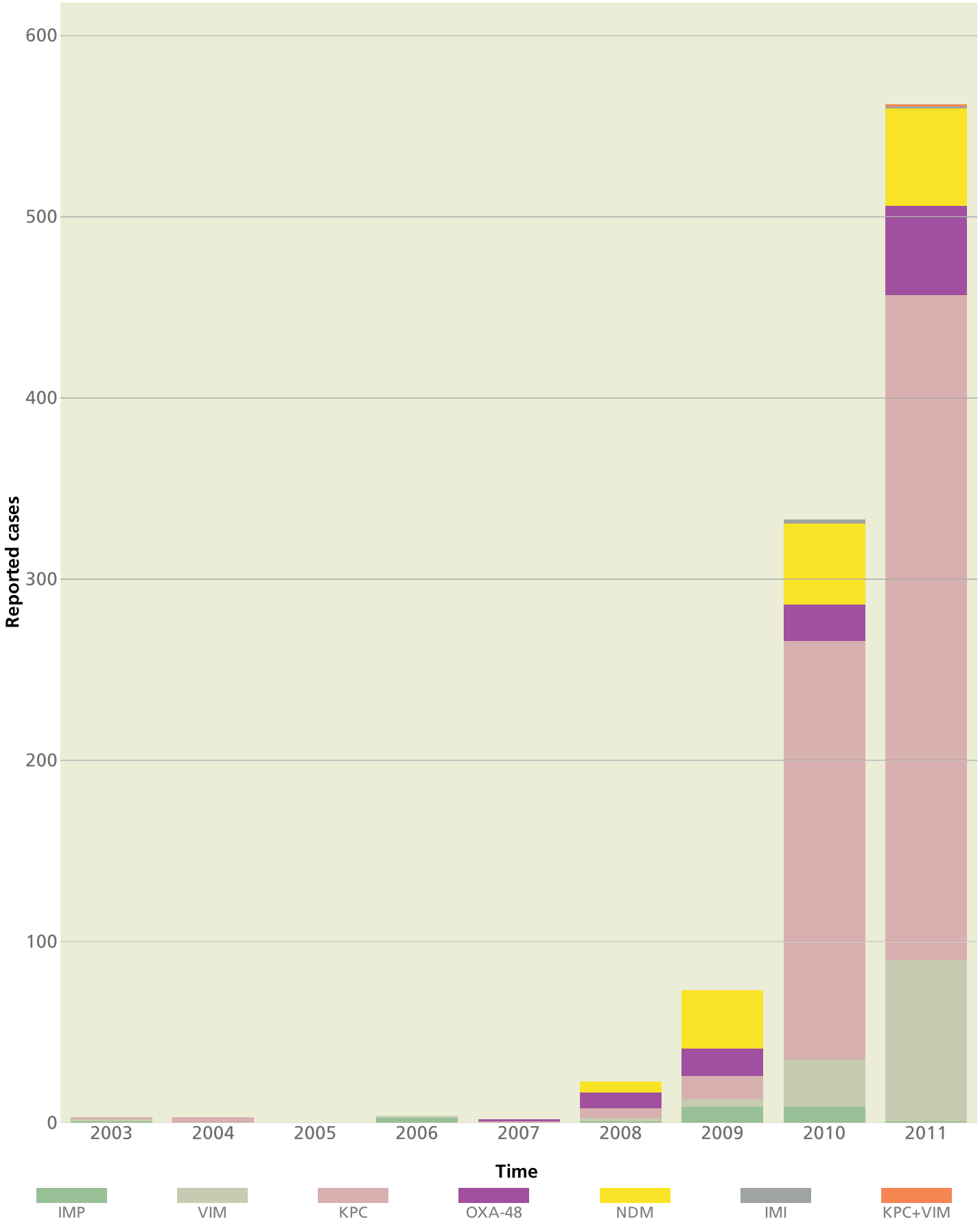
Antimicrobial stewardship

Antimicrobial stewardship embodies an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness. It has three major goals:[17]

- Optimise therapy for individual patients
- Prevent overuse, misuse and abuse
- Minimise development of resistance at patient and community levels.

A delicate balance must be struck between discouraging indiscriminate use of antibiotics and promoting the timely and appropriate treatment of probable bacterial infections. Urgent treatment with broad-spectrum antimicrobials is life-saving in severe sepsis and septic shock. However, indiscriminate use of broad-spectrum antimicrobials is undesirable for two reasons. Firstly, broad-spectrum antimicrobials, as well as killing a wide range of bacteria, also remain active against multi-drug resistant bacteria. Prescribing these agents where narrow-spectrum drugs are effective creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, allowing such strains to proliferate and spread. Secondly, in addition to killing harmful bacteria, broad-spectrum antimicrobials also kill normal commensal flora. Normal flora form a component of host defences against infection by competing with harmful bacteria. Disruption of normal flora can leave patients susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. The principles of responsible antibiotic prescribing were summarised by the Royal College of Physicians in 2011[18] (see Box 1).

Figure 5.2: Trend in carbapenemase-producing Enterobacteriaceae cases referred to HPA (Colindale), United Kingdom, 2003 to 2011



Source: HPA. English National Point Prevalence Survey on Healthcare Associated Infections and Antimicrobial Use, 2011: Health Protection Agency, England; 2012. (Dr Susan Hopkins & Dr Alan Johnson, personal communication)

Box 1

Effective antibiotic prescribing – top ten tips

Antibiotics are essential to modern medicine and may be life-saving, but abuse leads to resistance. All physicians who prescribe antibiotics have a responsibility to their patients (and public health) to prescribe optimally.

- Institute antibiotic treatment immediately in patients with life-threatening infection.
- Prescribe in accordance with local policies and guidelines, avoiding broad-spectrum agents.
- Document in the clinical notes the indication(s) for antibiotic prescription.
- Send appropriate specimens to the microbiology lab; drain pus and remove foreign bodies if indicated.
- Use antimicrobial susceptibility data to de-escalate/substitute/add agents and to switch from intravenous to oral therapy.
- Prescribe the shortest antibiotic course likely to be effective.
- Always select agents that minimise collateral damage (i.e. selection of multi-resistant bacteria/*C. difficile*).
- Monitor antibiotic levels when needed (e.g. vancomycin).
- Use single-dose antibiotic prophylaxis wherever possible.
- Consult your local infection experts.

Historical context

Responsibility for antimicrobial stewardship in UK healthcare traditionally lay with medical microbiologists and infectious-disease doctors. In hospitals, however, pharmacists routinely review prescriptions and lead in developing and co-ordinating medicine policies. From 2000, this led to the development of specialist antimicrobial stewardship pharmacists to complement medical microbiologists and infectious-disease doctors in promoting good antimicrobial usage.

Table 5.1 summarises evidence of the progress in UK hospitals over the past two decades in developing and implementing antimicrobial stewardship. This needs to be sustained and increased. A national point prevalence survey of antimicrobial use carried out in England in 2011, with 99 hospitals participating, showed substantial unexplained variation in prescribing rates between regions. The unadjusted proportion of patients receiving antibiotics was 34.7%, varying from 29.2% in the South East Coast region to 39.9% in the North East. This differential is unlikely to be due to differences in case mix alone and while it is unclear what the appropriate expected proportion of patients receiving antibiotics *should* be, the difference in prescribing rates does illustrate the need for initiatives to drive quality improvement.[8]

Outcomes of antimicrobial stewardship

Several individual English hospitals have evaluated the impact of stewardship programmes and demonstrated associated changes in prescribing behaviour –particularly for cephalosporin and quinolones – with linked reductions in problem pathogens, particularly *C. difficile*.[21, 22] Preliminary

Table 5.1 Implementation of antimicrobial stewardship strategies in UK hospitals – progress over two decades

Year	1994	2006	2012 (ongoing)
Source	**BSAC[19]**	**Wickens & Jacklin[20]**	**ESGAP & ISC* (unpublished)**
Sample	**n=427 UK hospitals**	**n=125 English hospitals**	**n=126 UK hospitals**
Guidelines for antibiotic therapy	62%	90%	100%
Guidelines for surgical prophylaxis	51%	87%	99%
Antibiotic formulary	79%	89%	99%
Restricted list	61%	69%	93%
Educational campaigns	52%	73%	100%
Automatic stop policy	26%	–	61% (stop/review)
Antibiotic committee	17%	56%	85%
Antibiotic audit	11%	78%	98%
IV-to-oral switch guidance	–	69%	92%
Microbiology ward rounds	64%	–	96%
Stewardship ward rounds	–	35%	86%
Antimicrobial consumption surveillance (WHO defined daily doses)	–	46%	69%
Dedicated antimicrobial prescription chart	1.5%	<1%	40%
Inflammatory marker testing (e.g. procalcitonin)	–	–	11%

*Acknowledgement: Provided by Professor Dilip Nathwani and Philip Howard

national data for English hospitals, collated in 2012, confirm that these reductions in cephalosporin and quinolone use have been replicated on a national scale. They have been associated not only with declining *C. difficile* infection, but also with the reversals in trends for resistance to cephalosporins and quinolones among *E. coli* from bacteraemia (see Figure 5.3).

Stewardship challenges

These reductions in cephalosporin and quinolone use are partly offset by increased use of broader-spectrum antibiotics, notably anti-pseudomonal penicillins (mostly piperacillin-tazobactam) and carbapenems (see Figure 5.4). These shifts, in turn, have coincided with an increased incidence of carbapenemase-producing Enterobacteriaceae (see Figure 5.2) – all of them highly resistant to piperacillin-tazobactam and most also resistant to the carbapenems.

It is plausible that, as Peterson put it in 2005, we are just 'squeezing the balloon', replacing prescribing of one group of broad spectrum antibiotics with another.[23] Such a view highlights the need for a more dynamic and intelligent approach to stewardship, avoiding reliance on single antimicrobial classes, which are then degraded in turn.

One strategy to consider is to encourage heterogeneous prescribing of antimicrobials[24] from different chemical classes, thus creating firebreaks to the spread of resistance. Further clinical trials are needed urgently to understand the impact of this approach on infection outcomes and resistance.[25] The alternative of 'cycling' antibiotics (i.e. preferring agents in turn) has undergone trials, but did not significantly reduce resistance.[26]

Our understanding of the optimum and shortest safest duration of antibiotic therapy for specific infections is also very limited. It may be possible to reduce overall prescribing levels by shortening treatment durations.

Diagnostics to overcome resistance

Despite current improvements in stewardship, antibiotics are often used wastefully. There are three main reasons for this:

- Diagnostic limitations mean that antibiotics are given to patients without infection or with viral infection.
- Because inadequate treatment doubles mortality in sepsis, these patients are given broad-spectrum empirical antibiotics. These should be 'de-escalated' once microbiology data become available, but de-escalation does not always occur.
- Antibiotics are abandoned as empirical treatment once resistance crosses a threshold. If patients with susceptible pathogens could be swiftly identified rapidly and reliably, this could re-allow the use of currently abandoned therapies.

These issues all reflect the fact that most antibiotic use begins without knowledge of the pathogen. Laboratory microbiology, if done at all, takes 48 hours: one day to culture bacteria and another to identify and characterise them. Faster microbiology could improve stewardship in two ways. Firstly, biomarkers could be used to better distinguish patients with a bacterial infection from those whose symptoms have other origins. This would reduce the numbers of patients given antibiotics inappropriately. This issue is considered further in the life-stage chapters of this report, particularly the perinatal chapter (where distinguishing between viral and bacterial infection is highlighted as potentially being problematic) and the older people chapter (where distinguishing between symptoms due to infection and those due to chronic illness is identified as an issue). Secondly, molecular microbiology could be used to identify bacteria and their resistances. This would allow earlier focusing of appropriate treatment and, through the implementation of appropriate antimicrobial stewardship, thereby reducing the selective pressure for the emergence of resistant strains.

Biomarkers

Established indicators of infection include leukocyte counts and C-reactive protein. Although sensitive, these have poor specificity, and recent interest has centred on procalcitonin.

Several randomised trials have been performed, involving more than 3,500 patients, mostly with pneumonia.[27] Deployment of procalcitonin measurement reduced antibiotic use by 30–80% without compromising outcomes. Savings reflected denial of antibiotics to those patients with low procalcitonin, and shorter treatment in patients whose procalcitonin swiftly fell to baseline. However, more trials are needed (and involving more infection types) before this marker is used more widely. There are concerns that patient types and trauma or surgery may 'falsely' raise procalcitonin. It may also be better to monitor multiple biomarkers rather than a single marker.

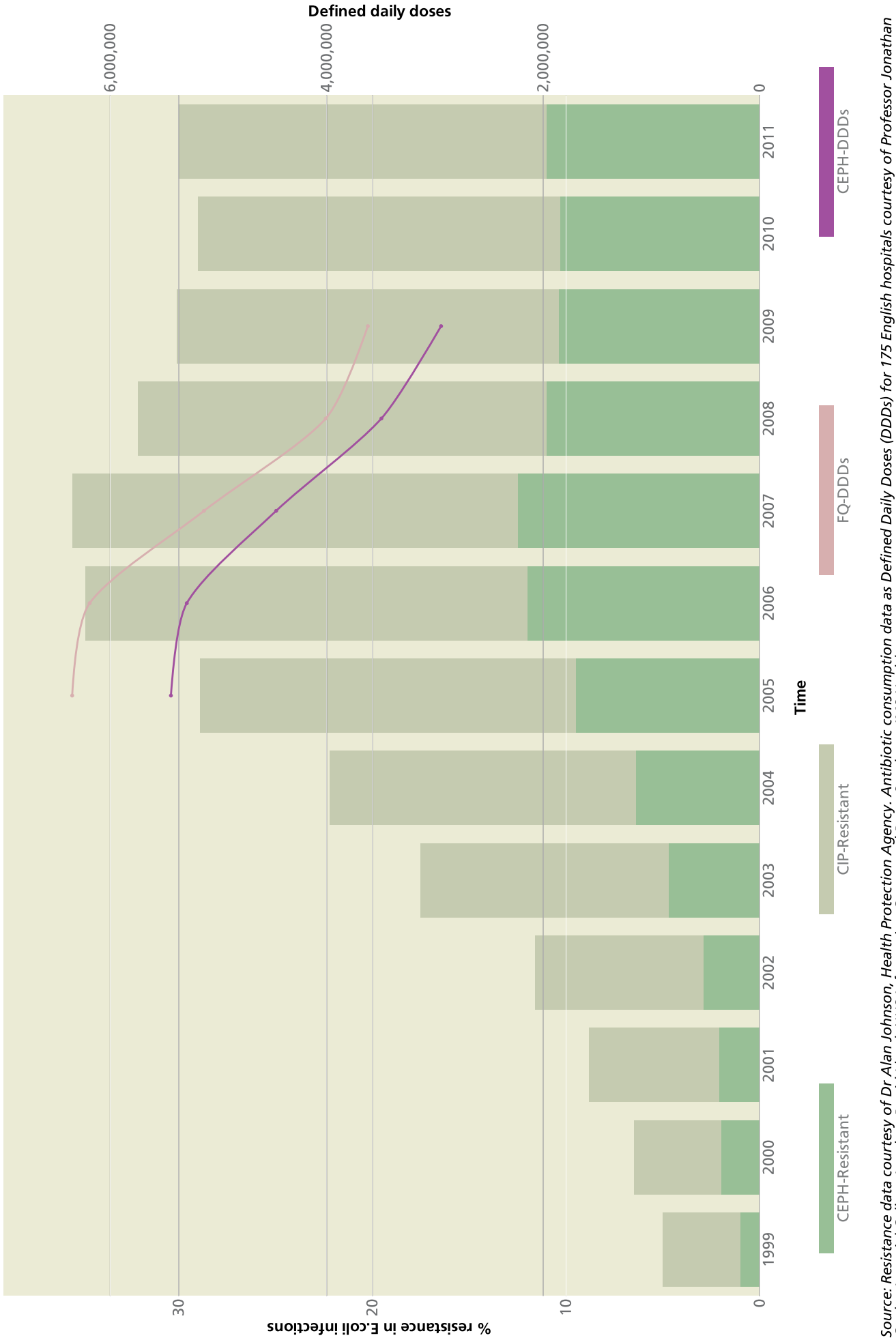
A recent study[28] (see Box 2) examined broader patient ranges, with positive results, although the patient numbers were small.

Box 2

Procalcitonin trials: Royal Hampshire Hospital[28]

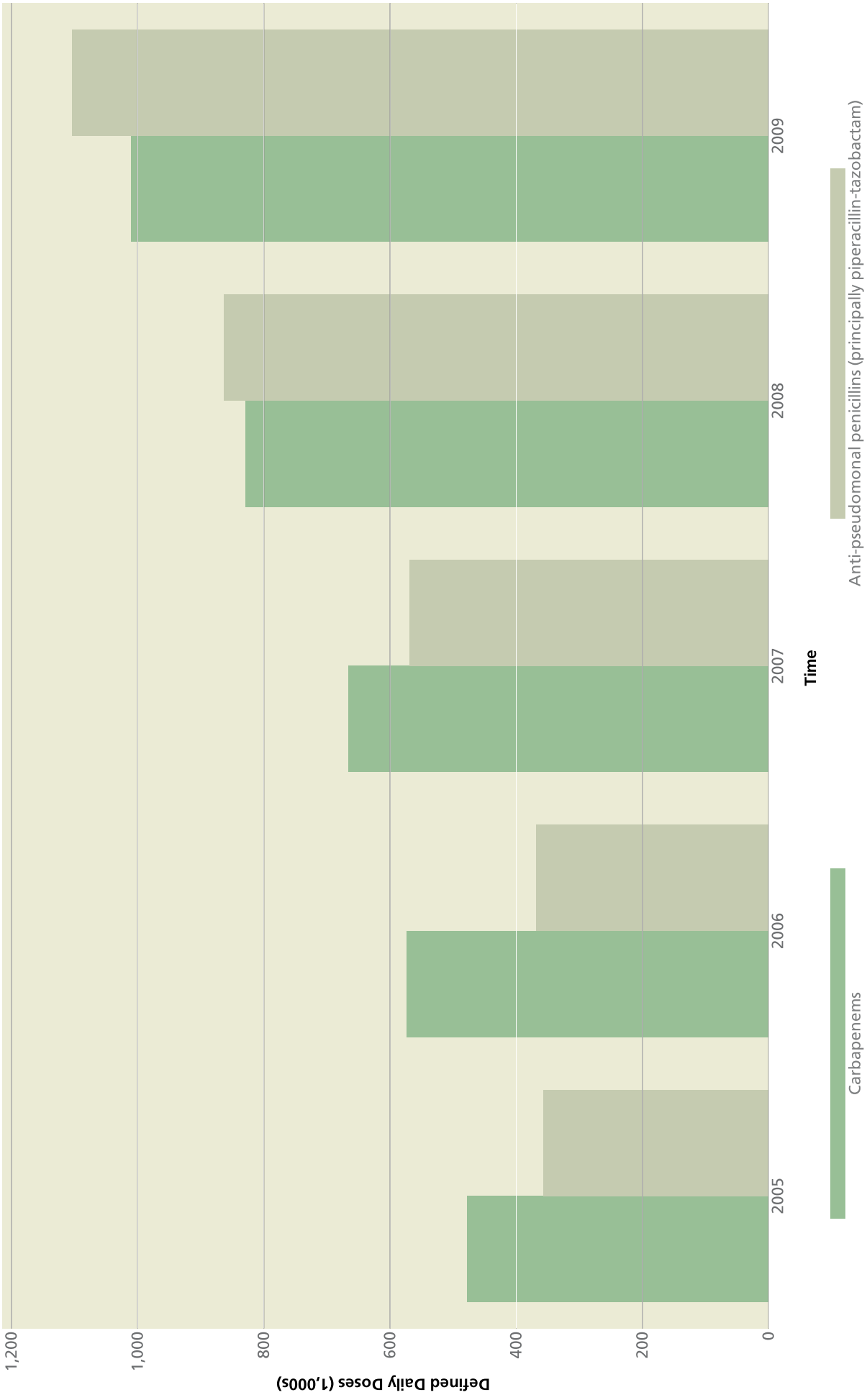
- 99 Medical Admissions Unit (MAU) patients with suspected infection
- 42 Intensive Care Unit (ICU) cases, with 87 procalcitonin tests done
- Procalcitonin results delivered within 90 minutes of request
- Antibiotics withheld in 52/99 MAU cases and on 42/87 occasions in the ICU on the basis of low procalcitonin
- 6 MAU patients died, but deaths were NOT infection related
- 5 ICU patients died with infection, but all were receiving antibiotics

Figure 5.3: Trend in antibiotic use and resistance in E. coli, England, Wales and Northern Ireland, 1999 to 2011



Source: Resistance data courtesy of Dr Alan Johnson, Health Protection Agency. Antibiotic consumption data as Defined Daily Doses (DDDs) for 175 English hospitals courtesy of Professor Jonathan Cooke, Imperial College London, David Lloyd, NHS Information Centre and Peter Stephens, IMS Health.

Figure 5.4: Trend in broad-spectrum antibiotic use in English hospitals (n=175), England, 2005 to 2009



Source: Antibiotic consumption data as Defined Daily Doses (DDDs) for 175 English hospitals courtesy of Professor Jonathan Cooke, Imperial College London, David Lloyd, NHS Information Centre and Peter Stephens, IMS Health. NB: The greater relative use of meropenem vs. piperacillin-tazobactam than apparent in Figure 4.4 of this report reflects the different denominators, common use of 3g meropenem per day, vs. 2g as the DDD, and, possibly, longer treatment durations.

Rapid identification of pathogen and resistances

The time to complete traditional microbiological tests – around 48 hours for most pathogens but several weeks for *Mycobacterium tuberculosis* – has already been highlighted. During this period antibiotic therapy is 'blind', with many patients over-treated, to prevent under-treatment of a few. If the period can be shortened there is scope to radically improve stewardship. A number of methods for more rapid identification are currently under development. Mass spectroscopy (MALDI-TOF)[29] allows near-immediate bacterial identification, whilst automated susceptibility testing delivers results in 6–12 hours. Both, however, need pure cultures, only available 24 hours after taking the specimen. Further improvement demands testing clinical material, without culture, and three types of method are being developed:

- **Gene detection for specific pathogens** Tests using PCR for specific pathogens are marketed to aid infection control, identifying patients colonised by (for example) MRSA, allowing decolonisation or cohorting. They are well validated in this role and are now also being used to identify these pathogens in material (e.g. pus or urine) from infections. Since they seek single pathogens, their main role is in outbreaks. For tuberculosis, validated assays are available to detect both the pathogen and the mutations conferring rifampicin resistance.[30] The National Institute of Health Research (NIHR) has commissioned an evaluation of their value for resistant tuberculosis.
- **Multiplex gene detection assay PCR** These seek genes for the pathogens responsible for most (around 90%) of cases of their target infection, delivering results in 4–6 hours. A few also seek resistances. Whilst broader than single pathogen tests, they are not comprehensive and leave the question of what to do when no pathogen is detected. Moreover, since they are better for seeking resistance genes than for excluding the possibility that a pathogen has any of a myriad of possible resistance genes, they are better equipped to detect patients with exceptionally resistant bacteria, needing non-standard antibiotics. A NIHR-supported UK study of one system is ongoing, but it examines only accuracy, not outcomes.[31]
- **Next-generation sequencing** Rapid, cheap genome sequencing of pathogens is increasingly available, as are the bioinformatic tools to analyse the data generated. Unlike PCR, sequencing with appropriate bio-infomatics recognises all species and known resistance genes within hours, and can track outbreak strains. Nevertheless, the challenges are considerable: detecting bacterial DNA when few bacterial cells are present, predicting resistance when it involves multiple genes, and predicting novel resistances from sequence homologies.[32]

Opportunities and challenges

There is potential for molecular methods to revolutionise and accelerate diagnostics, benefitting antibiotic stewardship. They will also allow early identification of patients with resistant pathogens, facilitating inclusion in clinical trials. Several challenges have been noted but broader issues deserve mention:

- Rapid diagnostics will deliver most advantage close to the patient; with gains eroded if specimens need time-consuming transport between hospital sites.
- With the exception of sequencing, these methods are additional to classical microbiology, increasing laboratory cost whilst gains accrue elsewhere.
- The relationship between carriage of a gene and expression of resistance is close but imperfect.
- Gains in stewardship will require wide deployment, not only use for 'special' patient subsets.
- The balance of risk and reward should be considered: treatment of many patients will be improved but that of a few may be worsened.

The economics of antimicrobial development

While better diagnostics and strengthening stewardship are critical, they are likely only to buy time whilst new antimicrobials are developed. Recent decades have seen rapid progress in many drug classes, but for antibiotics the pipeline is dwindling. Like all private businesses, pharmaceutical companies allocate scarce resources to maximise profits. The return on investment for a new antibiotic is frequently lower than in other therapeutic categories. There are various reasons for this,[33] including:

- High cost and scientific challenges in R&D – especially for antibiotics that are effective against Gram-negative bacteria, which have considerable impermeability and efflux.
- Antibiotics are used for short treatment courses compared with drugs for chronic conditions.
- Where antibiotics are reserved for future use, their effective patent period – and investment return – is reduced.
- Challenging trial requirements: trials are required in each infection site (urine, skin, lung etc.), whereas a heart drug (for example) needs only to work in one indication. Moreover, trial requirements have changed repeatedly, particularly as a result of guidance from the US Food and Drug Administration.

The under-provision of new antibiotics is a 'market failure' from a societal perspective, since society benefits from a steady pipeline of new effective antibiotics. Governments, institutions and the third sector, working with the pharmaceutical industry, need to better align the private and social risks, costs and benefits, incentivising R&D in antibiotics.

Smith and Coast[34] draw an analogy with climate change for the economic and social costs of antimicrobial resistance. Currently, the additional economic costs of antimicrobial resistance are relatively small, as mitigating action (switching

prescribing to other antibiotics) can be taken. However, when this is coupled with growing rates of resistant organisms and a declining number of new antibiotics in development, the potential future costs are very high.

What incentives might foster R&D?

There are four main categories of incentives to foster antibiotic R&D: 'Push', 'Pull', 'Lego-regulatory' and 'Hybrid push-pull'.[33, 35]

- **Push** incentives reduce the marginal cost of R&D and include public funding (e.g. from the EU) and tax incentives (see Box 3).
- **Pull** incentives foster R&D via financial rewards, e.g. monetary prizes for delivering specific results, advance market commitments or offering patent buyouts.
- **Lego-regulatory** incentives are 'outcome-based market-determined rewards' and include adjusting pricing and reimbursement, extending patent lives or expediting regulatory reviews. Examples include the US Generating Antibiotic Incentives Now (GAIN) Act (2012) or the US 'Limited Population Antibacterial Drug' (LPAD) Approval Mechanism, where a limited licence is proposed, based upon safety and effectiveness data in small clinical trials.
- **Hybrid push-pull** incentives include product development partnerships.

Box 3

Examples of incentives to foster R&D in new antibiotics

- Grants and fellowships
- Funding translational research
- Research-related tax incentives
- Money prizes
- Health impact funds
- Patent buyouts
- Advance market commitments
- Expedited regulatory review
- Pricing and reimbursement adjustments
- Intellectual property (IP) patent pools, patent extensions and wildcard extensions
- Call options for antibiotics model
- Orphan drug legislation
- Product development partnerships.

In short, there are many innovative methods to align incentives and risks of different stakeholders. However, the challenge is to balance these approaches and to ensure that actions are cost-effective, sustainable, safe and do not discourage private innovation.

Reshaping the challenge and raising the profile

The global profile of antimicrobial resistance is rising. The World Health Organization has promoted resistance awareness and options for action through its 2011 World Health Day and a recent publication.[36, 37] The Swedish government's 2009 EU presidency led to the creation of the TransAtlantic TaskForce for Antimicrobial Resistance (TATFAR) with the US Government, a European Commission Action Plan and investment into the Innovative Medicines Initiative (IMI). The ReAct – Action on Antibiotic Resistance network, an independent global network for concerted action on antibiotic resistance, has played an important role in raising awareness of resistance, including engaging with the World Economic Forum's Risk Response Network. The World Economic Forum Global Risks 2013 report includes a section on "The Dangers of Hubris on Human Health", which focuses on AMR. This report uses evidence generated from an annual survey of over 1,000 experts from industry, government, academia and civil society. Survey responses connected the risk of AMR to other global risks including vulnerability to pandemics, failure of the international Intellectual Property (IP) regime, rising rates of chronic disease and unforeseen consequences of new life science technology.[38] The Global Antibiotic Resistance Partnership (GARP) has been established with support from the Bill and Melinda Gates Foundation.

Despite these positive steps, more is needed to bring a steady supply of antibiotics to market. More generally, the incomplete evidence base complicates the development of policy responses. In particular, there is weak understanding of the systemic risk to health systems. Given the widespread reliance of so many healthcare interventions on antibiotics to prevent or control the development of infection, growing rates of antimicrobial resistance could potentially make these interventions untenable.[34]

All this highlights the need to meld the scientific challenge, the economic problem and the policy debate, and to better align incentives with short- and long-term risks.

The UK must play its part in aligning national and international objectives, influencing the various forums outlined above to drive actions and outcomes. A framework is needed to align incentives – specifically the public health goals of governments and the private goals of pharmaceutical companies.[39] This requires:

- Methods to measure the societal risk and impact of resistance
- Building broader public awareness of the risks of resistance
- Coordinating actions around surveillance, stewardship, licensing regulation and product supply; with all this done on a sufficient international scale to have impact.

The future direction of stewardship and diagnostics in England

The changing resistance challenge demands a flexible and agile approach to resource deployment. It is essential that government, public and professional focus extends beyond MRSA and *C. difficile* to a broader range of challenges, particularly those posed by Gram-negative bacteria. A typical large 1,000-bed acute NHS hospital now has 2–3 MRSA bacteraemias per year and 50–60 *C. difficile* cases but 400–500 bacteraemias involving Gram-negative bacteria, 10–15% of them due to strains resistant to cephalosporins, piperacillin-tazobactam and, increasingly to carbapenems, antibiotics which should be reserved for hard to treat infections.

The changing health system provides a number of new opportunities and levers for improving antimicrobial stewardship. In the future this could include a move to audit antimicrobial stewardship systems and outcomes in the Department of Health mandate to the NHS Commissioning Board as well as widening the remit beyond MRSA and *C. difficile*. A potentially effective measure to improve the implementation of antimicrobial stewardship would be for the NHS Commissioning Board to consider designing elements of the national provider contract to support antimicrobial stewardship. It could also include antimicrobial stewardship across the NHS Outcome Domains. However for this to occur it will require the development of robust antimicrobial stewardship quality indicators that could be requested from ARHAI or other relevant, expert body. It seems likely that local commissioners will need support to prioritise antimicrobial stewardship and to improve infection outcomes. Potentially this could be achieved through the NHS Improvement Body (National Institute for Innovation and Improvement) developing packages to encourage innovation in antimicrobial stewardship.

There is also a need for the development and maintenance and promotion of a compendium of evidence-based antimicrobial guidelines. Specific consideration should be given to increasing awareness of guidance on heterogeneity of prescribing to slow the development of resistance. While this could well fit with the developing role of the National Institute for Health and Clinical Excellence (NICE), this would require commissioning (perhaps from Public Health England). NICE may also be best placed to develop a quality standard on antimicrobial stewardship.

While most action around antimicrobial resistance will require a concerted effort across the whole health system, specialist commissioning of diagnosis, management and prevention is needed to ensure an appropriate response to the small number of cases of multi-resistant classical infections, including tuberculosis and gonorrhoea.

Without a specific driving force to push the antimicrobial resistance agenda, realising the above opportunities seems unlikely. The UK 2013–2018 antimicrobial resistance strategy and action plan will seek to be this driving force. It should be be noted that the Department of Health's Antimicrobial Resistance and Hospital Acquired Infection (ARHAI) Advisory Committee, have recommended the establishment of an 'English Surveillance Progamme for Antimicrobial Utilisation and Resistance'. The aims of such a programme would focus on the operational monitoring and data capture aspects of antimicrobial stewardship, with one key aim being "to provide oversight, integration and analysis of the varying antimicrobial usage datasets, including primary and secondary care, as well as mental health trusts and non-NHS providers". Certainly consideration needs to be given by the relevant stakeholders as to how the appropriate clinical, professional and managerial leadership for the use of antimicrobials in the NHS, along with innovation in the use of relevant diagnostics, will be achieved. Thought needs to be given to the development of mechanisms through which work with stakeholders to develop innovative, effective and sustainable public and patient engagement strategies to preserve antimicrobials can be achieved and improved.

Vital to improving antimicrobial stewardship will be the education, training and workforce priorities of healthcare and public health professionals. Health Education England will need to consider its role in this, but developing and embedding antimicrobial stewardship competences in professional curricula is one clear approach.

Controlling prescribing for Critically Important Antimicrobials is of key importance to the national strategy for AMR. National surveillance agencies, and in particular, Public Health England, therefore need to establish robust systems to monitor antimicrobial use in the community and hospitals, with the development of local benchmarking.

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Chapter 6

Life stage: Perinatal

Chapter authors

Mike Sharland[1], Shamez Ladhani[2], Mary Ramsay[3], Paul Heath[4], Sonia Saxena[5], Elizabeth Koshy[6], Alex Bottle[7], Jo Murray[8], Paul Griffiths[9]

1 Professor of Paediatric Infectious Diseases, Paediatric Infectious Diseases Unit, St George's Healthcare NHS Trust
2 Paediatric Infectious Diseases Consultant, St George's University London
3 Consultant Epidemiologist, Health Protection Agency
4 Professor of Paediatric Infectious Diseases, St George's University London
5 Clinical Senior Lecturer, Imperial College London
6 NIHR Doctoral Research Fellow, Imperial College London
7 Senior Lecturer in Medical Statistics, Imperial College London
8 PhD Student, Imperial College London
9 Professor of Virology, University College London

Overview

Perinatal and infant mortality rates in England are among the highest in the European Union (EU). The management of infection in the perinatal period (preceding, during and subsequent to birth) remains therefore of strategic importance, as the consequences of infection during this time have a very significant impact on long-term outcomes. Perinatal infection is influenced by social inequality, but there is clear evidence that targeted interventions can sharply reduce the transmission of infections from mother to child (for example in HIV). As the birth rate in England increases, the management of perinatal infection remains key to improving our unacceptably high perinatal mortality and morbidity outcomes in an ethnically diverse population. Infection leads to higher rates of prematurity. Premature babies are, in turn, vulnerable to higher rates of infection – much of which is potentially avoidable healthcare-associated. Further advances to reduce perinatal infection through maternal vaccination and other interventions are in progress. The focus should now move from a series of single disease-specific interventions to an integrated multi-disciplinary clinical and research programme of perinatal infection prevention.

This chapter sets out the current burden of infection, the impact of prematurity and then discusses areas of future concern and potential interventions for specific viral and bacterial infections.

The burden of perinatal infection

Maternal infection

Pregnant and post-partum women represent a vulnerable population with an increased risk of infection and consequent adverse outcomes for the mother, the unborn baby and the infant.

Maternal mortality remains low in the UK (approximately 90 deaths per year between 2006 and 2008), but mortality rates from sepsis in pregnancy have more than doubled from 0.4 per 100,000 in the late 1980s to 1.1 per 100,000 in 2006–8. Sepsis, most commonly due to invasive group A streptococcal infection, is now the most common direct cause of death in pregnant women. Underlying each maternal death is a much larger number of cases of sepsis; provisional data on 200 cases of severe sepsis in pregnancy shows that *Escherichia coli* (33%), group A streptococcus (15%) and group B streptococcus (12%) are the most common bacteria implicated.[1] A multi-centre cohort study conducted in 2009 found a high rate of post-operative wound infections or endometritis following caesarean section, affecting nearly 10% of the women studied. Viral infections are also important: hospitalisation of healthy pregnant women due to influenza occurs at a rate of 1–2 per 1,000; around 20 times that of healthy non-pregnant women.

Perinatal and infant mortality

In 2010 there were 3,714 stillbirths and 1,657 deaths in infants under 7 days of age, a Perinatal Mortality Rate (PMR) of 7.4 deaths per 1,000 total births. This represents a 44% fall since 1980, but it remains one of the highest in the EU.[2]

There is a clear social dimension to the pattern of perinatal mortality. The highest rates are among babies with fathers employed in semi-routine occupations (9.0 deaths per 1,000 total births) and lowest among higher professional occupations (5.7 deaths per 1,000 total births).

Maternal origin is also very important, with the highest mortality rates in babies of mothers born in Pakistan (13.2 deaths per 1,000 live births), Bangladesh (11.7 deaths per 1,000 live births) and Africa (11.3 deaths per 1,000 live births), compared with 6.9 deaths per 1,000 total births for mothers born in the UK.

The England and Wales infant mortality rate (deaths in the first year of life) in 2010 was 4.3 deaths per 1,000 live births. This also represents one of the highest rates in the EU, with most larger countries achieving rates of 3.2–3.6 deaths per 1,000 live births. The rate of decline in infant mortality is also lower than in many EU countries.[3]

Prematurity and infection

Premature birth is strongly linked to maternal infection

In England around 8% of infants are born prematurely (before 37 weeks' gestation), including 2.4% before 32 weeks' gestation and 1% before 28 weeks' gestation.

The reasons why women go into premature labour are multifactorial and complex; those especially at risk are young, single or unsupported mothers, especially if they smoke or are underweight. Intrauterine infection is a frequent and important mechanism leading to preterm birth. Studies suggest that infection accounts for around 25–40% of preterm births, although this may be a minimum estimate. **The earlier the gestational age at which women present with preterm labour, the higher the frequency of intrauterine infection.**

Premature infants are also at substantially increased risk of infection

The highest incidence of infection in any age group is in the neonatal period, and the great majority of infections within this period occur in infants born prematurely. A range of infections occur, including septicaemia, pneumonia and meningitis. The overall incidence of bacteraemia is around 4 per 1,000 live births but is 40 per 1,000 neonatal admissions, and the majority of cases occur in infants who are born before 37 weeks' gestation and are of low birth weight (born weighing less than 2,500g).

There are high rates of neurodevelopmental impairment in premature infants, and there is increasing evidence that infections in premature infants have adverse long-term consequences. A recent Swiss study, for example, reported that among premature infants born at 24–28 weeks' gestation, proven sepsis was independently associated with cerebral palsy and neurodevelopmental impairment at 2 years of age.

Case study 6.1

A baby born prematurely at 26 weeks' gestation, now at 25 days of age, was noted to have episodes of apnoea. He had recently been weaned from oxygen and was on half nasogastric feeds (donor breast milk) and half intravenous nutrition administered through a central venous catheter, which had been in place for one week. He was also noted to be more lethargic and had mild abdominal distension. Intravenous antibiotics were started. Over the next 24 hours, his oxygen requirement increased and he required intubation and ventilation. Blood cultures at 24 hours grew a *Klebsiella* infection. He remained intubated and ventilated for a further five days. Several further episodes of clinical sepsis requiring short courses of antibiotics complicated his stay on the neonatal unit and he was ultimately discharged home at 3 months of age. On follow-up he was noted to have moderate neurodevelopmental delay.

This case study highlights the risk of neurodevelopmental complications of late-onset infection.

Areas of concern and potential interventions

Early-onset sepsis (EO)

Early-onset infections (occurring within the first few days of life) are usually caused by organisms acquired from the mother's genital tract. In the UK, the incidence of early-onset sepsis (48 hours of age or less) is estimated to be around 1 per 1,000 live births, with group B streptococcus (58%) and *E. coli* (18%) the most common organisms isolated from blood cultures. Around half of early-onset sepsis occurs in infants born at full term.

Late-onset sepsis (LO)

The majority of late-onset infections, those occurring after 48 hours of age, occur in premature infants. Arguably, **these should be considered as potentially preventable healthcare-associated infections (HCAIs)**. The reasons for this very high rate of HCAI in premature babies include the very prolonged hospital stays, the immaturity of their immune system and the need for multiple indwelling central venous catheters for intravenous feeding, as well as exposure to multiple, prolonged courses of broad-spectrum antibiotics. Data from the recent HCAI point prevalence survey in England and Wales demonstrate that neonatal intensive-care units have the highest rates of HCAI per admission of any intensive-care facility.

Coagulase-negative staphylococcal infections are the most common causes of late-onset sepsis, accounting for around half of all late-onset sepsis infections, and are usually associated with the presence of indwelling catheters. Such infections are rarely fatal, although they account for significant antibiotic use in neonatal units. Gram-negative bacteria cause 42% of all late-onset sepsis, of which 30% are due to *E. coli*, 22% *Klebsiella*, 22% Enterobacter, 13% *Pseudomonas*, 6% *Serratia* and 6% Acinetobacter. Gram-negative bacteria infections have a very high case fatality of around 25%, while survivors have longer intensive-care stays and significantly more neurodevelopmental complications, with all the associated lifetime social care costs. Gram-negative bacteria, in particular, are associated with antibiotic resistance and often occur in outbreaks, causing distress to families and staff and generating considerable disruption to the effective functioning of neonatal clinical networks. Approximately 15% of UK neonatal units have been investigated for a 'recent' infection control issue, and 12% per year close temporarily for this reason.

Infection control

Outbreaks reflect a breakdown in infection prevention measures. Poor hand hygiene, overcrowding, inadequate spacing between cots, low nurse–patient ratios, environmental colonisation (especially of water systems), inadequate cleaning of common-use equipment, injudicious overuse of antibiotics (particularly broad-spectrum and prolonged courses) and delaying the introduction of maternal breast milk all contribute to preterm and sick babies becoming colonised or infected with Gram-negative bacteria. The recent 'Independent Review of Incidents of *Pseudomonas aeruginosa* Infection in Neonatal Units in Northern Ireland' by the Regulation and Quality Improvement Agency (www.rqia.org.uk) highlighted many of these issues. A recent Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) report on the detection and management of outbreaks of HCAI in neonatal units in England highlighted the operational and research agendas (http://www.dh.gov.uk/health/about-us/public-bodies-2/advisory-bodies/arhai/).

Group B streptococcus

In the UK, group B streptococcus (GBS) is the single most important infectious cause of neonatal death, the most common cause of early-onset sepsis and the most common cause of neonatal and infant meningitis. During 2003–5, it was mentioned in almost one-third (87/273 cases, 32%) of neonatal death certificates where a bacterial infection was specified. A UK national surveillance study conducted in 2000/1 identified 568 cases of group B streptococcus infection in the first 3 months of life, of which 377 were early-onset (under 7 days of age) (an early-onset incidence of 0.5 per 1,000 live births) and 191 were late-onset. The

overall case fatality was 10%. Subsequent Health Protection Agency surveillance suggests a steady increase in the number of neonatal cases since 2000. A recent UK surveillance study (2010–11) revealed that 51% of cases of meningitis in the first three months of life were due to group B streptococcus (150 cases). Meningitis is of particular importance, as it is associated with significant long-term disability (50% with neurodevelopmental sequelae at five-year follow up).

In the UK, around 20% of pregnant women are colonised with group B streptococcus, approximately 50% of their babies will become colonised and 1% will develop invasive infection. Pregnant and postpartum women have a significantly increased risk of invasive group B streptococcal disease compared with non-pregnant women, and group B streptococcus is associated with premature delivery and stillbirths. The only currently available prevention strategy is intrapartum antibiotic prophylaxis (IAP). UK guidelines recommend IAP based on the presence of clinical risk factors, but these have proved difficult to implement in the NHS. An effective group B streptococcus vaccine holds the greatest promise for the prevention of neonatal and pregnancy-associated group B streptococcal infections.

Case study 6.2

A baby was born at full term in good condition; breast fed well and was discharged on the following day. Mother was well, the pregnancy and birth uneventful. At 10 days of age the baby was noted to be feeding less, was irritable and had a low-grade fever. On assessment in the Accident & Emergency department, the baby was lethargic with poor peripheral perfusion. Focal seizures were observed on admission to the ward. Cultures were obtained and antibiotics commenced. A lumbar puncture on the following day showed meningitis. Blood and subsequently cerebrospinal fluid cultures grew group B streptococcus. The baby received 21 days of antibiotics. Follow-up hearing tests revealed significant bilateral sensorineural deafness, and neurodevelopmental impairment was documented at 12 months of age.

Why preventing prematurity is important

Infants born prematurely are at increased risk of serious infections in infancy. These include potentially vaccine-preventable infections such as pertussis, rotavirus, pneumococcal disease and Haemophilus influenzae type b. Immune responses to routine immunisations are often lower in premature infants than in older infants, although the majority achieve protective levels. **Timely vaccination with primary doses and, especially, booster doses of routine vaccines is essential, yet preterm infants are often undervaccinated.** Premature infants are also at increased risk of viral infections, especially affecting the respiratory tract. Such infections often require multiple admissions to hospital and severe cases may even require intensive-care admission. In particular, respiratory syncytial virus (RSV) is a major cause of hospitalisation and of viral-related death in the first year of life among infants born prematurely and those with underlying medical conditions. Routine use of anti-RSV monoclonal antibody in selected high-risk infants is expensive but can reduce this burden, although some uncertainty remains about the most cost-effective targeting strategy.

Perinatal viral infections

HIV

In the mid-1990s, only around 30% of HIV-infected pregnant women were diagnosed before delivery. This rose to 60% by 1999. Routine HIV testing for pregnant women was introduced in many English units by the end of 2001 and throughout the UK by the end of 2003. The uptake of antenatal HIV testing has been over 95% since 2005. Currently, 98% of HIV-diagnosed pregnant women are on antiretroviral therapy (ART) at the time of delivery. There is no evidence that ART causes any congenital abnormalities (2.1%, similar to the background rate of 2–3%). The mother-to-child transmission rate of HIV has dramatically reduced from 25% in untreated women to less than 1%, following the widespread uptake of ART in pregnancy, the option of elective caesarian section (although most women with a persistently undetectable viral load are now having a normal vaginal delivery) and exclusion of breastfeeding. Since 2006, there have been fewer than 10 babies a year who have been infected through mother-to-child transmission in the UK and Ireland (www.nshpc.ucl.ac.uk/www.nshpc.ucl.ac.uk/) and most such cases occur in those who did not receive any antenatal HIV screening in pregnancy, or who developed HIV infection in late-pregnancy after being tested negative at booking.

CMV

Congenital cytomegalovirus (CMV) infection is a 'glandular fever' type of virus that causes problems in those with impaired immune systems. It is now the commonest congenital infection in England, occurring in around 0.3% of all births. It can damage the developing brain both before and after birth, making it the commonest known viral infectious cause of cerebral palsy and sensorineural hearing loss. The babies most at risk are those whose mothers experience primary infection during pregnancy. Vaccine-induced maternal immunity has the potential to control this virus even further, and recent clinical trials suggest that it may be possible to produce an effective vaccine against CMV. A further option, based on the success in perinatal HIV, may be to detect mothers having a primary CMV infection or re-infection during pregnancy and give antiviral therapy to reduce the rates of vertical transmission.

Congenital CMV is a major cause of cerebral palsy and deafness. In England and Wales, it is estimated that around 30–50 children per year are born with severe symptomatic congenital CMV, and on follow-up around 40% have moderate or severe neurodevelopmental impairment. Around a further 30–50 babies per year will develop moderate/severe sensorineural hearing loss.

Early treatment with antiviral therapy in the newborn period significantly reduces the rate of long-term sensorineural hearing loss and may improve neurodevelopmental outcome. Improved screening for congenital CMV – possibly through clinical integration with the National Hearing Screening Programme – offers the potential for early detection, treatment and improved clinical outcomes.

Hospital admissions for minor infections in infancy

There has been a marked increase in the absolute numbers and rates of admission to hospital for children in England, especially for infants and children under 5. This follows the national trend of increasing hospital admission rates for all ages, along with decreasing length of stay.

For all paediatric admissions in England, the mean length of stay is now around 2 days. The number of children being admitted to hospitals in England for these short stays increased by around 40% between 1996 and 2006, against a background overall increase of admissions of 20%. The five most common illnesses that led to short-stay admissions included upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI), asthma, abdominal pain, and fever. Short-stay admission rates for infections in infants (aged under 1 year) and preschool children (aged 1–4 years) have continued to increase from 2006 to 2011.

Admission to hospital in infancy is very largely driven by fear of serious infection. A very small proportion of infants and young children with a fever will now have a serious bacterial infection, as discussed in Chapter 7 (Life stage: Child). While the chance of a baby unwell with a high temperature having a serious bacterial infection has never been lower, the chance of them being investigated and admitted to hospital has never been higher. There is an urgent need to work with primary care and acute paediatric services to reclaim the role of managing minor infections in children in primary care. A stronger evidence base is needed in the optimal management of fever and minor infections within a Paediatric Assessment Unit/A+E setting including a clearer evidence base for the decision on when to admit to hospital. This needs to include further evaluation of clinical algorithms, point-of-care testing using combination biomarkers and rapid microbiology diagnostic tests to prevent the unnecessary use of routine admission and empiric antibiotic prescribing in the management of minor viral infections.

Strengthening perinatal infection management

A wide range of different infections can cause significant morbidity in pregnancy and the newborn period. Through an active commissioning process, nearly every acute NHS Trust already has a midwifery lead for HIV, with regular multi-disciplinary team meetings between obstetric and paediatric departments. Services for other perinatal infections are less well developed. Information-sharing between different teams may be inconsistent, sometimes to the detriment of patient care.

One potential approach is to build on the success of HIV and broaden this approach to include other infections. An integrated Perinatal Infection Service, bringing together primary care providers, clinical commissioning groups, midwives, obstetricians, neonatologists, paediatricians and microbiologists would allow a joined-up approach to management and improved monitoring of outcomes for all infections, within a continued Quality Improvement Programme.

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Chapter 7

Life stage: Child

Chapter authors
Michael Levin[1], Mike Sharland[2]

1 Professor of International Child Health, Imperial College London
2 Professor of Paediatric Infectious Diseases, St George's Healthcare NHS Trust

Overview

Infection in young children causes great anxiety to parents and healthcare providers alike, due to the high incidence of life-threatening bacterial infection in the first years of life, the difficulty in distinguishing severe infection from trivial viral illness, and the speed with which severe infections can progress. Vaccines have been highly effective in reducing the incidence of some infections, but the emergence of new strains, changing epidemiology and a lack of vaccines against other important pathogens highlights the need for continued surveillance and training of medical staff in the recognition and treatment of childhood infection.

Burden of childhood infection

Bacterial infections

The introduction of conjugate polysaccharide vaccines against *Haemophilus influenzae* b, meningococcus serogroup C and pneumococcus has been remarkably effective at reducing the incidence of these infections.[1] However, the persistence of group B meningococcal infection, for which there is currently no effective vaccine, and the potential for strain replacement of pneumococcal strains not covered by current vaccines[2] necessitates continued training of both paediatric services and parents in the recognition of severe bacterial infection, as well as ongoing epidemiological surveillance. While vaccine-preventable infections have declined, severe infections including septicaemia, necrotising pneumonias, and bone, joint and soft-tissue infections caused by group A streptococcus and *Staphylococcus aureus* are emerging as important problems and are discussed in this chapter. Hospital acquired infection is an increasingly important cause of bacteraemia in children, causing 23% of all Blood Stream Infection reported to the HPA (Blackburn 2012).

Vaccine-preventable infections

Despite the availability of highly effective vaccines against measles and mumps, low levels of vaccine uptake and waning immunity have resulted in outbreaks of these infections, particularly in older children. Similarly, poor uptake of pertussis (whooping cough) vaccine and the growing population of adults and older children with low levels of pertussis immunity result in outbreaks of pertussis in young children.[3] As pertussis in the first months of life may be fatal, re-vaccination of pregnant women is now recommended to prevent neonatal pertussis.

The increased mortality nationwide associated with the H1N1 influenza pandemic strain has highlighted the importance of influenza vaccine as a means of preventing severe disease in young children.[4] Influenza continues to account for a large number of hospital admissions, highlighting the need to extend the availability and uptake of annual influenza immunisation to the childhood population.

Varicella (chicken pox) remains an important cause of childhood illness in both the community and hospitals, and is associated with life-threatening infection because of secondary bacterial infections, particularly those due to group A streptococcus and *Staphylococcus aureus*.[5] Cases of severe bacterial infections following varicella are often misdiagnosed due to health professionals believing that the child's illness is explained by varicella. Varicella also remains a major concern in immuno-compromised children and in the newborn period. Varicella vaccine is in routine use in some countries,[6] and better epidemiological data on post-varicella complications and comparison with countries using the vaccine is needed to guide future decisions on vaccine use in the UK.

The hepatitis viruses B and C continue to pose a threat of both perinatal and horizontal transmission within affected families. There is no current vaccine for hepatitis C and, in the absence of routine hepatitis B vaccination for all children in the UK, continual awareness of perinatal transmission in high-risk groups is warranted for targeted prevention of transmission within families.

Chapter 11 includes horizon scanning for future vaccines, many of which are particularly relevant to childhood.

Non-vaccine-preventable viral infections

Respiratory viral infections (particularly those due to respiratory syncytial virus, RSV) account for a large proportion of hospital and paediatric intensive-care admissions during the winter months.[7] Outbreaks of enterovirus infection, sometimes associated with life-threatening myocarditis, encephalitis or sepsis-like picture, occur in young children.[8] Herpes simplex infection remains a rare but important cause of encephalitic illness.

The highly successful programme to prevent perinatal transmission of HIV has reduced the numbers of UK-born HIV-infected infants.[9] Unfortunately, the huge burden of HIV infection in many other countries results in new cases continuing to be seen in the UK due to travel and migration of children from high-burden areas.

Life-threatening bacterial infection or trivial illness?

Febrile children are often referred to medical services and for hospital admission in order to rule out life-threatening bacterial infections.[10] Only a small proportion of all children presenting with fever to GPs or Accident & Emergency departments have bacterial infections, and the vast majority suffer from trivial, self-limiting, viral infections. Unfortunately, there are no reliable clinical findings or laboratory tests that clearly distinguish trivial viral illness from early bacterial infection.[11] As a result, a large proportion of the workload of all paediatric services is devoted to investigation and treatment of children with suspected severe bacterial infections. Standard management is to undertake a 'septic screen' including lumbar puncture in young children, and to commence intravenous antibiotics while awaiting the results of bacterial cultures. Only a small proportion of children

undergoing a 'septic screen' will turn out to have a bacterial infection; however, in the absence of an accurate means of distinguishing bacterial from viral infection, treatment with intravenous antibiotics while awaiting results remains the only safe approach. The availability of a rapid test that accurately distinguishes bacterial from viral infection would greatly reduce hospital admissions, intravenous antibiotic usage and investigation of febrile children, and is a priority for child health research.

Case study 7.1

Patient X presented to her GP with a 24-hour history of fever, irritability and vomiting. Her GP thought that she was suffering from a 'viral infection' and advised regular antipyretics. Eight hours later her parents took her to the Accident & Emergency department at her local hospital, where a junior doctor again informed her parents that she was suffering from a 'viral illness'. Four hours later her parents noted that she was drowsy, breathing rapidly and had cold hands and feet. They took her again to the Accident & Emergency department, where she was found to have tachycardia, tachypnoea, prolonged capillary refill time and cold peripheries. A rapidly evolving petechial rash was noted and a diagnosis of meningococcal infection was made. Despite intravenous antibiotics, transfer to intensive care, and ventilatory and inotrope support, she developed multi-organ failure and peripheral gangrene. Despite aggressive intensive care, she died 36 hours after admission.

Comments

The early description of this patient is typical of the many children who present initially to paediatric or GP services with what appears to be an uncomplicated viral illness. A very small proportion of these patients subsequently re-present with life-threatening bacterial infection. Such cases highlight the need for continued awareness of life-threatening bacterial infections.

Specific bacterial infections

Meningococcal disease

Serogroup B meningococcal disease remains a major problem affecting young children. In addition, there has been an increase in the incidence of meningococcal disease due to serogroups Y and W135.[12] Serogroup A meningococcal disease remains a major problem in sub-Saharan Africa, where very large epidemics have occurred, and there have been recent outbreaks of serogroup Y and W135 in Africa and South America.[12] **Vaccination of travellers to regions where meningococcal disease is epidemic with quadrivalent vaccines remains an important public health measure.**

The difficulties in early recognition of meningococcal disease have been highlighted above. Although the disease is readily diagnosed once the characteristic non-blanching purpuric lesions are present, the rash may not be present, and early clinical features overlap with those of trivial viral illness. Limb pain, cold periphery, confusion, vomiting and headache are characteristic features, but are also commonly seen in influenza.[13]

A number of reports have highlighted the improved prognosis in children with meningococcal septic shock and meningitis through early and aggressive intensive care.[14] The most severely affected patients now have a mortality rate below 10% with optimal intensive care. Unfortunately, many of the patients who die or are left with severe complications such as amputations, skin grafting and neurological damage have had delayed or inadequate treatment at early stages of the disease. There is therefore a continued need for parents, university students and healthcare professionals to be provided with information on the early signs and the need for prompt treatment and referral of suspected cases.

Deaths from meningococcal infection are only likely to be eliminated through the introduction of an effective vaccine against serogroup B strains. Two serogroup B protein vaccines are nearing licensure, and their introduction into clinical use is under review by the Joint Committee on Vaccination and Immunisation (JCVI).

Pneumococcal infection

Despite the success of the pneumococcal conjugate vaccine in reducing invasive disease, infection due to non-vaccine strains continues to occur in young children, and increases in the incidence of strains not included in current vaccines have been seen in some countries.[15] There remains concern that vaccine efficacy will be reduced by strain replacement by non-vaccine strains. **It is thus important that surveillance programmes are maintained to identify the strains responsible for invasive pneumococcal disease.**

Emerging Gram-positive infections

Strains of *Staphylococcus aureus* producing the Panton-Valentine leukocidin (PVL) toxin are being seen with increasing frequency in the UK. PVL-producing *Staphylococcus aureus* is associated with a spectrum of severe infections, ranging from boils and relatively minor soft-tissue infection to necrotising pneumonia, septicaemia, multi-organ failure and devastating bone, joint and soft-tissue infections.[16, 17]

Characteristically, patients with severe PVL infections are previously healthy children and teenagers. Minor injuries are sometimes noted preceding the infection. Presentation is characteristically with high fever, muscle aches, abdominal pain and confusion, with progression to shock and multi-organ failure and thrombotic complications.

Case study 7.2

A 14-year-old boy suffered a minor injury to his thigh while playing football. Two days later he developed increasing thigh pain, high fever and confusion. On admission to hospital he had a temperature of 40°C, a heart rate of 140 beats per minute, a respiratory rate of 30 breaths per minute and was confused. Despite commencement of antibiotics, his condition rapidly deteriorated, with the development of hypotension, respiratory failure and multi-organ dysfunction. He was transferred to the paediatric intensive-care unit, where he was given ventilation and dialysis. Exploration of his thigh revealed extensive necrosis and pus formation extending throughout the thigh muscles and into the pelvis. An MRI scan revealed multi-focal osteomyelitis, abscesses in kidney and spleen, necrotising pneumonia and a spinal epidural abscess.

Prolonged treatment with intravenous antibiotics and repeated surgical drainage of his bone and soft-tissue collections was required. His condition slowly improved after 3 months on a paediatric intensive-care unit and a long period of rehabilitation. *Staphylococcus aureus*-producing PVL toxin was recovered from multiple abscess sites and from his blood at the time of admission.

Comments

This case illustrates the severe nature of PVL infection and its propensity to be associated with multi-organ failure, thrombotic complications and destructive damage to bones and soft tissues.

Although the majority of PVL strains causing invasive disease in children in the UK remain meticillin sensitive, antibiotic treatment during the early stage of the disease before sensitivities have been established should cover meticillin-resistant strains. There is evidence that PVL toxin production is decreased through the use of antibiotics such as clindamycin, rifampicin and linezolid.[17] Although there have been no clinical trials, intravenous immunoglobulin has been recommended in severe cases. Early and aggressive detection and surgical drainage of abscesses/infected tissue is essential in the management of such cases. As the strains of PVL may circulate among family members, decontamination of contacts and family members should be undertaken.

In addition to severe disease due to PVL staphylococcal infection, staphylococcal toxic shock syndrome remains an important cause of life-threatening infection and presents with high fever, erythematous rash, conjunctival injection and multi-organ failure. As with PVL staphylococcal infection, intensive-care support is essential and an aggressive search for a focus of staphylococcal infection is required in order to remove the site of toxin production.

Group A streptococcal invasive disease

Invasive group A streptococcal infections are important causes of critical illness in children. The spectrum of disease ranges from soft-tissue infections such as cellulitis to necrotising fasciitis, pneumonia, and bone and joint infections, and may be associated with shock and multi-organ failure.[18]

A significant proportion of life-threatening infections caused by group A streptococcal infection are associated with varicella.[19] Typically, children present after the third or fourth day of the varicella rash with high fever, systemic toxicity and evidence of focal infection. Despite publicity of the dangers of secondary bacterial infection during the course of varicella infection, misdiagnosis of serious invasive bacterial infection as being uncomplicated varicella remains common. Delayed diagnosis is a major factor in the development of devastating consequences of the disease.

Any focal infection or pain in a child with high fever and deteriorating condition should arouse a suspicion of group A streptococcal invasive disease, particularly if there has been preceding varicella. There is a need for better surveillance of invasive group A streptococcal infection in children and its association with varicella.

Otitis media and pharyngitis

Otitis media and pharyngitis are among the commonest causes of children being brought to medical attention. Although a high proportion of patients presenting with otitis and pharyngitis are suffering from viral infections, a significant proportion of cases are caused by bacterial infection, including group A streptococcal pharyngitis, pneumococcal and haemophilus and branhamella otitis media.[20] **Clinical distinction between bacterial and viral causes of otitis media or pharyngitis remains unreliable.**[20] The public health campaign that has been conducted over the past few years to limit antibiotic use in febrile children with otitis media and pharyngitis may have resulted in children with significant bacterial infections not receiving antibiotics. There is concern among paediatric units that they are seeing increased numbers of children with complications of bacterial infection (including scarlet fever, bacterial tracheitis, mastoiditis, sinusitis, and other invasive infections following tonsillitis and otitis media) who have not received antibiotics in the belief the illness was 'viral'. The publication of a definitive placebo-controlled trial of antibiotic use in otitis media has confirmed that antibiotic treatment is beneficial in otitis media in young children and lessens the risk of complications.[21]

There is clearly a difficult judgement to be made by all those involved in the care of febrile children with signs of upper respiratory tract or otitis media infection. **While limiting the use of antibiotics remains an important public health measure to reduce the spread of antibiotic resistance, the consequence might be inadequate or late treatment of patients with severe bacterial**

infection. There is concern among the paediatric community that the pendulum may have swung too far in advocacy of the need to reduce antibiotic use in febrile children with upper respiratory tract infections. While restriction of antibiotic usage in mildly ill children is warranted to prevent the development of antimicrobial resistance, better publicity of the severe consequences of missed or late diagnosis of bacterial infections also needs to be provided to those undertaking primary and secondary care of febrile children. Future research may make it possible to distinguish bacterial from viral upper respiratory infections more easily.

Gastrointestinal bacterial infections

Young children continue to be the major group at risk from salmonella, campylobacter and *E. coli* infections associated with gastroenteritis and they suffer a range of more severe complications. Salmonella disease should particularly be suspected in patients with travel to Africa or Asia.

Outbreaks of haemolytic uremic syndrome due to *E. coli* O157 remain an important paediatric problem leading to admissions with renal failure and sometimes multi-organ failure. Many of the *E. coli* outbreaks are related to contaminated food sources.[22] Children present with a short history of bloody diarrhoea followed by acute renal failure, thrombocytopenia and anaemia. Supportive treatment to correct dehydration and provide renal support is essential, together with a blood transfusion in severely anaemic patients.

Respiratory infections

Acute respiratory infections are a major cause of attendance by children to primary and secondary care, as well as tertiary hospital admissions. RSV is the most common cause of a bronchiolitis picture in young infants and is a particular danger to children who have chronic lung disease or oxygen dependence. Admissions of infants with bronchiolitis to paediatric units and intensive-care units accounts for a significant proportion of all admissions during the winter months. Treatment is largely supportive, with oxygen, continuous positive airway pressure (CPAP) and ventilation for those with severe involvement.[23] RSV remains an important cause of nosocomial infection in paediatric wards during the winter months. While cohorting of children with bronchiolitis is usually undertaken as a means of reducing the spread in children's wards, this depends on rapid viral diagnosis as only a proportion of the children presenting clinically with bronchiolitis have RSV and others may have influenza or other viral infections. The development of a vaccine against RSV remains one of the highest priorities for paediatric services worldwide in view of the high admission rate and continued burden from RSV infection.

Severe respiratory illness in young infants due to influenza or other respiratory viruses is difficult to distinguish from RSV and the availability of rapid multiplex PCR diagnostics is increasingly showing that severe respiratory infection is caused by a spectrum of viruses with overlapping symptoms and signs.

Bacterial and viral co-infection

There is increasing evidence that respiratory infections due to viruses and bacteria are not clearly distinct problems, but that viral infection may predispose to severe invasive bacterial infection. Epidemiological and animal studies have shown that initial influenza infection alters the immune response and facilitates invasive bacterial infection. As improved viral diagnostics have entered clinical use it has become increasingly apparent that many patients admitted with severe pneumonia have one or more viral pathogens (including influenza, RSV, parainfluenza, rhinovirus or adenovirus) detected in their upper airway, while also having features of high white blood cell count, high C-reactive protein (CRP) and the presence of bacteria such as Staphylococcus aureus, pneumococcus or group A streptococcus in airway secretions. As bacteraemia is only present in a small proportion of bacterial pneumonias, the problem of how to identify the bacterial aetiology of pneumonia, particularly in patients who also have viruses detected in the upper airway, has become a major problem for paediatric services.[24] While it is prudent to treat all patients with severe pneumonias with antibiotics, even if viral pathogens such as influenza are detected in the upper airway, research on the interaction between bacteria and viruses in predisposing patients to invasive infections is a priority.

Case study 7.3

A 3-year-old previously well male developed high fever, cough and breathlessness and was admitted to hospital. Two older siblings had suffered from fever and cough in the preceding week. On admission he was tachypnoeic, tachycardic and poorly perfused, and X-ray showed evidence of bilateral pneumonic changes. Laboratory investigations revealed a white count of 30,000, and a C-reactive protein of 200 mg/l. Bacterial cultures from blood and the upper airway were negative. Viral studies revealed the presence of influenza A as well as rhinovirus.

He required admission to intensive care, prolonged ventilation and intravenous antibiotics. His condition slowly improved and he recovered after a 7-day period of paediatric intensive care.

Comments

This patient is typical of the large numbers of infants admitted with severe pneumonia who have features of bacterial infection with high C-reactive protein and white count, but in whom the only pathogens identified are upper airway viruses. The question remains as to whether viral infections in some patients are associated with a 'cytokine storm' and an inflammatory response typical of bacterial infection, or whether the virus has laid the ground for lower airway invasion by bacteria. Distinction between bacterial and viral causes of pneumonia remains a major problem.

Hepatitis B and C

Despite targeted vaccination to prevent mother-to-child transmission of hepatitis B, the global prevalence of hepatitis B and C infections, and the influx of patients from countries where these viral infections are prevalent, necessitates continued efforts to identify and treat affected patients. In view of the vast experience of adult hepatitis clinics in the treatment of hepatitis B and C infected patients, shared care with adult treatment services is a model which should be more widely adopted.

Childhood tuberculosis

Tuberculosis (TB) continues to be an important health problem in children, particularly among ethnic groups from India, eastern Europe and Africa, including refugees and families with social deprivation.[25] **A high proportion of childhood TB cases continue to arise from a family member with active infection, highlighting the need for continued public health efforts to prevent intra-family transmission by adequate contact tracing and preventive treatments.**

Diagnosis of childhood TB is particularly difficult because of the insidious nature of the disease, the non-specific nature of the symptoms and poor yield in microbiological diagnosis due to the pauci-bacillary nature of the disease and the difficulties in obtaining sputum in children.[25] New diagnostic approaches, including saline-induced sputum induction, are not yet widely adopted in the UK despite clear evidence of their value in studies from Africa. An important future research agenda is the development of better diagnostic tests for TB in children, as the vast majority of children with TB are currently treated on clinical suspicion alone and microbiological confirmation of the diagnosis is successful in only a small proportion of cases. Continued awareness of the threat of TB, the need to aggressively find and trace contacts of adult cases of TB, and the need to maintain BCG immunisation in high-risk populations are all important priorities for control of childhood TB.

Kawasaki disease

Kawasaki disease (KD) has emerged as an important and common childhood condition with worldwide occurrence. **KD is now recognised as the commonest cause of acquired heart disease in children in developed countries, and as an important cause of long-term cardiac disease in adult life.**[26] The aetiology remains unknown but current thinking suggests that KD is an unusual inflammatory response to one or more as-yet-unidentified pathogen(s), occurring in genetically predisposed individuals.

Although the majority of patients with KD recover without long-term consequences, the disorder is associated with vasculitis affecting the coronary arteries, which results in coronary artery aneurysms in over 20% of untreated patients. Around 2–3% of untreated cases die as a result of coronary artery thrombosis, myocardial infarction or, rarely, aneurysm rupture. Patients with giant (8 mm or more) coronary artery aneurysms are at long-term risk of developing aneurysm thrombosis, or coronary artery stenosis and myocardial infarction, even years after the acute illness.

Intravenous immunoglobulin (IVIG) has been shown to reduce the risk of aneurysm formation to approximately 5%. Patients who do not respond to IVIG are at increased risk of developing coronary artery aneurysms. There is now evidence that patients unresponsive to IVIG benefit from additional treatments, including steroids.[26] In the UK, lack of awareness of KD among GPs and paediatric services results in the diagnosis often being considered too late to provide optimal treatment to prevent coronary artery aneurysms.

There is a need for increased awareness of KD by GPs and paediatric services, earlier consultation with paediatric infectious-diseases specialist units for advice on treatment, and further randomised treatment trials to establish optimal identification and treatment of IVIG non-responsive cases.

Opportunities

The implication of growing rates of antimicrobial resistance is the need for paediatric services to reduce unnecessary antibiotic usage. To achieve this a major priority for future research is better clinical or laboratory distinction of bacterial and viral infection. Rapid tests which accurately distinguished bacterial from viral infection would result in reductions in hospital admissions, unnecessary intravenous antibiotic usage and investigations of febrile children. Improving the evidence base around the interaction between bacteria and viruses in predisposing to invasive infections is also an important area that could lead to better clinical care and potentially more targeted antibiotic use.

Given the past successes, vaccine development is clearly key to addressing the remaining burden due to infections. In view of the high admission rate and continued burden from RSV infection this is a particular priority.

The corner stone of improving services lies in developing surveillance systems. This can both identify service issues but also be used to help understand the epidemiology of childhood diseases. The two identified areas within this chapter where additional information could immediately impact on current practice, particularly vaccination policy, are:

- Better surveillance of varicella in children, and of life-threatening bacterial infection in the weeks following varicella
- Better surveillance of invasive group A streptococcal infection and PVL staphylococcal infection in children and their association with varicella.

Despite the potential impact that improved diagnostics, surveillance and the development of new vaccines could have, the effective implementation of current public health interventions remains central to reducing the burden of infectious disease in childhood. Continued awareness of the threat of TB, the need to aggressively find and trace contacts of adult cases of TB, and the need to maintain

BCG immunisation in high-risk populations are all important priorities for control of childhood TB. Because of the difficulty in clinical diagnosis of meningococcal disease, there is a continued need for parents, university students and healthcare professionals to be provided with information on the early signs and the need for prompt referral of suspected cases. Ensuring high vaccine uptake rates is likely to be the single most effective intervention in reducing the burden of infectious disease. These activities and other similar interventions should not be lost sight of when considering the opportunities to reduce infectious disease in childhood.

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Chapter 8

Life stage: Adolescents and young adults

Chapter authors

Nigel Field[1], Laura Shallcross[2], Russell M Viner[3], Robert W Aldridge[4], Anne M Johnson[5]

1 NIHR Academic Clinical Lecturer, University College London, and Public Health Registrar, London Deanery
2 MRC Clinical Research Fellow, University College London, and Public Health Registrar, London Deanery
3 Professor of Adolescent Health, University College London
4 Wellcome Trust Research Training Fellow, University College London and Public Health Registrar, London Deanery
5 Professor of Infectious Disease Epidemiology, University College London

Overview

Adolescence and young adulthood is a period of rapid physical and social development. Challenges relating to lifestyle and behaviour are encountered for the first time, increasing the risk of certain infectious diseases. Sexually transmitted infections (STIs), vaccine-preventable disease and health-service design are the main themes within this chapter.

This is an important period for sexual health as commissioning responsibility transfers to local authorities and co-ordinated effort is required across young people's services to maintain sexual health as a priority. Under-25s experience the highest rates of STIs and safe sexual behaviour is a key life skill. Sex and relationship education can help young people acquire appropriate knowledge before their first sexual experience and should be strengthened.

Recent increases in vaccine-preventable diseases such as pertussis have been observed in young people, and consideration should be given to the infrastructure required to implement vaccine programmes targeted at adolescents.

Health-service use by adolescents and young adults is dependent on confidentiality, perceived and actual respect for young people's rights, and accessibility; these factors must be considered when designing services for this group.

Introduction

Young people aged 10–24 years, encompassing adolescence and young adulthood, made up 19% of the UK population in 2010. Traditionally, this period of life has been seen as the healthiest. The transition to adulthood is an exhilarating phase of life, full of opportunity and often free of dependents. Not only do young people provide society with 'energy, innovation, productivity, and progress' and an economic dividend,[1] but a healthy adolescence will underpin a healthy adulthood and influence the health outcomes of future generations.[2]

At the same time, rapid physical and social development introduce new challenges relating to lifestyle and behaviours that may increase the risk of infectious disease and offer opportunities for prevention and interventions.[3] Dramatic brain development allied with puberty drives the initiation of risk behaviours (over 90% of lifetime tobacco, alcohol and drug use is initiated in adolescence), first sexual activity and sexual risk taking. Young people also assume responsibility for their own health and healthcare access from parents and guardians. Over 75% of lifetime mental health problems, obesity, asthma and autoimmune conditions first present before age 25.[4] Health and behaviours begun in adolescence therefore strongly influence health outcomes across the life course.

Recently, there has been an epidemiological shift in traditional morbidity and mortality patterns, so that adolescence is no longer the healthiest time of life**. For the first time in human history, mortality rates among those aged 15–24 are now above rates for those aged 1–4, and adolescence is the only life phase where substantial improvements in health outcomes have not occurred over the past 50 years**.[1, 3, 4] There is a risk that the health issues and preventative opportunities for this population group are insufficiently recognised, falling between child and adult healthcare, and it is therefore timely that the 45th session of the United Nations (UN) Commission on Population and Development in April 2012 selected 'Adolescents and youth' as its core theme.

Young people's health behaviours are strongly influenced by the social, economic and political milieu.[5] **Powerful social determinants of peer influence and neighbourhood engagement, together with the family, schooling and structural determinants, influence young people's health from an early age.**[6, 7] Previous life experience, education and deprivation influence the risk of infectious disease outcomes for young people, who may suffer inequalities such as inadequate vaccination, poor health promotion and education opportunities, and barriers to services. **This is also an age group where social mixing, in peer groups, schools and higher education institutions, may have a profound impact on the acquisition of serious infections, including STIs, measles, meningococcal meningitis and influenza.**

Sexually transmitted infections

Chlamydia and gonorrhoea

Most people will have sex for the first time between the ages of 15 and 24 (the median age at first intercourse is 16 years),[8] and this is a critical phase in developing good sexual health and safe, happy relationships. Among sexually active people aged 16–24, 87% reported using at least one method of contraception, but only 41% of men and 31% of women used condoms every time they had sex in the previous 4 weeks.[9] **Diagnoses of new STIs have tended to increase over the past 10 years, and young people under 25 experience the highest rates of STIs.**

There are particular healthcare challenges associated with STI control for this group. These challenges relate to the asymptomatic nature of many STIs and the barriers to treatment, such as social stigma, risk awareness and service access,[10] demonstrated by the gonorrhoea outbreak described in Case study 8.1, one of a number of similar outbreaks of gonorrhoea and syphilis occurring recently among young adults in England.[11, 12] This is an important period of transition for sexual health services, as commissioning responsibility transfers from primary care trusts to local authorities as part of the **Health and Social Care Act 2012** reforms. **Effective working across local government, health-service providers and public health teams will be essential to ensure that sexual health remains a priority.**

Gonorrhoea is the second most common bacterial STI in the UK (chlamydia is the first). Young people and men who have sex with men are at the highest risk; in 2011, 57%

(6,678/11,778) of heterosexual gonorrhoea infections were in people aged 15–24 years.[13] Risk factors, as for chlamydia, include frequent change of partner, sex without condoms and previous STI diagnoses.

Case study 8.1

In August 2011, a local sexual health service in the north of England noted a marked and sustained increase in gonorrhoea diagnoses among young heterosexual adults living within a small geographical area. Background incidence had been 2 to 4 cases per month, but rose to 7 to 12 cases per month. Over 15 months from April 2011, 98 gonorrhoea cases were diagnosed (Figure 8.1). Of these, 69% were people aged 16–24 years and 53% were women. Concurrent STIs were diagnosed in 38%, emphasising the high level of STI risk within this small group of people. The majority of those infected (63%) came from deprived backgrounds.

Three key public health actions were taken: (i) enhanced surveillance to investigate the outbreak epidemiology, identifying complex overlapping sexual networks, with some chains of transmission linking up to five cases (Figure 8.2); (ii) dual testing of chlamydia and gonorrhoea on samples from a defined region by the National Chlamydia Screening Programme (NCSP) as a short-term control measure, with 24 confirmed gonorrhoea cases; (iii) recruitment of young people's organisations and healthcare services to contact those at most risk and raise awareness of STI infection, prevention, diagnosis and treatment, including a social media advertising campaign.

Importantly, this demonstrates a multifaceted approach, targeting individuals and communities in the management of such complex outbreaks.

Chlamydia control

The NCSP is one of the largest national public health interventions aimed specifically at young people in England. The programme targets sexually active women and men under 25 for opportunistic testing to diagnose and control chlamydia infection.[14] In 2010, the Health Survey for England (HSE) found 17% of men and 27% of women in the general population aged 16–24 had been tested in the previous 12 months, with testing rates higher among those with known STI risk factors.[15] The Health Protection Agency estimate is slightly higher: 20% of young men and 41% of young women were tested in 2011, with 7.1% of tests resulting in a positive diagnosis.[16] The programme has not yet reached the activity levels previously predicted to impact significantly on chlamydia prevalence, and its cost-effectiveness is debated,[17] but recent modelling data point to a reduction in prevalence driven by the screening programme.[18] The Health Protection Agency is working with the Government to improve cost-effectiveness and the targeting of those at highest risk within the NCSP, with the aim that all sexually active young people are routinely offered screening and opportunities to discuss sexual health as part of primary care and sexual health consultations.

Human papillomavirus

Persistent infection with high-risk human papillomavirus (HR-HPV) types is necessary for development of cervical cancer,[19] and low-risk HPV (LR-HPV) types cause most genital warts.[20] Genital HPV is typically acquired through sexual contact in adolescents and young adults; a large cross-sectional survey in Britain detected HR-HPV in 28% of women aged 18–24.[21] The incidence of diagnosed genital warts is increasing, with over 76,000 diagnoses in sexual health clinics in 2010/11, such that genital warts are the most frequently diagnosed viral STI in UK sexual health clinics, and this is at significant cost.[13]

Since 2008, females aged 12–13 years and a catch-up group of those up to 18 years have been offered a bivalent HPV vaccine, Cervarix®, which effectively prevents infection with two HR-HPV types (16 and 18) responsible for most cervical cancer. From September 2012, the UK will use Gardasil®, which also protects against LR-HPV types (6 and 11) that cause the majority of genital warts. This programme has been successful, with over 84% of girls aged 12 in September 2010 receiving three vaccine doses by the end of August 2011.[22] It has been estimated that vaccinating girls before first sex will prevent at least 60% of cervical cancer,[23] and we can also now expect large reductions in genital warts in women and, due to reduced heterosexual transmission, men. The extent to which vaccine uptake varies by socio-economic status or ethnicity is not yet known and it will be important to assess these potential inequalities.

HIV

Although most HIV positive children are infected around the time of birth, as for other STIs, sexually active young people are also at risk of acquiring HIV. The highest proportion of likely recent HIV infections (infected in the previous 4-6 months) among heterosexuals was in women and men aged 15-24 years, similarly, over one quarter of newly diagnosed men who have sex with men (MSM) under 35 years were recently infected[24]. HIV awareness and public health prevention activities, such as promotion of condom use, are therefore critical to achieve reduction in both risk and infections, particularly for young MSM. Highly active antiretroviral treatment (HAART) has signficantly improved long-term survival of HIV-infected children, with increasing numbers transitioning into adult services.[25] In 2011, 2,241 young people aged 15-24 and 752 children aged 1-14 were accessing HIV care in England[26], of whom half were born outside the UK.[27] This group face a number of challenges, including psychological issues associated with their diagnosis, medical issues associated with infection and long-term treatment and, not least, difficulties in establishing sexual relationships.[28] Notably, HAART refusal or poor adherence appears more common in young people than adults.[29] Ensuring smooth transition from paediatric to adult care may be complex, but it is essential. There is a need for joint clinics, where paediatricians and adult physicians can work together with their patients to support this transition and help these young people live normal lives.

Vaccine-preventable disease in adolescence

Routine immunisation, which includes a booster containing tetanus, diphtheria and polio given to those aged 13–18, has been highly successful in achieving significant reductions in the burden of vaccine-preventable disease. Disease risk is largely mitigated by accepting childhood vaccination, a decision taken on the adolescent's behalf by their parents or guardian. Overall vaccine coverage is high, but varies between vaccines. **In 2010/11, 89% of 2-year-olds were fully immunised against measles, mumps and rubella (MMR), whereas 96% were fully immunised against diphtheria, tetanus, polio, pertussis and *Haemophilus influenzae* type b.**[30] These data forecast good protection for the next generation of adolescents. Vaccination against rubella is particularly important in this age group because this can have a major impact on reproductive health. Rubella infection in pregnancy causes birth defects, stillbirth and miscarriage. The impact of mumps includes orchitis, which affects one-fifth of males infected after puberty, leading to a (usually temporary) drop in sperm count in approximately 7–13% of infected men.

Adolescents may experience increased exposure to infectious diseases in the community, because they have comparatively high rates of social contact, in settings such as schools, colleges, universities and sports teams. Young people may also be at increased risk through travel. The risk is exacerbated in closed populations such as boarding schools or institutional settings, where high-frequency close social contact can be the catalyst for large outbreaks.[31, 32] The risk of infection increases if population vaccination coverage declines. This is illustrated by the rise in measles cases between 2006 and 2009, following unfounded historical concerns over the safety of the MMR vaccine that caused reduced uptake when the current adolescent generation were children. For mumps and pertussis there is some evidence that adolescents and young adults vaccinated in childhood may experience waning immunity, leaving them susceptible to infection, particularly in the context of a school- or university-based outbreak (see Case study 8.2).[33, 34]

Case study 8.2

Between December 2011 and March 2012, a major pertussis outbreak was reported from a large boarding school in England (see Figure 8.3). A total of 55 suspected cases were notified, 19 of which were confirmed by nasal swab or serology. Almost all (54 cases) occurred in pupils, two-thirds of whom were children aged 13–15 years. Although all cases had received primary vaccination,[30] only five children had received a pre-school booster dose, suggesting waning immunity from the vaccine may have contributed to this outbreak. Following a full risk assessment, the decision was taken to mass-vaccinate pupils and staff members. This presented a logistical challenge as the school closed for Easter at the end of March, but 62% of pupils and 22% of staff were vaccinated and no new cases were reported when school resumed for the summer term.

Pertussis immunity is estimated to wane 4–20 years after natural infection and 4–12 years after vaccination, although vaccinated cases tend to display milder symptoms.[34] In the UK, a pertussis-containing pre-school booster vaccine was introduced in 2001, so children currently aged 16 or above are likely to have received their last pertussis-containing vaccine in infancy. Recently, increasing numbers of confirmed pertussis cases in adolescents and adults have been reported from countries with long-standing vaccination programmes.[35, 36] This may be partly explained by improved case ascertainment and cyclical secular trends, but is also likely to reflect, in part, waning immunity. Some countries, including the USA,[36] Australia[37] and parts of Europe,[38] have introduced an adolescent booster dose of pertussis vaccine for which clinical effectiveness is proven. The cost-effectiveness of vaccinating this age group is still under review due to uncertainty about the indirect protection afforded to infants.

Health services for adolescents and young adults

The Department of Health and the World Health Organization have recognised the importance of providing services that are 'youth friendly' to improve health outcomes at this age. More than with any other age group, health-service use by adolescents and young adults is dependent on confidentiality, perceived and actual respect for young people's rights, accessibility (opening hours, nearness to schools and colleges, accessibility by public transport) and gender choice of provider. Young people, particularly those at the highest risk, will forego needed healthcare if they perceive that services do not meet their needs.[39, 40]

Opportunities

Over 60% of young adults attend their general practice at least once a year.[41] This is an opportunity for GPs to engage young people and reduce their risk of a range of infections, through health and travel advice, appropriate screening and vaccination. Linked to this, healthcare services for adolescents and young adults need to be designed to appeal to and cater for the needs of this group in order to be successful and to ensure a smooth transition from paediatric to adult services. An important example is that such services are offered to HIV positive young people.

The move to commissioning of sexual health services within local authorities brings significant challenges but also raises opportunities for dedicated services to work together to improve young people's health. **Under the new arrangements, a priority should be that these services – including personal, social and health education (PSHE) programmes in schools, drugs and alcohol harm reduction, and sexual and reproductive health – are carefully co-ordinated across provider sectors**. Specific

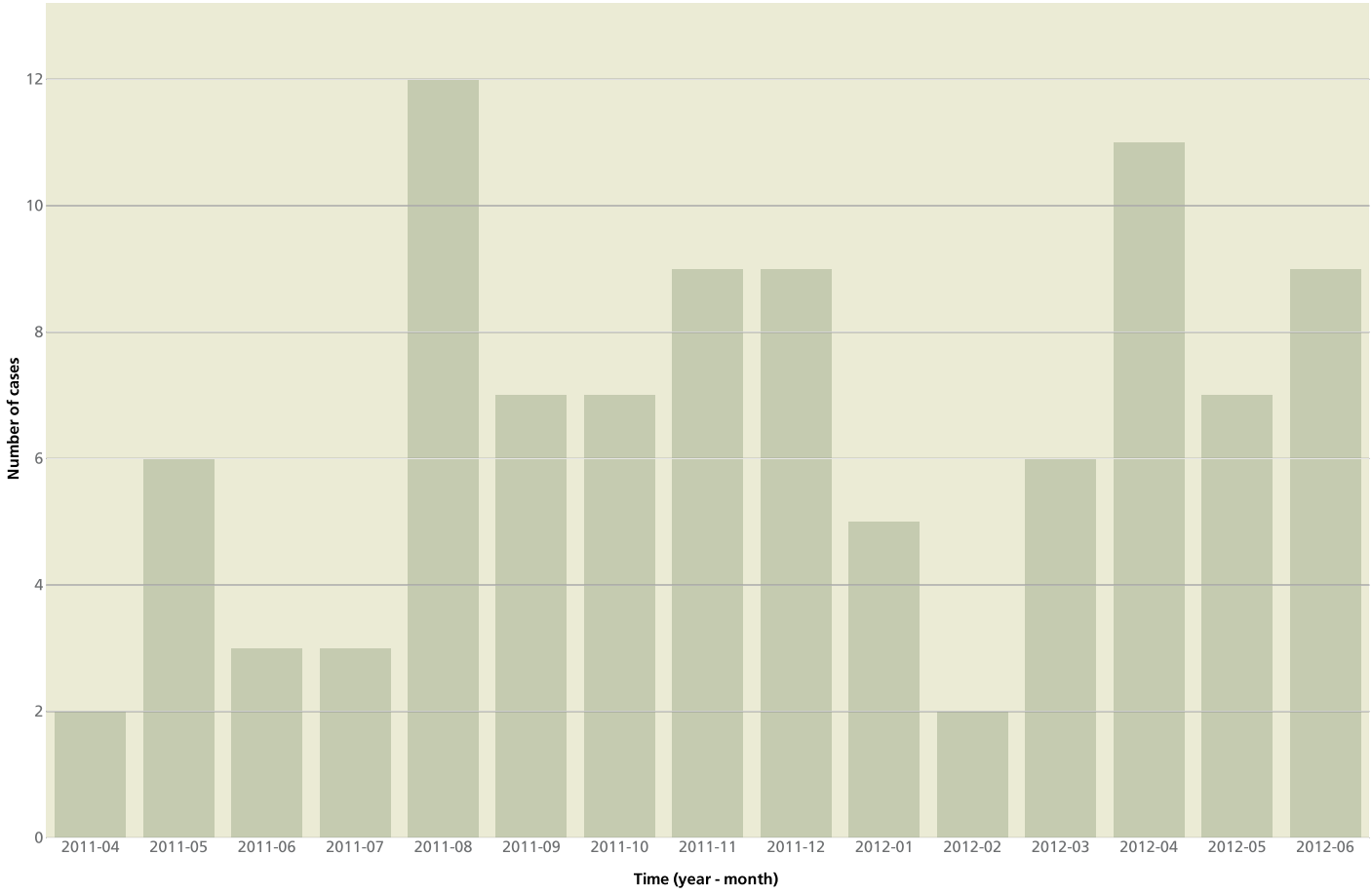
research is needed to provide an evidence base and guidance across sexual health and social services to develop the content and structure of model sexual health services within the new commissioning structures.

Safe sexual behaviour is a key life skill to ensure healthy intimate relationships and prevent STIs. Young people ideally acquire the necessary education to develop this life skill, which itself may delay first sex, before their first sexual experience. To this end, the Government has committed to a review of PSHE, and the House of Lords Select Committee on HIV and AIDS in the United Kingdom has called for broader sex and relationship education within the curriculum,[10] for example to encompass relationships and stigma. The House of Lords recommendation needs to be supported and this work should be taken forward as a matter of urgency.

Recent events have shown adolescents to be at increased risk of some vaccine-preventable diseases. The Joint Committee on Vaccination and Immunisation has already recommended a meningococcus group C adolescent booster vaccination, which is being rolled out in 2013, and there is ongoing consideration of the cost-effectiveness of offering pertussis, varicella and influenza vaccines to adolescents. It seems likely that adolescent vaccines will play a growing role in national vaccination programmes.

Public Health England and organisations implementing major public health interventions such as new vaccination programmes now need to consider how to address the complex systems and infrastructure required to deliver potential new vaccines to young people. Robust health-service evaluations of major interventions directed at young people (e.g. the NCSP and the HPV vaccination programme), to understand their impact and reach, are a clear priority in their own right. These will provide the essential evidence base for good policy decisions and for cost effective implementation of future programmes.

Figure 8.1: Gonorrhoea cases diagnosed in heterosexuals in a town in North England, April 2011 to June 2012



Source: The Outbreak Control Team convened by North East Health Protection Unit. HPA.

Figure 8.2: Sexual networks identified in an area of the North of England through enhanced surveillance

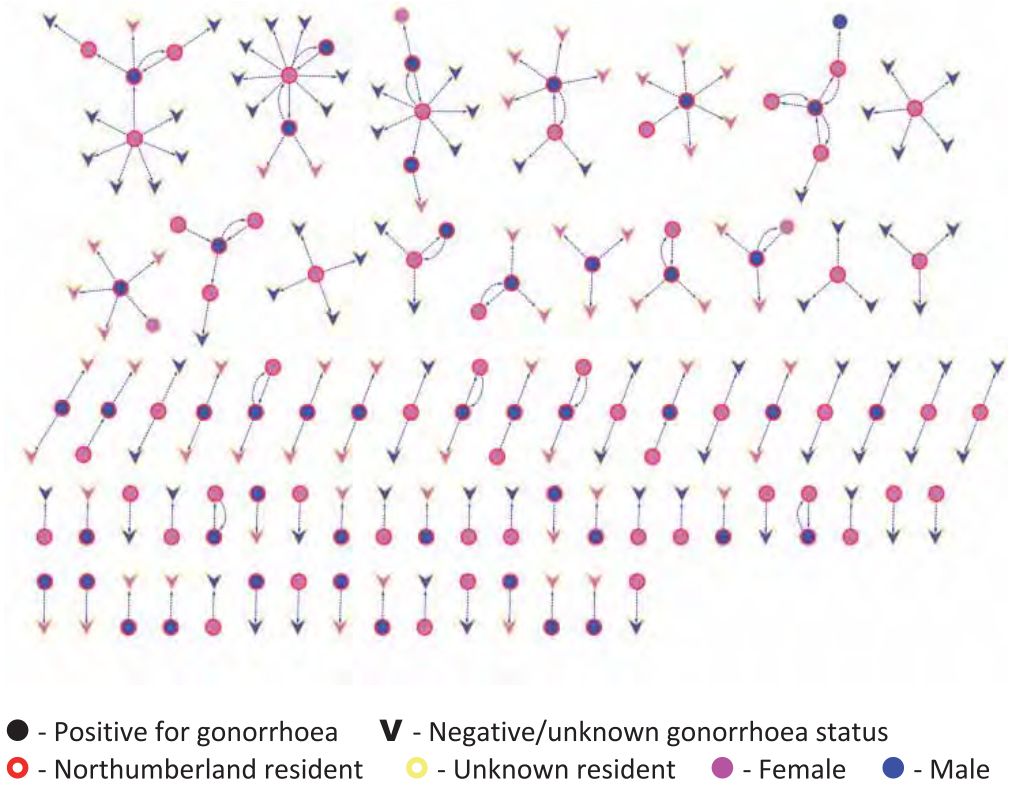
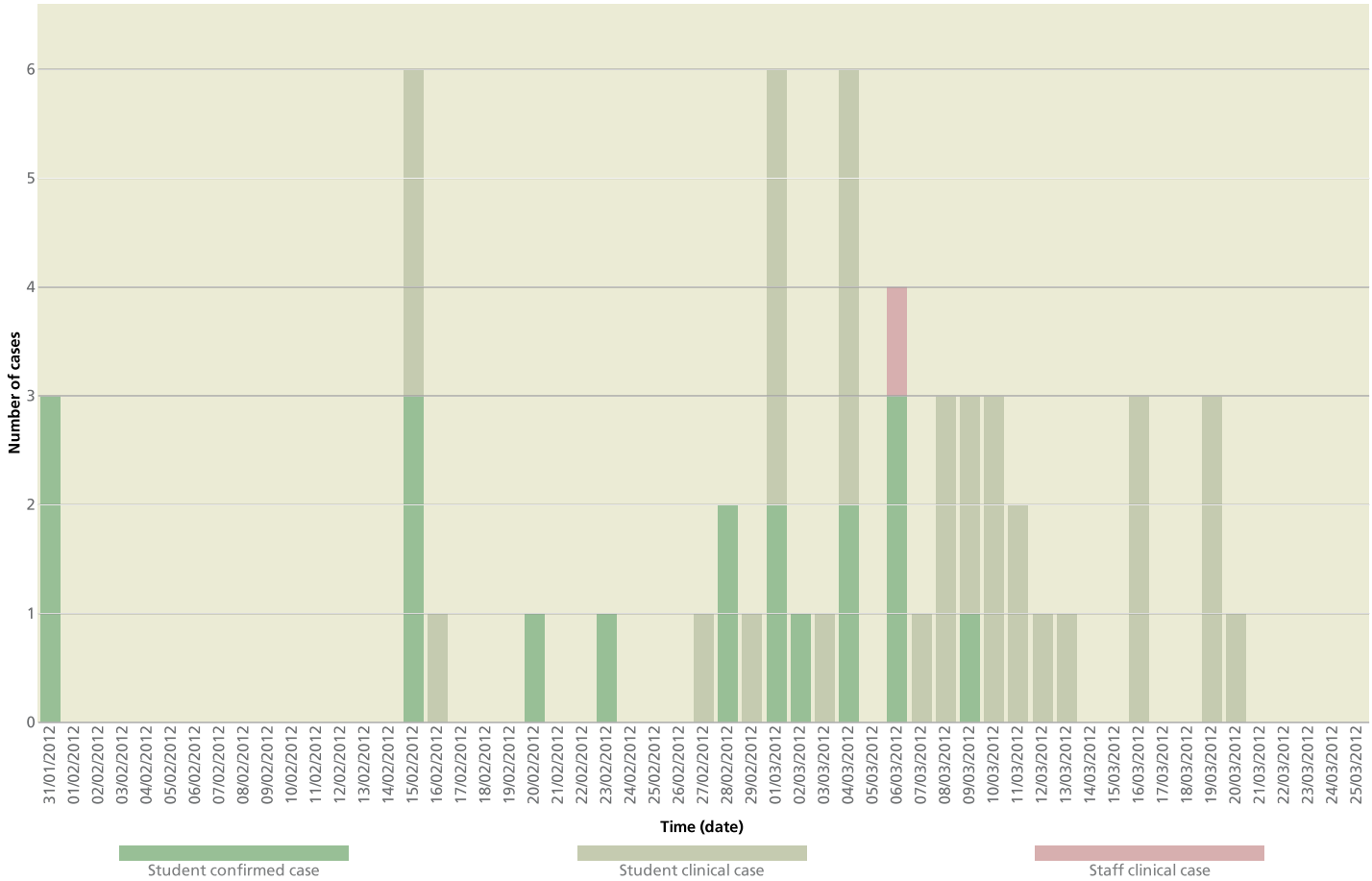


Figure 8.3: Clinical and confirmed cases of pertussis in students boarding at a school in South East England, January-March 2012



Source: The Outbreak Control Team convened by Thames Valley Health Protection Unit, HPA.

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Chapter 9

Life stage: Adult

Chapter author
E L C Ong[1]

1 Consultant Physician and Honorary Senior Lecturer, Department of Infection & Tropical Medicine, Royal Victoria Infirmary, Newcastle upon Tyne

Overview

While most people are physically healthy at the adult life stage, there are particular challenges relating to lifestyle and behaviours that may increase the risk of infectious diseases and offer opportunities for prevention and interventions. Previous life experience, education and deprivation influence the risk of infectious diseases for such age groups, and in particular migrant populations, travellers and offenders, in respect of blood-borne viruses such as hepatitis C, hepatitis B and HIV, tuberculosis and malaria.

The majority of long-term migrants to the UK are young adults and they will have a similar range of health concerns to UK-born people in the same age bracket. Health risks to the non-UK-born population living in the UK can continue for many years after their arrival in the UK. Primary care practitioners play a vital role in early identification of infectious diseases such as hepatitis C and HIV, as this can improve health outcome. Consideration of patients' country of birth when evaluating their risk exposure will aid differential diagnosis of presenting symptoms.

UK residents travelling to visit friends and relatives in their country of origin are the major risk group for UK reports of several important travel-associated diseases, including malaria.

Offenders are a challenging population to treat effectively, as their health and social needs are extensive and diverse. However, their detention represents an opportunity to engage with normally excluded populations, and **prison health services can offer diagnostic tests as part of screening or active case-finding programmes such as testing for blood-borne viruses.**

Infection burden among migrant populations

Migrants comprise an increasing proportion of the UK population. In 2010, 12% of the total UK population were born abroad, whereas in 2001 the figure was nearer to 8%.[1]

This population comes from all over the world. While the majority of long-term migrants will have a similar pattern of health needs as UK-born individuals of the same age group, a small sub-population bears the greatest burden of infectious diseases. In 2010 about 60% of newly diagnosed cases of HIV, 73% of reported tuberculosis cases, and 80% of hepatitis B infected UK blood donors were born abroad.[2]

Case study 9.1

A 26-year-old Zambian student presented with a chronic dry cough of 6 weeks' duration and night sweats. He consulted his GP when he noted that he had lost 6 kg of weight. He had arrived in the UK with his family 6 years previously. On examination, he was noted to have bilateral non-tender cervical lymphadenopathy. A chest radiography showed characteristic bilateral perihilar enlargement and an induced sputum smear showed presence of acid fast bacilli, which subsequently grew a fully sensitive *Mycobacterium tuberculosis* complex. He was offered HIV testing and was shown to be positive with a CD4 count of 60 cells per cubic millimetre (indicating late diagnosis of HIV infection). The blood-borne viral screening tests showed hepatitis B core antibody was positive but surface antigen negative, hepatitis C antibody was negative and hepatitis A IgG was positive. Screening for sexually transmitted infections, including syphilis and gonorrhoea, was negative.

He successfully completed antituberculosis treatment and started on antiretroviral therapy. Contact tracing and partner notification for both tuberculosis and HIV were undertaken.

Comments

This case demonstrates the clinical challenges that a medical practitioner encounters in clinical practice with a patient presenting with multiple infectious diseases.

Primary care practitioners play a pivotal role in early identification of infectious diseases, as there is strong evidence that people diagnosed late with HIV have a tenfold increased risk of death within one year of diagnosis compared with those diagnosed promptly. Yet the most recent data, from 2011,[3] show that heterosexuals born outside the UK are more likely to be diagnosed late than those born in the UK.

National UK HIV testing guidelines in 2008[4] and recent recommendations by the National Institute for Health and Clinical Excellence (NICE)[5, 6] have supported the offer of HIV antibody testing in geographical areas where the prevalence of HIV is 1 in 2,000 or greater. **Using indicator diseases of HIV[7] to target testing is one of the clinical approaches in primary and secondary care settings to reduce the current 25% of late presenters of newly diagnosed HIV.**[8] In a recent national audit of HIV testing,[9] only 10% of newly diagnosed HIV cases in 2010 were identified in a primary care setting.

Patients' country of birth should be regarded as a factor in risk assessment and a guide in the diagnosis of presenting symptoms not only for HIV but also for tuberculosis (TB) and hepatitis B. This is because a higher proportion of non-UK-born TB cases present with extra-pulmonary disease (54% in 2010, compared with 31% in the UK-born).

The total number of TB cases reported in the UK increased by 24% between 2001 (6,864 cases) and 2010 (8,483 cases). This increase is mainly due to increased case numbers in the non-UK-born population. In the UK-born population, case numbers and rates have remained stable throughout the past 10 years. The highest rates of TB in the UK-born are in minority ethnic groups.

About 5–10% of people who are infected with TB (but are not infected with HIV) become symptomatic at some time during their life but the infection can remain latent for many years. People co-infected with HIV have a higher risk of disease. Routine offering of HIV testing is recommended in any adult with a diagnosis of TB. In 2010, in England, Wales and Northern Ireland, 4.9% (378/7,658) of TB cases aged 15 and over were co-infected with HIV. This proportion peaked at 9% in 2003 and 2004.[10, 11] It is essential that a co-ordinated approach to the clinical management and notification of these infections is in place to ensure appropriate care and public health action.

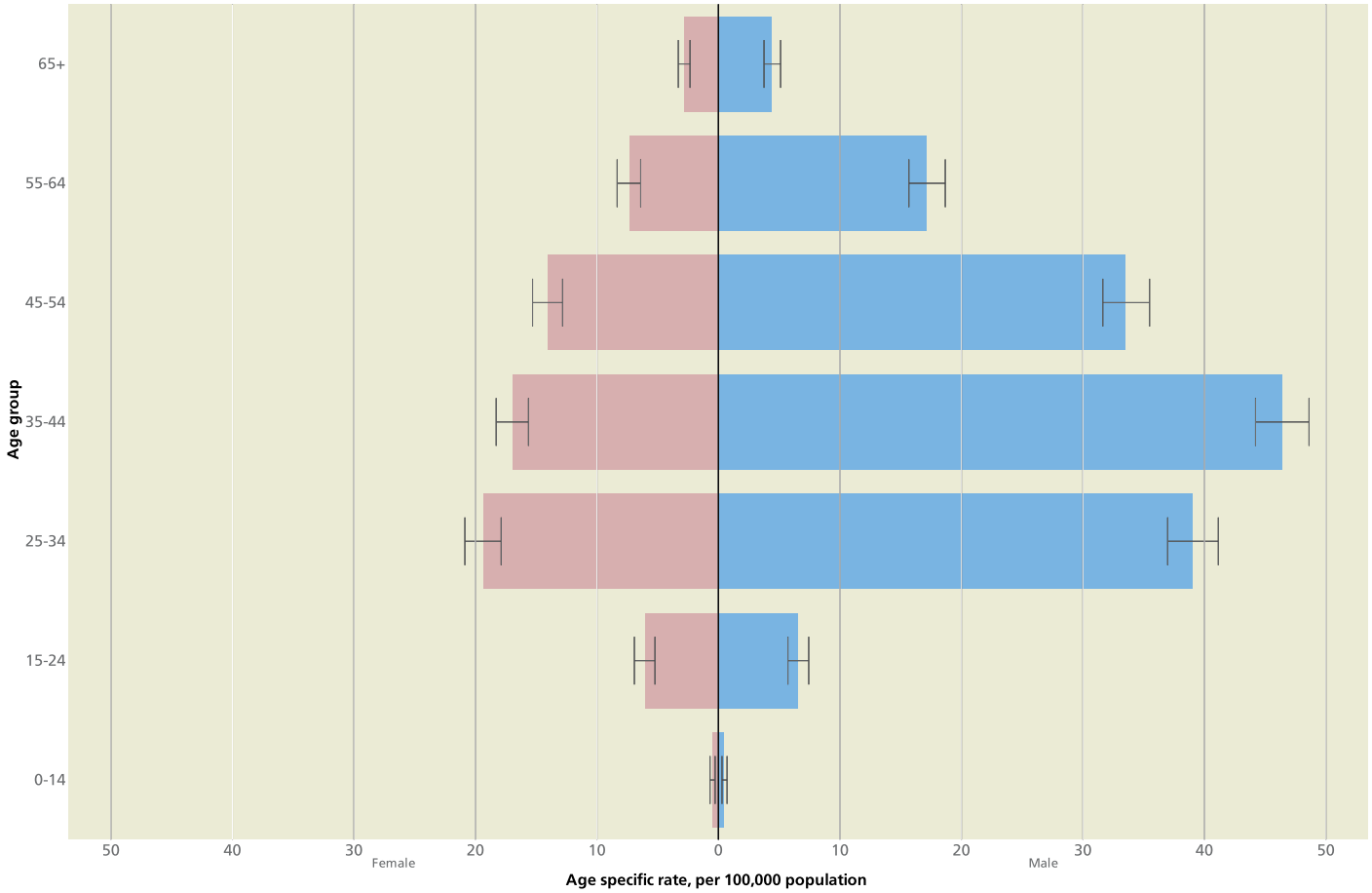
Hepatitis C

The most recent national estimates suggest that around 216,000 individuals are chronically infected with hepatitis C (HCV) in the UK.[12, 13] Injecting drug use continues to be the most important risk factor for HCV infection in the UK. Data from the Unlinked Anonymous Monitoring survey of people who inject drugs suggest that levels of infection in this group remained high in 2011 (45% in England). **Up to 75% of patients are not aware of HCV infection until liver disease or cancer develops many years later.**[14]

More than two-thirds (69%) of reported new diagnoses of HCV in England in 2010 were in men, and half of all reports received (49%) were in individuals aged between 25 and 39 years. This age/sex distribution is likely to be a reflection of the pattern of injecting drug use, which continues to be the predominant risk factor for acquisition of infection.[15] Figure 9.1 shows the age and sex distribution of laboratory reports of HCV infection in England for the period 1996–2011.

The number of new HCV diagnoses reported increased by 25% between 2010 and 2011, from 7,892 to 9,908. The number of laboratory reports, which is known to underestimate true levels of diagnosis, increased each year between 2004 and 2009 following concerted efforts to improve diagnosis rates and raise awareness. The marked increase in 2011, however, is probably largely explained by the introduction of statutory laboratory reporting in October 2010.

Figure 9.1: Hepatitis C laboratory report rate by age and sex, England, 2010



Source: Centre for Infections laboratory data, HPA. 2010 population estimates, ONS. (Analysis by HPA)

Owing to recent advances in combination therapy, with directly acting antiviral agents such as boceprevir and telepravir in genotype 1 HCV infection when sustained viral responses are favourable,[16] **medical practitioners should be actively offering testing to at-risk populations, including migrants and current and former injecting drug users.** The reduction in HCV infection rates and morbidity through prevention is an important ongoing public health issue in institutions such as prisons.

Hepatitis B

The prevalence of chronic hepatitis B (HBV) infection in the UK is estimated to be 0.4%,[17] but this varies among different ethnic groups and those born in countries where HBV is endemic. A total of 521 acute HBV cases were reported in England in 2010. The incidence of reported acute HBV in England in 2010 was 0.99 per 100,000.

In 2010, 91 blood donors tested positive for markers of HBV infection, equivalent to 3.5 per 100,000 donations. The majority (93%) of these infections were chronic and among new blood donors (equivalent to a rate of 37.9 infections per 100,000 new donations). About two-thirds of UK blood donors testing positive for markers of HBV infection were of non-white ethnicity. Only 3% of all UK blood donors were of non-white ethnicity. Around 60% of UK blood donors testing positive for markers of HBV infection in 2010 were born in Africa or Asia.

HBV and HCV presently cause a relatively small number of deaths and hospital admissions. However, these numbers are expected to rise over the next few years, particularly in minority ethnic communities, and case-finding in such minority ethnic populations is therefore recommended.

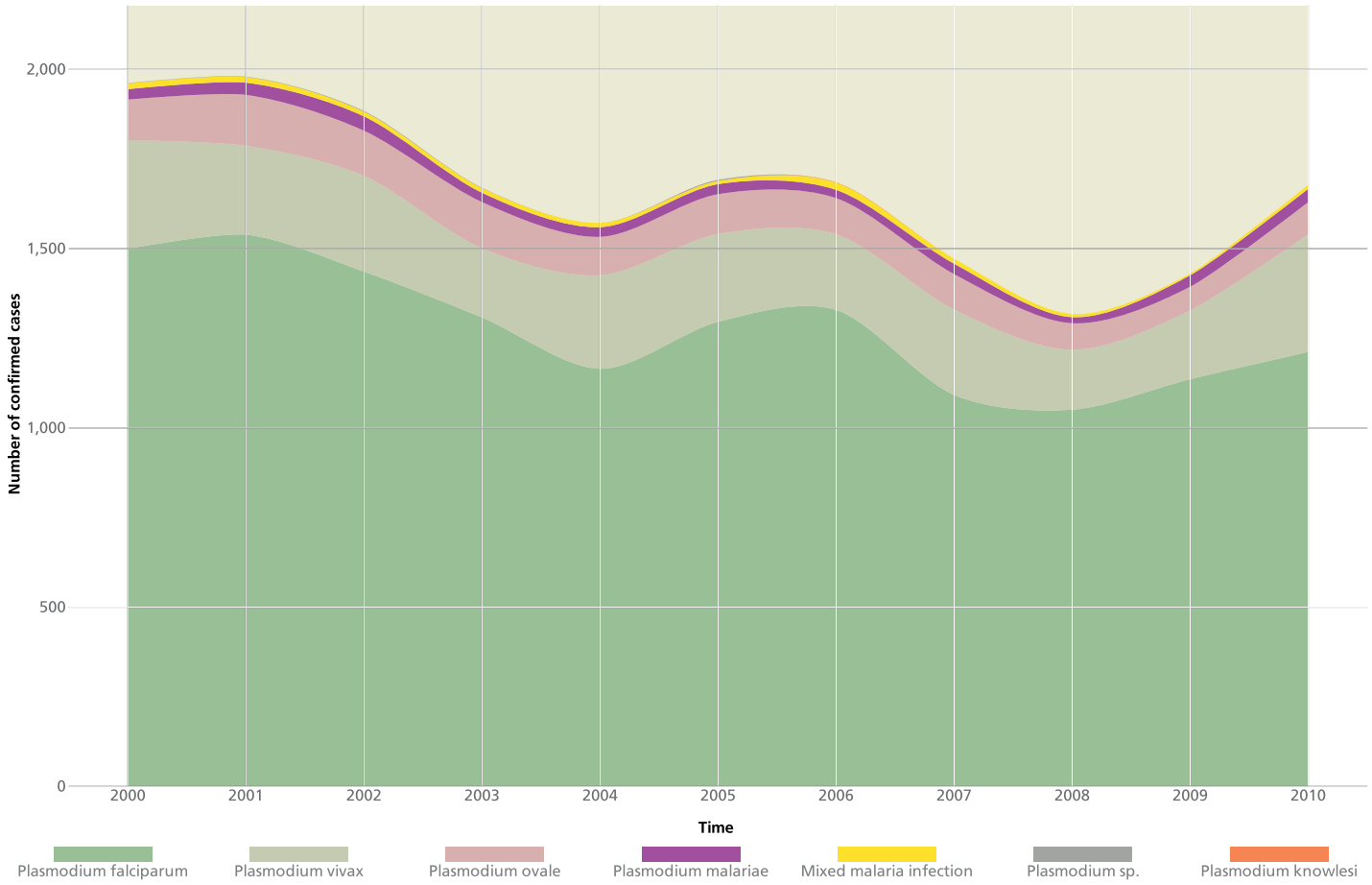
Data from sentinel surveillance of hepatitis showed that 65% of HBV infections and 68% of HCV infections reported between 2007 and 2010 were diagnosed in primary care settings.[18]

Impact of travel-related illness

In 2007, nearly 70 million UK residents travelled abroad. Depending on their destinations, travellers may be at increased risk of acquiring infections that are uncommon or rare in the UK. One of the most important of these imported infections is malaria.

Malaria is predominantly a disease affecting Africa, South and Central America, Asia and the Middle East. The heaviest burden is in Africa, where around 90% of the approximately one million deaths from malaria worldwide occur each year.

Figure 9.2: Trend in number of laboratory confirmed malaria cases by type of malaria, England, 2000 to 2010



Source: Malaria reference laboratory, HPA.

The most common type of malaria reported in the UK is the potentially fatal falciparum malaria (see figure 9.2), which is usually acquired in West Africa. This type of malaria continues to account for the majority of cases (1,149) reported in the UK, but in 2011 a quarter of cases (416) were caused by vivax malaria, which is more commonly acquired in India and Pakistan. This proportion has increased from 20% in 2010 and may indicate that travellers are unaware of the risk of malaria in the Indian subcontinent.[19]

Case study 9.2

A previously fit 32-year-old man presented to his GP with a 2-week history of feeling unspecifically unwell, with intermittent fever and sweat associated with myalgia and aching joints. He had just recently come back from a 2-week package holiday in the Gambia along with his partner. Neither had sought travel advice prior to their holiday and therefore had not taken any malaria prophylaxis nor received any vaccinations relevant to their travel destination. Falciparum malaria was diagnosed following hospital admission and was successfully treated.

Comments

This case demonstrates the importance of public awareness of the need to seek travel health advice, as well as the need for clinicians to consider travel history in the diagnosis of unexplained fever.

In 2011, eight deaths from malaria were reported: six from falciparum malaria acquired in Africa and two from vivax malaria acquired in India. Figures from the Health Protection Agency show that, despite a 5% decrease in reported malaria infections between 2010 (1,761) and 2011 (1,677), the number of cases among travellers returning from the Indian subcontinent increased by 22%, from 274 in 2010 to 334 in 2011.

The increase in cases from the Indian subcontinent in 2011 was largely due to a doubling of cases of *Plasmodium vivax* malaria acquired in Pakistan.

Malaria is an almost completely preventable disease when precautions are taken, but the latest figures show that, where the history of taking antimalarial medication was obtained, 84% of cases (803 out of 954 with information available) had not taken precautions.

The group who continue to be at the highest risk of contracting malaria are those visiting friends and relatives. In 2011, where the reason for travel was known, 80% (610/765) of cases who were travellers from the UK were visiting friends and relatives in their own or their family's country of origin. This group are more likely to acquire malaria for a number of reasons, including not seeking or being unable to access appropriate medical advice before travelling, receiving poor advice, not adhering to advice, or not perceiving themselves to be at risk because the destination is familiar to them.

As with other imported infections, medical practitioners in primary and secondary care settings should familiarise themselves, as part of their continuing professional development, with the presenting features of such infections, so that they can recognise and identify them early and refer such cases promptly and appropriately.

Public education and awareness play a pivotal role in encouraging people to seek health advice prior to travel, to minimise the risk of acquiring infections.

The issues raised by increased global travel, both as part of migration and for other reasons, highlight the importance of taking global action to reduce the burden of infection. Where there is an impact internationally, this is to the benefit of the UK. An example of this is the World Health Organization global programme for the eradication of polio. While the greatest benefit will be outside the UK, there will be a direct benefit when Nigeria and Pakistan interrupt transmission, as the UK has high levels of flow between itself and these countries. In the long term, if we are successful at eradicating polio, there will no longer be a need to vaccinate against it.

Offenders' health in relation to infection

Prisons and other places of detention pose particular risks for the causes and transmission of infection and are unique challenges to medical practitioners. This is due to three main factors: the nature of the environment, the nature of the population and the prevalence of disease. Prison and detention establishments vary in their age, design, construction and healthcare facilities. Access to healthcare services differs from place to place. Cell sharing is common, and staff levels and skill mix vary.

The standing prison population in England and Wales is nearly 87,000,[20] with an estimated 115,000 or more people entering prison each year. A typical prisoner is young and male,[21] and violence is the most common cause for detention, with acquisitive crime and sexual and drug offences also being common. People in prison and detention centres often come from populations or groups at higher risk of certain infectious diseases, namely blood-borne viruses, HIV and sexually transmitted infections, and tuberculosis.

A high percentage of individuals in prison are drug users, which puts them at risk of contracting HCV, HBV and HIV infections. A study[22] of a sample of 1,457 newly sentenced adult offenders from 49 prisons in England and Wales found that 80% of them had used an illicit drug during their lives and 40% of the sample aged 21 years and over had injected a drug during the 4-week period prior to custody.

A survey of HCV services in England between September and November 2011[23] showed that HCV diagnostic services are now offered in all but one of the 110 prisons that took part in the survey but only 74% have a written care pathway in place to describe what happens to offenders who test positive for

HCV infection. Only 40% of blood samples are routinely PCR tested if they are positive for HCV antibodies (which indicates a current or past infection). Laboratories should ensure that all blood samples that test positive for HCV antibodies are routinely tested by PCR for the presence of HCV RNA (to determine current infection status) as the first step in accessing a care pathway in prison.

Offenders themselves are a challenging population to treat effectively. Their health and social needs are diverse, with many of them entering such institutions with poor physical and mental health. Their frequent relocations and, at times, short sentences make their engagement with healthcare difficult, with lack of continuity. Exposure to illicit drugs, physical violence and victimisation is common, and offenders are therefore reliant on prison staff for almost every aspect of their existence, including the many factors that affect their health.

Prisons and places of detention therefore represent an opportunity to engage with normally excluded populations and can offer diagnostic tests as part of screening or active case-finding programmes such as testing for blood-borne viruses. They also offer opportunities to undertake vaccination programmes against preventable infectious diseases such as hepatitis B.

Primary healthcare teams in prisons can ensure effective disease prevention, diagnosis, surveillance, treatment and care of such populations in both community and hospital services. This would have an impact on the protection of the health of the wider community.

Opportunities

When considering the challenges presented by infectious disease to the adult population, it is clear that there remains a vital role for medical practitioners in the early identification of infectious diseases. This will require them to accurately identify those individuals at higher risk and act appropriately. **Medical practitioners need to give consideration to patients' country of birth when evaluating their risk exposure;** this will aid differential diagnosis of presenting symptoms such as tuberculosis, and blood-borne viruses including HCV, HBV and HIV. This helps to determine when the offer of testing should be undertaken. Furthermore, any trained healthcare professional should be able to obtain consent for testing for HIV, especially when indicator diseases are present, so as to reduce the percentage of late presenters in the UK. **Training and continuing professional development needs to include a specific focus on this, so that medical practitioners and healthcare professionals are equipped with the right skills for the challenge.**

There remains an ongoing need for the general public, as well as medical practitioners and healthcare professionals, to be aware of the risk activities associated with infection, particularly those associated with the transmission of blood-borne viruses. This is important in terms of reducing risky behaviour, but also in encouraging risk-mitigating actions, such as the use of needle-exchange facilities, and in encouraging at-risk groups, such as former intravenous drug users, to access healthcare.

UK residents travelling to visit friends and relatives in their country of origin are a major risk group for imported diseases, including malaria. There is a need for the general public to educate themselves about the risks. To help promote this, different methods of advising people of the health risks of travelling, and ways of encouraging people to seek travel-related health advice, need to be explored by Public Health England and the Foreign Office.

Offenders are a challenging population to treat effectively, although their detention represents an opportunity for prison health services to offer diagnostic tests as part of screening or active case-finding programmes such as testing for blood-borne viruses. Immunisation against hepatitis B is recommended for all sentenced offenders and all new inmates entering prison in the UK. However, implementation of this simple and effective intervention can be problematic. Uptake of vaccination for hepatitis B should be actively promoted as part of offenders' entry health assessment. Even where prisoner movement presents challenges to ensuring the full course of hepatitis B vaccination, a vaccination course should be commenced at entry and every attempt should be made to complete the course.

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Chapter 10

Life stage: Older adult

Author and editor:
John Watson[1], Colin Brown[2], Gavin Dabrera[3], Elizabeth Sheridan[4], Nicola Lovett[5], Christopher P Conlon[6]

1 Head, Respiratory Diseases, Health Protection Agency
2 Academic Clinical Fellow in Infectious Disease and Microbiology, Health Protection Agency
3 Specialist Registrar (Public Health), Health Protection Agency
4 Consultant Microbiologist, Health Protection Agency
5 Specialist Registrar in Geratology, Oxford University Hospitals NHS Trust
6 Reader in Infectious Diseases and Tropical Medicine, University of Oxford

Overview

Average life expectancy in Britain exceeds 82 years in women and 78 in men. Many older adults live active lives into their seventies, eighties and nineties in the expectation of a healthy 'third age' and a 'good death'. The reality for many older adults, however, is far from this ideal. Many suffer with chronic illness and substantial disability in their later years, are subjected to inappropriate management of health problems when they occur, and die much earlier than they could reasonably hope. Treatment and care for illness in older adults results in a high burden for those who help provide their care and a high economic burden for the taxpayer.

The size of the population of older adults is increasing. With increasing age, the prevalence of chronic illnesses and vulnerability to infection increase. Infection is an important cause of illness and premature mortality in older adults and can hasten the decline in the health of an otherwise active older person. Many of the infection problems in older adults are preventable and many of those that do occur could be managed better in order to avoid further problems resulting from the treatment of the infections themselves. An understanding of the infections that pose the greatest threat to older adults, the factors that increase the threat, and the circumstances that can complicate the management of infection problems, can contribute to enabling older adults to have a healthier old age.

Three particular problems for the older population are influenza, healthcare-associated infections and urinary tract infections. These are described in the sections that follow.

Case study 10.1

Mrs Wallace (not her real name) was 88 years old and normally managed pretty well at home with a carer coming in once a day. One day she became a little confused and her GP sent her to hospital, where a urinary tract infection was diagnosed. She was given intravenous antibiotics for the infection, which was thought might have spread to her bloodstream. Mrs Wallace initially improved and her confusion cleared but, some days later, she became more unwell. She was found to have pneumonia, possibly a complication of the fact that her swallowing had been slightly impaired by a stroke 3 years previously. This pneumonia, acquired in hospital, required a further course of broader-spectrum antibiotics for 5 days. Despite this setback, she slowly improved. It was felt she might need a bit more assistance at home, so she stayed in hospital waiting for a new care package to be organised. A couple of days before her planned discharge from hospital, Mrs Wallace complained of abdominal pain and diarrhoea. The diarrhoea persisted and stool tests showed infection with *C. difficile*. She received a 2-week course of another antibiotic targeted at this infection and her symptoms settled after about 6 days. When she was eventually discharged home, her mobility was less good and she had lost some confidence, so an increased care package with twice-daily visits was arranged.

The hospital-acquired pneumonia and, following its treatment, the *C. difficile* diarrhoea led to a delayed discharge, so that Mrs Wallace spent at least 2 weeks longer in hospital than expected when first admitted. Fortunately she was able to return home, but she required more care than previously. This case illustrates the risks to which vulnerable and frail elderly people are exposed when fairly trivial infections upset their equilibrium. Such patients make up an increasing proportion of patients on medical wards in hospitals in the UK.

Influenza

Influenza epidemics occur every year in the UK but vary considerably in their impact. The recent 2009 pandemic of influenza predominantly affected children and young adults; older adults were relatively spared, probably as a result of acquired immunity to similar viruses to which they were exposed in their younger years.[1] Seasonal epidemics of influenza, however, usually have their greatest impact on older adults, with almost all of the excess mortality observed during these epidemics occurring among the over-65 year age group.[2] While some older adults may die from the direct effects of influenza infection itself, more are likely to die as a result of the exacerbation by influenza of underlying chronic conditions leading to illnesses such as pneumonia, heart failure and stroke.

Uptake of influenza vaccine in the UK each year, prior to the onset of seasonal influenza activity, approaches 75% in 65 year olds and over.[3] Observational studies among older adults who have and have not been vaccinated indicate that the immunisation programme is likely to have prevented much ill health and many deaths.[4]

Protection from influenza in older adults is, however, lower than in younger adults and children, and may be very low in some years when the match between vaccine and circulating strains of influenza is poor.[5] Healthcare workers are as susceptible to influenza as other adults and may spread infection to their vulnerable patients. Uptake of influenza vaccine among healthcare workers, at about 45% in 2011/12, has increased but is not yet high enough. Increasing vaccine uptake in this group would contribute significantly to reducing mortality and morbidity in the older population.

Modern influenza antiviral drugs (the neuraminidase inhibitors, oseltamivir and zanamivir) are effective in preventing or reducing the illness due to influenza infection if given early in the illness. They are also safe and well tolerated by older adults. They may be prescribed to any older person with an illness compatible with influenza infection during the periods of the year when influenza is circulating in the community. In practice, however, few older adults are prescribed influenza antivirals. In part this may be due

to the fact that older adults often present for healthcare with an illness that does not look like 'typical' influenza and the diagnosis is missed. In addition, older adults may often delay seeking care until they are very ill and beyond the stage when antivirals may help. Familiarity of GPs with prescribing antivirals has increased following the recent pandemic but experience of their use in older adults is still limited. Maximum benefit will be achieved by increased awareness of the potential benefit of antivirals among older adults and healthcare providers, a low threshold for their use when influenza is circulating, and the earliest possible commencement of treatment.

Many older adults continue active lives while living in residential accommodation or nursing homes. Outbreaks of influenza, observed frequently in the otherwise quiet influenza season of 2011/12, can have a substantial impact on older adults in these settings, with rapid spread of infection, severe illness and, all too often, death.[2] This has been observed despite high vaccination levels. A high index of suspicion needs to be maintained for influenza outbreaks in these settings, which may occur outside the period of circulation of influenza in the general community, and control measures (including isolation, infection control and the use of antivirals for treatment and prevention of influenza) need to be instituted promptly.

Healthcare-associated infections

Older adults have, on average, more contact with healthcare services (both hospital and community)[6, 7] than younger adults or children. This, combined with the decline with age of the body's defences to infection, means that this age group is at greater risk of healthcare-associated infections (HCAIs).

MRSA, an antibiotic-resistant form of the *Staphylococcus aureus* bacterium, is found more commonly in healthcare settings than in the community and causes, in particular, bloodstream and surgical wound infections.

The number of MRSA bloodstream infections fell by 84% between 2002 and 2011. A national hand-hygiene campaign in hospitals, combined with changes in infection control measures, is believed to have contributed to this decrease.[8] Older adults remain, however, the most commonly affected group. From January to March 2012, a third of all these infections occurred in those aged 75 years and over, and a further sixth occurred in the 65–74 year age group.[9]

C. difficile is a bacterium which can cause infections following treatment with antibiotics. It produces a toxin which causes diarrhoea and affects older adults particularly severely. This infection spreads easily between patients in health and social care facilities. The number of *C. difficile* cases, based on reports of laboratory-confirmed infections, halved from 36,095 (in the two year period 2008 to2009) to 18,005 (in the two years 2011 and 2012).[10] As with MRSA, however, rates of infection remain highest in the over-75 age group.

Those aged 65 to 74 years have the next-highest rates of *C. difficile* infection, with men having slightly higher rates than women (71 and 64.7 per 100,000 per year, respectively).[10] The prevalence of antibiotic administration in hospitals in a recent survey of HCAI was 36.7% in those aged 65–79 years, and 31.6% in the over-80s, though the highest prevalence was seen in the 2–15-year age group.[11] Norovirus, or the 'winter vomiting bug', is another cause of debilitating diarrhoea in older adults that is spread particularly easily in hospitals and residential care facilities.

Urinary tract infections

Urinary tract infections (UTIs) are common and important healthcare-associated problems in older adults. In an HCAI prevalence survey among patients in acute general hospitals in England, UTIs were the second most common HCAI after respiratory tract infections, comprising 17.2% of the total.[11] More than two in five of the UTIs were associated with recent urinary catheterisation. Urinary catheters are used relatively frequently in older patients as part of care in the management of conditions such as dementia, prostate disease and incontinence from other causes. UTIs may be the initial focus for further spread of infection, accounting for nearly 20% of all reported bloodstream infections.[11] UTIs are most frequently caused by *E. coli* bacteria. The highest rates of *E. coli* bloodstream infections in England were among those aged over 75 years in both men and women, followed by the 65–74 year age group.[12] Unlike MRSA and *C. difficile* infections, rates of *E. coli* bloodstream infections have continued to rise in recent years. The use of urinary catheters is not, however, restricted to hospitals, as they are often used for long-term care in community settings: up to 40% of older care-home residents are catheterised at some point and most catheters are in place for at least 28 days,[13] increasing the chance of catheter-associated UTIs.

Discussion

The problems caused by infections in older adults highlight the urgent need to improve the appropriateness and quality of care for these patients. This includes changes in how care is delivered, with a shift to a model that is based where possible in the home and community health settings, with the hospital reserved for management of acute and serious illness. This shift would contribute to a reduced risk of HCAIs such as MRSA, *C. difficile* and norovirus infections.

The importance of improving the quality of care, through strengthened training of staff and reallocation of resources, has also been increasingly recognised. The rise in both online courses and dedicated training support to improve infection expertise for care-home staff[14, 15*] has

* Note: these are 2 illustrative examples chosen at random from the many providers of such courses and do not represent a specific endorsement.

demonstrated the increasing demand for better-quality care. The 'Skills for Health' consultation (on common induction standards for healthcare support workers and adult social care workers in England) addresses 'preventing the spread of infection'.[16] It builds on the Code of Practice for Infection Control in the Health and Social Care Act 2008.[17] These illustrate the increasing value placed on the need to train staff appropriately to prevent the spread of HCAIs.

Simple interventions, such as reminders to review the need for urinary catheters, with a view to removing them as soon as possible, have been demonstrated to be effective in reducing the duration of catheter use and catheter-associated UTI rates for up to 6 months.[18] It is important to identify the occurrence of bloodstream infection associated with UTIs so as to identify risk factors and permit more effective preventive action. This will require the development of additional surveillance for these infections.

Optimising influenza vaccination rates in older adults, and in their carers (including healthcare workers), is a priority. Patients with dementia living in the community (such as in their own homes) are less likely to have been vaccinated against influenza than patients (with or without dementia) living in care homes.[19] Simple low-cost measures in general practice, such as personal vaccination invitations to patients, nomination of a staff lead for identifying eligible patients, and searching practice electronic patient record systems, are associated with increased vaccination rates among those aged over 65 years.[20] Low-cost measures like these can be an effective way of balancing vaccination for older adults with other service demands. Better strategies are needed, however, to vaccinate those who may find it difficult to access surgery-based services, such as patients with dementia living in the community.

Antiviral medications have the potential to alleviate the impact of influenza in older persons. Older adults are at increased risk of the complications of influenza and may benefit if they receive antivirals early. Greater use of these medicines in older adults should be expected now that experience of their use has increased.

An additional potential benefit of the use of influenza antivirals is the protection of older adults living in settings such as care homes when an outbreak of influenza occurs. Other residents may be offered antiviral prophylaxis to reduce the risk of developing illness due to influenza and the further complications of the infection. To achieve this benefit, potential outbreaks of influenza need to be identified early. This requires the raising of awareness among health and social care professionals.

Opportunities

Good communication between healthcare workers and other carers, in hospitals, residential institutions and the community, is essential to co-ordinate effective care of older adults. Improvements in information technology within the NHS have the potential to contribute to better communication and, in particular, support the transition from hospital to general practice and allied community health teams.[21]

Developments in rapid and more sensitive diagnostic tests have the potential to change existing practice for some conditions that predominately affect older adults. A number of respiratory infections are responsible for rapid worsening of chronic obstructive pulmonary disease (COPD) or chronic bronchitis, which can result in severe illness and death. Molecular diagnosis of the bacterial and viral infectious agents responsible for these exacerbations, including those infections not yet routinely identified by microbiological practice, will permit timely and more effective interventions due to the 'rapidity, convenience, and sensitivity' of these techniques, coupled with better targeting of antimicrobial therapy.[22] The rapidly emerging field of whole-genome sequencing, and the potential for its use in diagnostic testing, will advance the potential of this approach.

Advances are also occurring in the development of novel vaccines for a number of the respiratory viruses responsible for acute exacerbations of COPD, such as respiratory syncytial virus, human metapneumovirus and parainfluenza viruses.[23] Despite early and repeated exposures to these infections during a lifetime, no lasting immunity against them is induced. A vaccine is also available which can prevent or reduce the severity of infection with the chickenpox virus (varicella zoster), which causes shingles, a condition which is both common and very debilitating in older adults. These vaccines, coupled with the pneumococcal and influenza vaccines which are already routinely offered to older adults, have the potential to bolster the protection of vulnerable older adults against these significant threats.

The success of treatments for chronic infections, such as HIV infection, means that an increasing number of people who are HIV infected are surviving into middle and older age. The consequences of prolonged survival with HIV infection, and many years of treatment, are not yet known, but there are suggestions already that the management of some conditions common in older age, such as cardiovascular disease and osteoporosis, may be affected in these patients.[24, 25]

There has been a recent increase in the understanding of the role that social inequalities play in the burden of ill health generally, and of infections in particular.[26] There is little research, however, that has specifically addressed the impact of social inequalities on the burden of disease in older adults, or on strategies to mitigate this burden.

If the additional burden of infectious diseases in older adults is to be reduced, researchers must actively include older adults within their research protocols, including trials of therapeutics, assessment of diagnostic advances and methods to alleviate social inequality. Older people differ from younger adults and children in response to interventions to improve or protect their health. More studies that include older adults are needed 'to improve the treatment and care available to them'.[27]

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Chapter 11

Future challenges

Edited by Tom Fowler[1,2]

with substantial contributions from

Kevin Dean[3], Martin Stewart-Weeks[4], David Cooksey[5], Stephen J Fowler[6], Paul Dark[7], Ashley Woodcock[8], Sue Hill[9], Tom Fowler[1,2], David Walker[10,11], David M Salisbury[12], Sharon Peacock[13,14], Danny Altman[15], Stephen Wyllie[16], Mike Catchpole[17], Andrew Hall[18], Derrick Crook[19]

1 Locum Consultant in Public Health, Department of Health
2 Honorary Research Fellow, University of Birmingham
3 Healthcare Director, Cisco Internet Business Solutions Group
4 Director, Global Public Sector Practice, Cisco Internet Business Solutions Group
5 Chair, Aegate Limited
6 Lecturer and Honorary Consultant Respiratory Medicine, University of Manchester
7 Reader and Honorary Consultant Intensive Care Medicine, University of Manchester
8 Professor of Respiratory Medicine, University of Manchester
9 Chief Scientific Officer, Department of Health
10 Regional Director of Public Health, East Midlands
11 Deputy Chief Medical Officer (Designate), Department of Health
12 Director of Immunisation, Department of Health
13 Honorary Consultant Microbiologist, Health Protection Agency
14 Clinical Microbiologist, University of Cambridge
15 Professor of Immunology, Imperial College London
16 Head, Zoonoses Team, Department of Environment, Food and Rural Affairs
17 Director of Infectious Disease Surveillance and Control, Health Protection Agency
18 Professor of Epidemiology, London School of Hygiene and Tropical medicine
19 Consultant Microbiologist, University of Oxford

1. Emerging and re-emerging diseases

Emerging and re-emerging diseases

The propensity for microorganisms to undergo rapid change, including the ability to exchange or share genetic material between strains or species, is an important factor in the emergence of new infectious diseases and the re-emergence of infections that had previously been controlled effectively (e.g. through immunisation). The greatest example of this is the influenza virus. This can give rise to worldwide epidemics (pandemics) when new strains arise that can escape the protection offered by natural immunity or current vaccines.

In addition to microbial change, the key drivers of emergence of new infections are susceptibility to infection, changes in land use and the associated environmental impact, human demographics and behaviour, technology and industry, international travel and commerce, and a breakdown in public health. Current legislation and regulation mitigates most of these in the UK.

Zoonoses

Analysis of global outbreak data from 1940 to 2004 has shown that around 60% of emerging infectious human diseases are of zoonotic origin. The majority of these originate in wildlife, and often in regions where surveillance reporting systems may be less effective.

Zoonoses are usually transmission cul-de-sacs but occasionally they develop the ability, through organism mutation, for human-to-human transmission. This is particularly a feature of RNA viruses (viruses that have ribonucleic acid (RNA) as their genetic material), as was seen with the global severe acute respiratory syndrome (SARS) epidemic in 2003. Influenza viruses are capable of mutating and reassorting and this commonly occurs in pigs and a variety of avian species with on rare occasions successful transmission to humans, although the establishment of such viruses as a transmissible human pathogen is complex. The potential role of other animal species in the emergence of pandemic influenza is considered less likely but could occur given the ability of influenza virus to transcend host species barriers. Influenza is the major threat in terms of zoonoses and emerging infections for the foreseeable future. The UK response to the recent influenza H1N1 pandemic was widely regarded as excellent. The challenge is to maintain the ability to respond rapidly and appropriately in the reconfigured public health system.

Climate change

A major driver of future emerging and re-emerging diseases is likely to be climate change. It is important to distinguish between the infectious disease impact from extreme weather events, the gradual increase of vector range due to climate change effects, and the potential for diseases to be artificially transported long distances by movements of humans, animals or goods.

In the UK, extreme weather events such as flooding – which can be associated with an increase in infectious diseases – will probably have the most impact in the short term. Some infections, particularly gastrointestinal infections, are associated with summer weather, and the predicted milder winters, warmer summers and wetter springs may also lead to increases in rates.

The projected increase in both summer and winter temperatures may affect the longevity and diversity of potential arthropod disease vectors, such as the mosquitoes *Aedes albopictus* and *Culex pipiens,* and some of the exotic tick species. This will affect the threat from future incursions of vector-borne zoonotic diseases, such as West Nile fever. There is already evidence of an increase in arthropod-borne infections in animals and humans in northern Europe, and a similar pattern may arise in the UK. Although this is not direct evidence of climate change effects on disease emergence, these patterns need to be studied as an early warning system for such changes.

There are many knowledge gaps in this area, not least the indirect impacts of climate change, such as social, political and land-use changes, which can impact on vector distribution or trade patterns. These gaps increase the need for surveillance across Europe and neighbouring countries for changes in patterns of disease and disease vectors (such as regular surveys of arthropod vectors) so that risk assessments can be updated on an ongoing basis.

Antimicrobial resistance

The continuing increase in organisms that are resistant to one or more antimicrobial drugs is one of the greatest threats that we face today. Some forms of resistance can be transferred between different species of bacteria and parasites, which can result in organisms that are resistant to many, most or even all drugs that are currently available.

Antimicrobial resistance is dealt with comprehensively in Chapters 4 and 5, covering healthcare-associated infections and antimicrobial resistance. These chapters discuss the challenges of developing new antibiotics and reducing the selective pressures on organisms to develop resistance, through antimicrobial stewardship, developing diagnostics to target treatment, and improving the evidence base to identify when antibiotic use is unnecessary or can be reduced.

When considering the medium to long term, the key issue beyond those discussed is that other forms of antimicrobial resistance are likely to become a problem – including antiviral resistance in the hepatitis viruses.

Conclusions

In the short to medium term there is no indication to suggest a change in the rate of new and emerging/re-emerging

diseases. The potential challenges that these present are well known (e.g. pandemic flu outbreaks). Climate change and antimicrobial resistance are the factors most likely to necessitate change in the way we respond to diseases. Climate change may shift the pattern of infections that occur, and antimicrobial resistance has the potential to mean that we can no longer respond to certain infections in the same way. However, much still remains unknown and surveillance (as described in the following sections) is key to informing our actions in response to these threats.

2. Surveillance

Infectious-disease surveillance is a core public health function that ensures that timely and accurate information is available about the occurrence and sensitivity to treatment of infectious-disease threats. Continuous monitoring is essential to detect clusters of cases, or individual cases of particularly serious infections, in time to prevent or contain outbreaks or epidemics. Surveillance also provides information that is needed to inform national policy on the prevention and control of infections, whether that be through national immunisation programmes, screening programmes, controlled use of antibiotics or hygiene and health education programmes.

Many of the infectious-disease surveillance systems in operation in the UK, currently run by the Health Protection Agency and soon to move to Public Health England, are recognised as world-leading.. These include the national reporting system for surveillance of infections identified by microbiology laboratories and the disease- or topic-specific surveillance systems for HIV and other sexually transmitted infections, and for healthcare-associated infection and antimicrobial resistance. There is a long history of innovation in surveillance in the UK, such as the unlinked anonymous HIV prevalence monitoring systems. Other examples include the British Paediatric Surveillance Unit, set up through a collaboration between the former Public Health Laboratory Service and the Institute of Child Health, which provided the evidence that demonstrated the link between the use of aspirin in children and the development of Reye's syndrome (now run by the Royal College of Pediatrics and Child Health). This has since been used as a model for surveillance systems for rare diseases around the globe. In more recent times, the Health Protection Agency has successfully implemented new "syndromic surveillance" systems for patients seen in emergency departments and walk-in centres. This was a cornerstone of surveillance during the 2012 London Olympics.

There are many examples of the public health value of surveillance. These include the identification of the extent of undiagnosed HIV infection in pregnant women (which led to changes in antenatal testing and reduction in neonatal HIV infections), the early detection of many outbreaks of food-borne infection (which has enabled rapid control measures to be undertaken) and the extensive use of surveillance data in modelling and other analyses (which has informed national policy on vaccination).

Short-term opportunities and challenges

In the short term, there are very significant opportunities to build on current strengths and successes in surveillance. In particular, there are the opportunities offered by the creation of Public Health England and the new Information Strategy for Health, *The Power of Information*. These will bring together systems and expertise across the broad domain of public health.

While many of the surveillance systems that are used for monitoring infectious disease in this country are class-leading, **there is significant added value to be gained by making better use of the information collected, particularly through linkage of the data and the systems currently used.**

There is a major challenge to exploit the potential to link data from surveillance systems (e.g. notifications, laboratory reports of infections and primary care reports) and hospital admissions data with surveillance of outcomes (e.g. cervical cancer registrations, human papillomavirus infection rates), lifestyle risk factors (e.g. incidence of other sexually transmitted infections, sexual behaviour survey results), potentially remediable risks from environmental tracking (e.g. water-quality monitoring reports, microbiological surveys of food and animals) and disease registers (e.g. congenital anomaly registers and cancer registers). To make such links realisable, **Public Health England, the Information Centre and the Commissioning Board will need to develop and promulgate clear information standards for surveillance, and interoperability standards for health information systems that will enable data from different sources to be linked efficiently and effectively.** While this is a technical challenge, the biggest potential issue is ensuring relevant legislation and guidance supports the sharing and linkage of health and social care data for the purposes of public health surveillance.

Medium- to long-term opportunities and challenges

New technologies, such as genome-based diagnostic testing and point-of-care testing, offer significant opportunities for more rapid and more discriminating surveillance (see below). To ensure these opportunities are realised, **any national strategy that encompasses the development and roll-out of genomic diagnostic testing for infections should include the delivery of real surveillance data as an integral part.**

It is clear that in both the short and long term the greatest challenge will be linkage, analysis and interpetation of incredible amounts of complex data. The availability of different types and forms of data is only likely to grow. This will include not just the type of information traditionally associated with healthcare, but a plethora of new information

sources (see Big Data, dynamic care and collaboration). In the future there will be a need to develop bioinformatics capacity to exploit genomic data from new diagnostic tests. Database mining and the development of new analytical technologies will also be needed to support rapid detection of potential threats.

Case study 11.1

Big Data, dynamic care and collaboration

written by Kevin Dean and Martin Stewart-Weeks, Cisco Internet Business Solutions Group

Wherever you go, whatever you do, in the 21st century you generate a data trail. At the moment, it is your credit and debit cards, mobile phone, laptop computer, tablet – or the retailer, bank, hospital or hotel systems – that generate the data. In the future, there will be many, many more sources of data: your car, clothes, medicines, food, and presence on video surveillance systems. In fact, the next-generation Internet will use a way of uniquely identifying 'things' (IPv6, for the geeks) that has the potential for every person on the planet to have billions of sources of data associated with him or her.

Just the data collected about people and things today has led to a growing industry dealing with high-volume, high-variety, high-velocity, virtual datasets ('the 4Vs', according to Gartner) – often called 'Big Data'. This is a controversial subject, yet mining our shopping habits, website visits, and credit-card use is already standard practice – whether for preventing fraud or targeting marketing campaigns. The growth of Big Data is an inevitable reality of a digitally connected world. If this is the case, what positive use can be made of this tidal wave of data in the world of infectious disease management? And how will we move from analysing past events to changing events as they happen?

Big Data – smart analytics

By collecting vast arrays of information – some seemingly unrelated – from a large number of different sources, Big Data combines pattern recognition, correlation and causality algorithms to seek unseen pictures of human behaviour, weather forecasts, security threats, public health risks and more. There is huge potential in the world of medicine and public health, despite concerns about the storage and integration of datasets on large scales. Well-known examples include Google Flu Trends (www.google.org/flutrends/), where Internet searches for influenza and related words are analysed, matched with location information, and used to predict the onset of flu ahead of traditional surveillance methods. Applications of Big Data are appearing ever more regularly – for instance, the Open Science Data Project by BT brings together large, published, non-patient-identifiable datasets from the NHS, Department of Health and 'arm's-length bodies' to create a resource that can be used to track prescribing habits against outcomes of using pharmaceutical treatments.

However, Big Data for analytics, powerful as it can be, is by definition retrospective (even if just by a few hours or days). The next wave of solutions is focusing on how the 'high-velocity' data can be used in real or near-real time to improve public health, avoid unnecessary admissions, and raise the speed and quality of patient journeys through care.

Dynamic care – changing the course of events

As the inexorable rise of the 'Internet of Everything' connects more 'things' – not only as data feeds but with real-time information on their location, speed, status ('busy', 'occupied,' etc.) and many other parameters – incredible changes become possible. This dynamic data is particularly useful in healthcare, where the patient experience can be transformed. To many managers in healthcare, 'patient experience' refers to surveys that are analysed once or twice per year. Yet to patients, patient experience is 'what happens to me, now, as I receive advice and treatments – not what I remember for a survey 6 months later'.

Using dynamic, high-velocity information, we can now change patient experience into a real-time concept, making better decisions more quickly. Examples of this are starting to appear. In Nottingham University Hospital, the Hospital at Night programme is managed using Nervecentre software (www.nervecentresoftware.com) to capture requests accurately from the wards, quickly find and send the work to an appropriate doctor, confirm that he or she owns the task, and then track its progress. The result? Many fewer incidents after hours, 8,000 hours given back to care, and an economic payback in less than 4 months (www.accaglobal.com).

Imagine applying a similar approach to governing the processes involved in managing outbreaks of infectious disease in the community. Dynamic care is appearing in other contexts, too. GPS-connected asthma inhalers (www.asthmapolis.com) allow real-time data to be collected, cross-referenced and used to identify hotspots of environmental problems for patients.

We are just at the start. As mobile health technology becomes more pervasive through the use of smart pills (www.proteusdigitalhealth.com/), smart dispensers (www.vitality.com/glowcaps) and apps on phones (www.alivecor.com), and as telehealth becomes the default mode of monitoring patients and delivering care (www.3millionlives.co.uk), the opportunities for real-time interventions and epidemiology will rise exponentially.

Building the bazaars – collaboration models for public health

Big Data in a more connected world challenges accepted governance and organisation structures for health, care and epidemiology. Navigating richer, more complex networks of people, information and knowledge demands similarly networked ways of organising and deciding.

We have to face up to changes in culture, incentives and responsibility. A powerful analogy is described in the paper 'The Cathedral and The Bazaar', written by Eric S Raymond in the 1990s, examining the rise of Linux open-sourced software. Raymond explains why the Linux 'bazaar' approach (open collaboration across loosely connected communities of developers co-ordinated by light structures and a few simple rules) has turned out to be much more effective at solving challenges more quickly because many, different people's skills were simultaneously applied. As Raymond notes, 'To a thousand eyes, all bugs are shallow'. Especially in conditions of uncertainty and rapid change, the bazaar often turns out to be much more adept at problem solving than traditional top-down, hierarchical 'cathedrals'.

The world of public health has to react ever more quickly to infectious disease threats, and has at its disposal a vast array of new data. The big 'cathedrals' in the public health system remain important, but they have to find and nurture new ways to connect with the bazaar – looser networks of individuals and communities who often have the most useful information, experience and expertise. How can we build more bazaars for public health, enabling open collaboration among citizens, patients, professionals and institutions, and enabled and powered by (not submersed in) the deluge of data that the connected world is creating?

Case study 11.2

The need for an early diagnostic for respiratory infections on the intensive care unit

written by Stephen J Fowler, Paul Dark and Ashley Woodcock of the University of Manchester

The complex clinical environment of ICU, combined with the severity of illness in ventilated patients, makes the reliable diagnosis of ventilator associated pneumonia difficult. When ventilation is required on an intensive care unit, there is a significant chance of developing pneumonia. Furthermore, such infections can be caused by highly virulent and/or drug-resistant organisms, such as MRSA or fungi, leading ventilator-associated pneumonia to be significantly associated with ICU-mortality and costs. When pneumonia develops in ventilated patients, the classical clinical features are often not present . Current best practice is therefore based on a pragmatic assessment of simple clinical signs and basic investigations that raise the suspicion of pneumonia but have poor diagnostic accuracy. The main problems that arise from the current approach are:

1 Over diagnosis and imprecise treatment – samples taken for identification of pathogens take 1-3 days to be processed, and even then may not provide detection in some cases. Antibiotics are often given unnecessarily to patients "just in case" and even when appropriate treatment is delivered, it often needs to be given 'blind' leading to greater use of broad spectrum antibiotics and antifungal therapies. This can contribute to the emergence of bacterial and fungal resistance, lead to unwanted-effects and excessive costs, and may prolong ICU length of stay.

2 Late diagnosis – where patients are immune-suppressed clinical features may not be present. In such vulnerable patients, late diagnosis may be fatal. All living organisms generate small molecules as by-products of their metabolism, and as these processes differ between organisms so the molecular mix produced will also differ. Indeed, in the laboratory, one can identify different types of organism, such as bacteria or moulds, by their "molecular fingerprint".

We wanted to investigate whether these molecular fingerprints could be detected in the breath of patients with infection on the intensive care unit. If so, then they may lead us to develop near-patient early warning systems to enable us to detect serious infections earlier, more reliably, and more accurately.

What we did

We have developed a technique for capturing the molecules in the breath that is relatively straightforward, and safe for use in critically ill patients being ventilated on the intensive care unit. The exhaled breath molecules are trapped in a small tube, which is then transported to the nearby University laboratory for analysis. Samples are collected regularly during the patients' stay, alongside the usual clinical surveillance tests that are done to warn of infection, including collecting bronchial lavage samples to look for laboratory evidence of infection. We then analyse the molecular data to see if the breath samples from patients with infections are different to those without.

What we found

Over a six-month period we collected samples from 46 patients without any reported adverse effects of the sampling procedure. The two biggest factors that affected the resulting breath molecular profiles were "personal breath signature" and the length of time that they had been in hospital (possibly due to the effects of immobility, nutrition and/or medication). However when these factors were taken into account, the presence or absence of infection was clearly identified in the breath of the vast majority of patients.

Implications

Our current techniques enable infection to be identified within approximately one hour of sampling the breath. If this test proves equally successful when tested in new groups of patients, and in other hospitals, then we will be able to diagnose infection more quickly and reliably than at present. When tested in larger numbers of patients we may also find molecular fingerprints that enable us to identify specific organisms, and thus target treatment. Further refinements to both the sampling and analytical processes will also be possible, that will further improve speed and accuracy. The availability of such a test should lead to great improvements in the quality of patient management and safety on intensive care.

Electronic prescribing and medicine-tracking systems

Important gaps exist in infectious-disease surveillance in terms of providing data to inform action in areas that are policy priorities, particularly with regard to action to improve antimicrobial stewardship and reduce levels of antimicrobial resistance.

Electronic prescribing systems and medicine-tracking systems exist and are being used around the world to address a range of issues (see "Case Study 'Data management – Aegate Limited' "). These systems are being implemented in the UK in an ad hoc fashion. Surveillance, based on electronic prescribing technologies and processes, needs to be implemented to monitor antimicrobial use in the community and hospitals, with local benchmarking. It is likely these systems will continue to be implemented in an ad hoc fashion, and to allow national surveillance interoperability standards will be key.

Case study 11.3

Data management – Aegate Systems

written by David Cooksey, Aegate Limited

Innovation in data management presents opportunities to improve both prescribing habits and mechanisms while also addressing the issue of counterfeit antibiotics. It has been estimated that antibiotics are the most counterfeited medicines, accounting for 28% of all global counterfeits at the turn of the millenium[1].

Counterfeit medicines are a growing issue internationally, but are unlikely to be wide spread in England. The Medicines and Healthcare Products Regulatory Agency (MHRA) reports only ten identified cases of counterfeit, prescription only medicines reaching patients through the legal supply chain in the UK since 2004[2]. However, improvements in data management and prescribing habits could contribute substantially to achieving effective antibiotic stewardship; a key ambition to reduce antimicrobial resistance.

An example of this is provided by Aegate, a Cambridge based company. Aegate provides authentication services at the point of dispense, i.e. checking that the medicine that is dispensed is not counterfeit, expired or has been recalled before it is given to the patient.

The Aegate system, which uses bar code technology, has been in operation for over five years in Belgium, Greece and Italy, where over ten thousand pharmacies have collectively been scanning millions of pharmaceutical packs every day. The Aegate system, in effect, digitises the pharmaceutical supply chain, improving data flow to each participant. The primary benefit of such a system is improved drug management, and the system has already been used to:

- ensure pharmacists receive real-time information from pharmaceutical companies and regulatory authorities, for example on medicine recalls,
- enable practice managers to access better information for financial management (processes can be set up for feedback on the cost effectiveness of medicines and patient outcomes), leading to changes in prescribing patterns, and
- allow patients to access links to online educational materials on the optimal use of their medicines and support improved compliance and patient outcomes.

Innovations in medicines monitoring, driven by the drug authentication agenda, could have a huge impact on addressing counterfeit antibiotics and improving antimicrobial stewardship. Systems like this, when coupled with electronic prescribing systems or other surveillance data, could lead to increasingly sophisticated information about prescribing patterns and patient outcomes. This in turn may seriously affect our approach to dispensing antimicrobial medications and help to develop best practice.

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Zoonotic surveillance

Surveillance for zoonoses is made more challenging by the fact that they may produce few, if any, clinical signs in the animals they infect. Zoonoses may not therefore present for veterinary investigation, and disease will first be detected in the human population.

The UK has an extensive virtual surveillance network for zoonoses, which aims to gather and present data from multiple sources so that multi-disciplinary scientific advisory groups such as HAIRS (Human Animal Infections and Risk Surveillance), ARHAI (Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infections) and ACDP (Advisory Committee on Dangerous Pathogens) can assess the risk and advice goverment.

The potential for emergence of zoonotic diseases outside the UK also reinforces the importance of the role of international agencies, such as the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) and the need for global surveillance to achieve early identification and risk assessment, and to enable the timely setting up of control measures.

In the long term it is clear that surveillance systems for detecting zoonoses will become more sophisticated and that we can expect emerging or re-emerging zoonoses to present new threats. What is unlikely to change is the need for close interaction between the veterinary and public health teams to determine and deal with these threats. The multi-disciplinary groups such as HAIRS, ARHAI and ACDP or their successors will be central to achieving this.

Conclusions

The greatest challenge of the future will be the linkage and analysis of new and existing sources of information. As a society we need to make sure this is possible. This involves recognising the benefits for all that result from better surveillance systems and ensuring that we are not held back by a lack of forethought when surveillance and information systems are being developed that make it impossible to link data from different sources.

Linking the information alone is not enough; we will also need to develop ways of analysing such large quantities of information. This will mean developing the professional skill base of those involved in public health surveillance, but also considering how we can open up such information to encourage and take advantage of the variety of communities that are engaged in trying to solve similar issues.

3. Workforce and resources

written by Professor Sue Hill, Doctor Tom Fowler and Professor David Walker

Convergence of resources – veterinary and human sharing

Zoonoses are an obvious area to explore the potential for convergence – the sharing of data, expertise and laboratory capacity between the veterinary and medical sectors, at a time when both are under increasing budgetary pressure. It provides the potential to avoid duplication of effort and facilities, and to combine teams to ensure the maintenance of critical mass. It may also permit capacity to be maintained across a greater range of diseases than either sector could afford independently. Even where physical co-location is not desirable or practical, it may be possible to provide complementary diagnostic services for certain diseases. Achieving this will present challenges in terms of improved alignment of diagnostic techniques and data systems, and the closure or relocation of some facilities.

Workforce challenges – the skills and knowledge base

The human genomics strategy report 'Building on our inheritance: Genomic technology in healthcare' (2012) describes the development of a sea change in the perception and use of genetic technology in healthcare. Over the past 5 years there has been a growing understanding of the crucial implications for the prevention, control, diagnosis and management of infection and the practice of the microbiology and virology of genomics – and its interpretative and closely aligned analytical partner specialty, bioinformatics.

The challenges facing the multi-professional workforce in infection

The diagnosis, management, prevention and control of infection is a prime example of the effectiveness of a multi-professional workforce which, when working in synergy, gives added value to patient care and protection.

Laboratory diagnostics for microbiology, and even more so for virology, have been transformed in recent years by the evolution of molecular techniques. Not only are these tests more sensitive than the culture of organisms but results can be achieved in a few hours, rather than several days, facilitating appropriate rapid treatment which greatly benefits patients. These advances have been achieved by collaborative working between scientists, doctors in the NHS, academia and industry. It is increasingly apparent that we need to foster an environment where cutting-edge scientific research and innovation can occur. For this to take place, a range of people with different scientific, clinical and public health skills will need to work collaboratively.

Understanding the developmental needs of the workforce

The human genomics strategy report identified that 'genomics is a relatively new field in medicine, and as such has not been part of standard medical or healthcare professional education and training'. While this is changing, it fundamentally means that the majority of those working in healthcare in England will have a limited knowledge of genomic technology – and even less practical experience of applying genomics within their role.

In relation to infection (which crosses virtually all clinical and service boundaries), there is a need therefore to develop an awareness, knowledge and understanding of genomics in relation to infection for all those who work in clinical medicine and in public health. For example, clinicians from all clinical backgrounds should:

- Understand the benefits (and limitations) of genomic technology and the information it can offer
- Have an awareness of how it can be applied clinically
- Have a basic understanding of the science of sequencing and testing, and the relationships between individual datasets and the wider genomic knowledge base
- Understand data-protection issues concerning the use, sharing and storage of genomic information.

Infection training and genomics

The accelerating developments in molecular diagnosis across all areas of microbiology open exciting possibilities and opportunities. Use of mass spectroscopy has become common in bacteriology diagnosis, and molecular methods will increasingly replace conventional diagnostics (e.g. faecal molecular panels already in regular use can diagnose salmonella, shigella and parasites; most bacteriology for sexually transmitted diseases is also now based on molecular technology). The potential of rapid and ever less costly whole-genome sequencing will further revolutionise our approach to scientific diagnosis, and will inevitably lead to an increased emphasis on skills in bioinformatics to handle enormous quantities of data (e.g. for point-of-care molecular testing).

To make full use of bioinformatics, we need scientists and doctors and other healthcare staff to work together to research, innovate and interpret the meaning, relevance and impact on patient outcomes of these sophisticated molecular analyses. In clinical settings, the clinical scientists and medical staff need to work collaboratively in large diagnostic laboratories, using their complementary knowledge and skills to create cutting-edge diagnostic services. Furthermore, scientists, medical staff, pharmacists, and nursing and care staff in hospitals, primary care and the community all need to be able to understand and communicate effectively and efficiently about infection issues and the importance of antimicoribial stewardship. The knowledge and skills gaps need to be assessed and the training needs identified and subsequently addressed through integration of the appropriate curricula and learning outcomes into formal training programmes and continuing professional development.

Current developments in healthcare science training through the Modernising Scientific Careers programme give the opportunity to ensure that genomics is a core element of training for all healthcare scientists. Indeed, academic and workplace training in molecular genetics is a common thread throughout all of the pathology-based clinical scientist curricula.

Future skill needs

All students and staff in the NHS and public health workforce receive training in infection and, in particular, infection control and antibiotic stewardship. However, to fully realise the potential benefits from advances in diagnostic testing, more specialist training to ensure the best that science and genomic medicine has to offer should be made available to enhance the skills not only of scientists but of the whole public health and specialist microbiology/virology medical and scientific workforce. Moreover, the entire healthcare workforce, and given their key role in antibiotic stewardship in particular pharmacists, needs to have sufficient knowledge and awareness of the application of genomics to infection control and management, to ensure that there is sufficient understanding of their application to the management of patients and to the epidemiology of infectious agents and outbreak control.

In addition, we need to be bold in planning the future specialist infection workforce. Medical staff, public health specialists and consultant clinical scientists trained in infection need to come together to optimise the enormous talent, expert knowledge and benefit that training in the new genomic/bioinformatics analytical techniques will bring to patients. For example, merely planning to 'replace' the current consultant clinical science workforce in microbiology and virology will not be good enough – we must 'see the future' in terms of this new science and employ the opportunities of training and education to ensure we have a workforce positioned to use it. Commissioners need to appreciate the complexity of these issues for both clinical and educational commissioning.

A fit-for-purpose specialist infection workforce requires the continued development of higher specialist training in medicine, public health, pharmacy and for clinical scientists in the infection specialities. Genomics, bioinformatics and antibiotic stewardship need to be at the core of this development. The Modernising Scientific Careers programme will establish systems to facilitate regular review of training and curricula so that, over the next 5–15 years, a cadre of consultant clinical scientists in infection can ensure that the

best science is being used for the benefit of patients and the NHS in all care settings. The Royal College of Physicians and the Royal College of Pathologists have designed a joint specialist training scheme in infection, moving away from segregated training schemes. This will produce consultants with a range of core skills who have also had the opportunity to develop specific skills in infectious diseases or clinical microbiology. **While this may go some way towards addressing future workforce needs, all specialist training curricula in microbiology, virology and public health (including non-medical public health specialists) also require such scrutiny to ensure that the future workforce develops the necessary skills and expertise**. General curricula need to emphasise surveillance, antibiotic stewardship and optimal management of patients.

4. New knowledge and technology

There are three areas that were felt to require a specific focus in the horizon scanning: the challenges for immunisation, the implications of whole-genome sequencing for diagnostic and public health microbiology and the implications of advances in genomic understanding and diagnostic testing, and future strategies for Research and Development. Specific sections were commissioned as stand-alone pieces for all three of these areas.

Challenges for immunisation

written by Professor David M Salisbury

An immunisation programme that does not change will not provide its recipients with the best protection against disease. In the future we can expect there to be many changes in vaccines, in vaccinations and in the organisation of the vaccination programme. Each of these brings challenges.

In 1796 there was one vaccine, while 200 years later there are licensed vaccines for around 30 diseases, vaccination has eradicated smallpox, and polio eradication is within our sights. As there is now better understanding of the immunological determinants of infection and immunity, along with the development of vaccines that generate specifically targeted immune responses, we can expect new vaccines against infectious diseases and also the application of 'vaccines' against non-infectious diseases. For example, vaccines that are effective against AIDS and tuberculosis are going to require the generation of both antibodies and T-cell-dependent responses. We already have two cancer-preventing vaccines (hepatitis B and human papillomavirus (HPV) vaccines), but we may see vaccines that contribute to the treatment of cancers by stimulating immune responses, and vaccines against conditions such as hypertension and substance addiction.

The application of 'systems biology' is already allowing the prediction of immune responses to vaccines through gene signatures, such that in the future efficacy may be assumed without formal trials.[1] When the World Health Organization undertook a prioritisation exercise for new vaccines in 2008, top of the list was the need for new influenza vaccines. **Experience in the 2009 pandemic showed clearly how valuable it would be to have influenza vaccine that was cross-protective against all strains and thus generated long-lasting immunity.**

If the prioritisation for development of new vaccines were done on the basis of the global burdens of disease, then HIV, tuberculosis and malaria would win. But if that prioritisation were done on the feasibility of successful candidate vaccines being developed, then other diseases may overtake these three. More promising candidates are detailed in the following list:

- Pneumonia and diarrhoea are major killers of children. With the advent of pneumococcal conjugate vaccine and rotavirus vaccine we are already making inroads into these conditions, but the use of pneumococcal conjugate vaccine has seen the emergence of replacement strains and rotavirus vaccines are not fully heat stable: better vaccines are needed.
- After many years of failed attempts, there are reasonable prospects for vaccines that will be effective in preventing infection with respiratory syncytial virus. This causes considerable morbidity in children less than 6 months of age, so requires either very early vaccination (when vaccines may not be effective) or vaccination in pregnancy. A further challenge is that infection does not ensure immunity from re-infection.
- Ebstein-Barr virus causes infectious mononucleosis and, while this is usually a self-limiting infection, it can cause prolonged fatigue and, rarely, encephalitis, hepatitis, severe haemolytic anaemia or thrombocytopenia. It is also associated with gastric and nasopharyngeal carcinomas, and Hodgkin's lymphoma. Again, there are some encouraging signs of progress towards vaccines.
- While congenital rubella syndrome has been eliminated in the UK, more cases of congenital infection, deafness and developmental delay continue to be caused by cytomegalovirus virus (CMV) than were caused by rubella in the pre-vaccination era. CMV reactivation is also problematic in immunosuppressed transplant patients. There are better prospects now for vaccines against CMV, but proving their effectiveness against fetal damage is likely to be complex.
- The UK has made huge inroads into the prevention of meningitis and septicaemia, with virtual elimination of *Haemophilus influenzae* b and meningococcal C cases; cases from pneumococcal infection by vaccine strains are also decreasing greatly. For many years, there have been hopes for vaccines that would be effective against group B meningococci and two candidate

products are getting closer. However, they are more complex products than the polysaccharide conjugates (*Haemophilus influenzae* b, meningococcus serogroup C and pneumococcus) and are unlikely to have such dramatic impacts on disease. Group B streptococci are the cause for an underappreciated burden of meningitis: most of the cases are in newborns or infants. There are encouraging signs that these cases might be preventable through maternal immunisation, raising the profile of the benefits from vaccination in pregnancy to prevent early disease for influenza, pertussis and meningitis.

The next decade may see not only new vaccines but also new ways to give vaccinations. Recently introduced vaccines, such as HPV, meningococcis serogroup C and *Haemophilus influenzae* b vaccines, are already much more thermostable than their predecessors, but the goal is for all vaccines to eventually no longer require a cold chain. However, removing some vaccines from the cold chain would have a relatively small impact on the vaccination infrastructure, as ideally all vaccines would need to be thermostable to have a significant impact. Perhaps this is ambitious, but vaccines could be administered by jet injectors, microneedles or dermal patches; aerosol and nasal vaccines already exist. New adjuvants will allow lower doses of antigens or weak antigens to become more immunogenic; vaccines may be 'harvested' from plant growth systems rather than human or mammalian cell lines.

We also have opportunities to be far more creative in the way we collect information, process it and communicate about vaccination. When HPV vaccine was launched in England, an award-winning communications package included a strong use of web-based social media, and mobile phone alerts will become a routine way of receiving information that is personalised and targeted. **GP databases that hold email addresses or mobile phone numbers should already be capable of scheduling influenza vaccinations.** Mobile phone ownership must be almost ubiquitous among young parents and appointments for infant vaccinations could be easily and more cheaply sent that way, rather than by post. Already, social media use puts more and more people in touch with each other and with access to information, some of which is correct and some of which is misleading. The ways in which individuals make decisions are changing and will continue to change: effective communication about vaccines will need to anticipate these changes.

Our present immunisation informatics system is world-leading in its ability to schedule immunisation, measure coverage and order vaccines. However, it is built on creaking systems that are diverse, cumbersome and fragmented. **We need a national, single web-based system that: identifies every individual, every vaccine that they need and when they need it; schedules immunisations; identifies defaulters; audits refrigerators' stocks and orders vaccines; and is easily interrogated.** Most of these functions can be run from a modern mobile phone. The fragmentation of computer systems to 'localism' threatens the effective interchange of data, bringing no benefits but only unneeded inefficiencies.

Finally, we need to be confident that, as English health systems evolve, the immunisation programme does not lose its way between a raft of new players such as Public Health England, the NHS Commissioning Board, local authorities, clinical commissioning groups and the Department of Health. As more vaccines come onto the scene and the immunisation programme needs to adapt, clarity of leadership and roles and responsibilities will be ever more important. The present processes of availability of expert advice, world-leading epidemiology, modelling and economic analysis will be needed to ensure that new vaccine programmes are cost-effective, so that the best use is made of resources bringing new vaccines and new vaccinations promptly to those who will benefit from them.

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Implications of whole-genome sequencing for diagnostic and public health microbiology

written by Professor Sharon Peacock

Rapid technological advances in DNA sequencing have led to the availability of benchtop sequencers that can sequence multiple bacterial or viral genomes in less than a day. This has been associated with a drastic reduction in cost, which is approaching a figure (around £95 per bacterial genome at the time of writing) that could be justified in routine practice if shown to be associated with cost-benefit. The challenge now is to identify where the use of this technology could provide tangible benefit to individuals with infectious diseases, and improvements in the health of the nation through enhancements in surveillance and control of infectious diseases.[1]

An obvious application for microbial sequencing is to support the investigation and control of outbreaks, such as those that occur following the ingestion of food or drink contaminated by a pathogenic bacterium. An important component of such an investigation is to detect and identify the causative organism in both patient samples and the putative contaminated source, typing of which can provide confirmation of the source as well as evidence for inclusion of cases. An important limitation of the available bacterial typing techniques is that they often have restricted resolution and may not be able to distinguish

the extent to which two or more organisms of the same species are, or are not, genetically related. By contrast, **whole-genome sequencing gives the ultimate in resolution between two related pathogens.**

The application of whole-genome sequencing to several high-profile outbreaks has been reported, including the *Escherichia coli* O104:H4 outbreak in Germany.[2, 3] Sequencing was performed towards the tail end of the outbreak and did not change its course, but it did provide an explanation for why so many people developed severe complications from their illness. Planning for the rapid deployment of sequencing during food-borne outbreaks is under way in several countries in Europe and in the USA, and it is highly likely that this will ultimately become incorporated as standard practice during outbreak investigations. In the longer term, microbial sequencing could be applied proactively (rather than reactively to an outbreak) to monitor the presence and spread of emerging clusters of bacteria, providing an early warning system to spot impending outbreaks. For example, **specified pathogens isolated in diagnostic laboratories could be sequenced and this information could be collated and compared over time to track disease trends. Such a system could also be used to monitor the emergence and spread of clinically important bacterial drug resistance.**

Outbreaks are also important in hospitals, where extensive infection control measures are effective in preventing most but not all outbreaks caused by pathogens such as meticillin-resistant *Staphylococcus aureus* (MRSA) and *C. difficile*. Most infections caused by these organisms belong to a very limited number of lineages – for example, most MRSA in hospitals belong to a single lineage called EMRSA-15. **Current typing techniques cannot usually distinguish between strains of EMRSA-15, but there is growing evidence that whole-genome sequencing can be used to map the spread of MRSA within or between hospitals, or between the hospital and community.**[4, 5, 6, 7] The reconstruction of transmission pathways in real time could provide the necessary information for infection control teams and healthcare workers to take corrective action to prevent further transmission from occurring. Sequencing could also be used to investigate and control outbreaks caused by Gram-negative bacilli,[8] which most often occur in intensive-care units and in association with bacterial strains that are resistant to numerous antibiotics.

Case study 11.4

The possible benefits to be gained from whole-genome sequencing of pathogens associated with infections that occur during admission to hospital are the subject of intensive study. MRSA is one of the organisms under consideration. The marked decline in MRSA bloodstream infection rates across the UK is a notable success story and the result of major infection control efforts, but other (usually less serious) types of MRSA infection continue to occur. Infection can only occur once an individual has become colonised with MRSA, and so stopping the transmission of MRSA from one person to the next is a key objective in the control of this residual problem. A recent study has given some insights into the type of information that could be gained.[7] This involved the investigation of a suspected MRSA outbreak that occurred on a special care baby unit (SCBU) in the UK. Genome sequencing of the MRSA isolate from 17 infants who became colonised with the organism was able to unequivocally identify 14 infants who were involved in the outbreak over a 6-month period, and exclude three infants who were MRSA positive but not involved in the outbreak.

But perhaps more striking were the results generated by the sequencing MRSA isolates grown from clinical specimens that had been submitted by GPs or outpatient departments around the same time period as the outbreak.

A collection of MRSA isolates with the same antibiotic resistance pattern as the outbreak strains was chosen for sequencing (19 in all), of which 10 proved to be a very close genetic match to the outbreak strains. A detailed evaluation of patient records demonstrated that all 10 cases could be linked back to the SCBU. Using the methodology currently available to infection control teams, it would have been difficult to make a link between the SCBU and MRSA-positive samples from people living in a relatively dispersed geographical area and presenting to numerous different clinical outpatient settings. What does this tell us about the potential for microbial sequencing? Although more detailed research is required, the preliminary evidence suggests that whole-genome sequencing of MRSA could represent a very important new tool for infection control teams whose aim it is to understand how and where MRSA is transmitted, and to put in place strategies to prevent this from happening.

Genome sequencing is also likely to gain a central role in the investigation of emerging pathogens, most of which are novel viruses. For example, this could be used to track in fine detail the behaviour of individual influenza virus lineages during the course of a single epidemic or pandemic. The type of information that can be generated was well illustrated by a retrospective study of the pandemic H1N1/2009 influenza virus infection in the UK.[9] It is likely that sequencing would be used at the start of any subsequent epidemic or pandemic viral infection to provide an accurate indication of national and international spread, and to monitor for genetic changes in a recently emerged virus that would be predicted to lead to increased transmissibility and a consequent rise in cases. Pathogen sequencing is also likely to become incorporated into the routine management of patients with a range of viral infections. This is already the case for people with HIV infection, with increasing use of viral sequencing to guide treatment with a specific drug (chemokine receptor blocker) in order to predict drug efficacy.[10]

The combination of the cost and complexity of whole-genome sequencing is likely to restrict its use in the routine diagnostic microbiology laboratory for the foreseeable future, but there are several situations where its use could actually reduce costs and yet improve patient care and public health. An important example is *Mycobacterium tuberculosis*, the cause of tuberculosis. The rapid institution of effective antibiotic treatment is important for individuals with tuberculosis, and also reduces the risk of spread to others. At odds with this need for speed, *M. tuberculosis* is slow to grow in the laboratory and this can lead to delays in completing tests of drug susceptibility. This problem has been overcome to some extent by the development of molecular tests that detect the presence of genetic markers of resistance. The number of drugs that can be tested for in this way is limited, however, and full testing using conventional methods may take several weeks to complete. A genome sequence could provide a complete inventory of drug resistance genes in a much shorter timeframe. One proviso is that accurate interpretation of sequence data will need to be underpinned by a comprehensive understanding of the relationship between variation in the sequence of genes that could influence drug susceptibility, and the actual susceptibility. The use of sequencing has also been described to investigate a tuberculosis outbreak in conjunction with social-network analysis.[11] ***M. tuberculosis* are routinely genotyped in the UK, and the sequence data generated to define drug resistance could be used in its place and at no extra cost.**

Whole-genome sequencing could also replace a range of other tests performed in reference laboratories, including bacterial identification of rare or difficult-to-grow pathogens, and the detection of genes that may be associated with virulence. If performed in local or regional laboratories, there could be immediate cost savings, obviation of postal delays that arise when bacteria must be sent away for reference testing, and simplification of workflow based on the fact that genome sequencing can give much or all of the information that is otherwise obtained through numerous and sometimes sequential tests. The Health Protection Agency is undertaking a review of the predicted bioinformatics needs associated with the future use of microbial sequencing for diagnostic and public health microbiology, which could provide the opportunity for the future transformation of reference laboratory functions through the introduction of genomics technologies.

Current barriers to the implementation of rapid whole-genome sequencing include the lack of automated tools that interpret sequence data and that provide clinically relevant information in a format that can be understood and acted upon by people with no specialist informatics expertise. Detailed assessments of the feasibility, utility and cost-effectiveness of rapid whole bacterial genome sequencing are also needed to determine the optimal strategy for deploying this technology in routine clinical practice. Despite these caveats, rapid whole bacterial genome sequencing has the potential to transform diagnostic and public health microbiology in the coming decade.

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Future strategies for R&D

written by Professor Danny Altmann

The research horizon with respect to infectious disease has arguably changed more in the past 5 years than at any time since Fleming. This is the result of rapidly changing methodologies and resulting datasets, along with the need to be responsive to a highly changeable landscape of emerging and re-emerging disease at a time of population movements and climate change.

The resulting impacts on research needs are considered under the following headings:

- Funder organisation and interactions
- Research topics
- Impacts of host and pathogen genomics
- Cohorts, surveillance and data connectivity
- Biologics and other new therapeutics
- Research into translation and policy.

Funder organisation and interactions

With the considerable challenges ahead, it is vital that the channels of funding available for infectious disease research can be accessed and utilised by research groupings to maximal advantage. Potential funders in this area include the National Institute for Health Research (NIHR) and Department of Health, the Medical Research Council (MRC), the Biotechnology and Biological Sciences Research Council (BBSRC), the Department for Environment, Food and Rural Affairs (Defra), the Veterinary Laboratories Agency (VLA), the Wellcome Trust, disease-specific charities such as the Cystic Fibrosis Trust, and biotech and biopharma bodies. There may often be a lack of clarity in understanding of the precise remits of these different agencies and thus who is responsible for building which aspects of the infectious-disease research response. Researchers need to understand the focus of funding bodies remits and the demarcation between them.

The successful implementation of the Health Innovation Challenge Fund (HICF) as a joint funding venture between the Department of Health and the Wellcome Trust is an excellent example of the added value and leverage of imaginative funder partnerships in this area. The 2012 HICF £13.8 million award for roll-out of diagnostic molecular microbiology promises massive impact, both nationally and internationally.

Research topics

As explored in detail at a workshop organised at the Department of Health (see Chapter 1), there are a number of widely agreed infectious-disease priorities for the coming years. These include the roll-out of molecular diagnostics, antimicrobial resistance in the context of bacterial infection, healthcare-associated infections, emerging and re-emerging diseases (including new influenza variants and other zoonoses), and the control of tuberculosis in the face of highly migratory population movements. While the UK clinical and basic science research community has considerable strengths in infectious disease, it is of finite size and does not cover expertise in all of the appropriate pathogens and pathologies. There are perhaps lessons to be learnt from the evolution of the research funder response to the 2009 influenza pandemic. From the peak of UK influenza research under John Skehel and others in the 1970s and 1980s, this had become a somewhat unfashionable area with funders and relatively little research infrastructure was in place to respond to the pandemic. As a result of targeted funding calls, several consortia of researchers were generated, including MOSAIC and FluWatch, often drawing in researchers from other areas. In planning for a future of changeable pressures imposed by diverse pathogens, it may be necessary to build the expectation that successful research careers of the future will be built around a similar flexibility to shift research priorities in response to societal need and corresponding funder strategies.

Impacts of host and pathogen genomics

The impact of changing technologies and lower costs for high-throughput genomic sequencing of humans, our pathogens and our commensals (microbiome sequencing initiatives) is changing this landscape rapidly. The most immediate consequences are starting to be seen in microbial diagnostics and drug resistance data. There had long been a sense that medical microbiology had to be brought into the 21st century and onward from the classical approaches of Fleming's day. A major step in this direction was the UK Clinical Research Collaboration Strategic Planning Group on Microbiology and Infectious Diseases 2008 report 'Developing Microbiology and Infectious Diseases Research in the UK',[1] from which a key outcome was the commitment of £16.5 million from a consortium of funders to fund the UKCRC Translational Infection Research Initiative (TIRI), which is now well under way. The issues were debated and summarised at the Public Health Infection Research Workshop organised by the NIHR and MRC at Chandos House in December 2009, and the findings were then passed to the Office for Strategic Co-ordination of Health Research OSCHR.[2]

Efforts from these initiatives will now be considerably strengthened by the 2012 HICF awards described earlier. There is no doubt that we now have the wherewithal to apply sequencing approaches to rapid diagnosis, assessment of drug resistance and geographical tracking of outbreaks. The great power of these new approaches brings its own new challenges. These include: the impacts on our models and costing for infrastructure of diagnostic services to the NHS (Health Protection Agency); analysis, management and storage of unprecedented amounts of genomic data; appropriate training of future generations of clinicians and scientists to enable them to engage

with this data, even in processed form, and to utilise it critically; and electronic linkage of this data to other clinical datasets. At the same time, increasing availability of data on patient genomics, from microarrays and genome sequencing, offers the potential for personalised medicine. Potential applications will be in identifying vulnerable populations for targeted care at the extremes of the disease susceptibility spectrum, and in predicting successful responders to specific therapeutics.

Cohorts, surveillance and data connectivity

Unique aspects of the UK healthcare infrastructure and research legacy arguably make us world leaders in the population health/epidemiology lessons that become accessible by having an electronically networked national health service in conjunction with well-funded, large-scale cohort-based research. The UK has an outstanding track record in this area. Large cohorts studies such as the Million Women Study, ALSPAC (Avon Longitudinal Study of Parents and Children) and Twins UK are now joined by the massive resources devoted to the UK Biobank (currently more than £96 million), along with the forthcoming 2012 Birth Cohort. These offer massive opportunities to UK researchers, at the same time as posing challenges for e-health connectivity and ethics.

Biologics and other new therapeutics

In infectious disease, as in other areas of medicine, many of the forthcoming therapeutics from drug development pipelines are biologics, especially monoclonal antibodies. Among countless recent examples has been the great success of Tysabri (Natluzimab) for multiple sclerosis. The new generations of drugs occupy an ever-larger part of the therapeutic armamarium, but come at a much higher health-service price due to the high production standards and costs. It is predicted that the size of this drugs market will hit $158 billion in the next few years.[3] Potential impacts on infectious disease come, for example, from investigations of widely cross-neutralising human monoclonal antibodies against HIV, influenza and *C. difficile*.

Research into translation and policy

The UK retains an outstanding record in basic medical research into infectious disease, punching well above its weight in several areas, including HIV, bacterial genomics and parasitology. Changing attitudes and greater caution in biopharma during the recession have contributed to the perception that the hurdles are higher than they have ever been for successful translation of potentially beneficial and financially lucrative discoveries. There is a strong case here for a reappraisal of the potential for nurturing and supporting small businesses aimed at the spin-out of new therapeutic breakthroughs from academia, as has been rather successfully applied in the USA. Even if we had a better pipeline for translation of research discoveries, there is enormous unmet need in our understanding of how to bridge the gaps between researchers, clinicians and policy-makers in such a way as to optimise the implementation pathway. A greater investment in the social science studies of successful research into policy strategies is warranted.

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Appendix 1

Recommendations

CHALLENGES AND OPPORTUNITIES

Antimicrobial resistance is increasing worldwide, the government needs to:

- put antimicrobial resistance on the national risk register (specifically, the 'National Security Risk Assessment')
- implement effectively the UK 2013-2018 cross government antimicrobial resistance strategy
- Improve global leadership and action, particularly around the development of new antibiotics and preserving the effectiveness of existing antibiotics (antibiotic stewardship)

Education and awareness needs to be improved around

- antimicrobial resistance, strategies for prevention
- and antibiotic stewardship, which should be part of routine curricula for all clinical professionals
- raising awareness of antimicrobial resistance and appropriate antibiotic use among the public, managers and professionals

Surveillance systems - Public Health England and the NHS Commissioning Board need to

- develop surveillance systems to underpin their strategies for prevention and antibiotic stewardship
- monitor infection
- monitor antimicrobial (in particular antibiotic) prescribing
- monitor antimicrobial resistance (AMR)
- link this information to other Health and Care datasets to inform future action

Diagnostic technology for infection – rapid diagnostics that allow movement aways from broad spectrum treatments to more tailored approaches is a key area of innovation

- Genomic technologies have a major role to play in the future and we need to be prepared to take advantage of this
- Developments in point of care diagnostics are also particularly important as these have the potential to substantially increase the speed of diagnosis.

Recommendations

Where

Defra	Department for Environment, Food and Rural Affairs
DH	Department of Health
HEE	Health Education England
HSCIC	Health and Social Care Information Centre
HWBB	Health and Wellbeing Boards
NHSCB	NHS Commissioning Board
PHE	Pubic Health England

Recommendation		Organisation
1	Infectious disease issues (particularly immunisation, TB and Flu) need to be included as standard in JSNAs and Health and Wellbeing Boards should explicitly consider how they will address inequalities due to infectious diseases in their local Health and Wellbeing strategy.	HWBB
2	Better management of process, such as standardisation of surgical practice, needs to occur. Consequently, NICE should be commissioned to produce evidence based guidance in this area. Surveillance systems must allow the monitoring of the effectiveness of such interventions.	NHSCB
3	There needs to be an expansion of our policy focus from a concentration on MRSA and *C. difficile* (though continued monitoring remains important), towards the inclusion of other significant infections.	Goverment and DH
4	Infection control policies of organisations responsible for the care of individuals should explicitly address the settings of care, including a focus on the home and community.	Government, DH and NHSCB

Recommendation		Organisation
5	Information standards need to be developed that allow national surveillance of infections, incorporating the information from emerging technologies and which also promote the local use of information. Public Health England, The Information Centre for Health and Social Care, and the NHS Commissioning Board will need to work together to develop and promulgate these information standards. This needs to be part of the work around inter-operatability standards for health information systems.	PHE, HSCIC, NHSCB
6	Public Health England and other organisations with a surveillance remit must invest in workforce skills around data mining and bio-informatics. Collaborations between these organisations and academic institutions must be explored. Ways need to be found that allow us to make data transparent and available so that the many communities interested in data can be encouraged to help solve some of the analytical challenges posed by infectious diseases.	PHE, HSCIC, NHSCB
7	Action is needed at the international, national and local level: antimicrobial resistance should be an issue that has the same level of political interest as MRSA and *C. difficile* in England. It should be placed on the national risk register (specifically, the 'National Security Risk Assessment') and the Government should campaign for it to be given higher priority internationally, including collaborations to ensure the development of new antimicrobials and vaccines such as Private Public Partnerships.	Government
8	The national approach to tackling antimicrobial resistance should be managed jointly between DH and Defra to ensure that a comprehensive integrated programme is developed. The UK 2013-2018 cross government antimicrobial resistance strategy and action plan is welcome. It provides a base for future working but this needs to be built upon.	DH and Defra
9	Rapid diagnostics enabling appropiate treatment and surveillance will be key to addressing the issues raised by imported infections. Identification of imported infections and carriage of organisms with antimicrobial resistance is critical. Once identified, effective infection control mechanisms exist for most infections. This should be a specific focus within the Public Health England surveillance strategy.	PHE
10	Public Health England, both through the NHS Commissioning Board and as part of its health improvement strategy, needs to consider how it will promote the understanding of the benefits and encourage the informed uptake of immunisations during pregnancy.	PHE
11	Vaccination uptake rates are a key priority and need ongoing monitoring. This is likely to be the single most effective intervention for reducing disease burden due to infection. Within the commissioning of immunisation by Public Health England from the NHS Commissioning Board, and through schools, there should be a requirement to ensure improvement of vaccination coverage in those groups with traditionally low uptake.	PHE
12	Public Health England and the NHS Commissioning Board should provide joint guidance for the commissioning of preventative public health programmes and services aimed at adolescents. This is a priority for sexual health services where the need goes beyond adolescents to other groups, particularly men who have sex with men where the rising HIV prevalence requires a reassessment of current approaches. Joint Strategic Needs Assessment's (JNSAs) should include an assessment of the effectiveness of joint working in this area, with Health and Wellbeing boards holding local commissioners to account.	PHE and NHSCB
13	Directors of Public Health should ensure that the school nursing system they commission is fit for purpose for the implementation of new vaccination programmes.	HWBBs
14	Training and CPD (continuing professional development) need to include a specific focus on infectious disease and risk groups, so that medical practitioners, healthcare professionals and managers are equipped with the right skills to deal with these challenges. The Royal Colleges responsible for CPD and Health Education England should ensure that this is incorporated effectively into current and future education initiatives.	Royal Colleges and HEE

Recommendation		Organisation
15	Public Health England, as part of its health improvement strategy, should include a focus on improving people's knowledge and behaviour around infection risks abroad. This should include encouraging the public to seek travel health advice before travelling.	PHE
16	There is good evidence of the effectiveness of improving staff knowledge and understanding of infection control in improving health outcomes. We need to extend and improve this expertise in health and care workers now, and continuing into the future. Making those organisations that are primarily responsible for care also responsible for infection control issues in care settings would be a key step in ensuring these issues are were addressed.	Government
17	Any national strategy that encompasses the development and roll-out of genomic diagnostic testing for infections should include the delivery of real surveillance data as an integral part.	DH

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Appendix 2

Data visualisation and interpretation

Data visualisation and interpretation

The Annual Report of the Chief Medical Officer 2011 is published in two volumes. Please refer to the section "How to use this report" in Volume One of the report for a detailed description of the methods used to visualise the data in this volume, the caveats to be considered when interpreting the data and advice on how to interpret the information displayed.

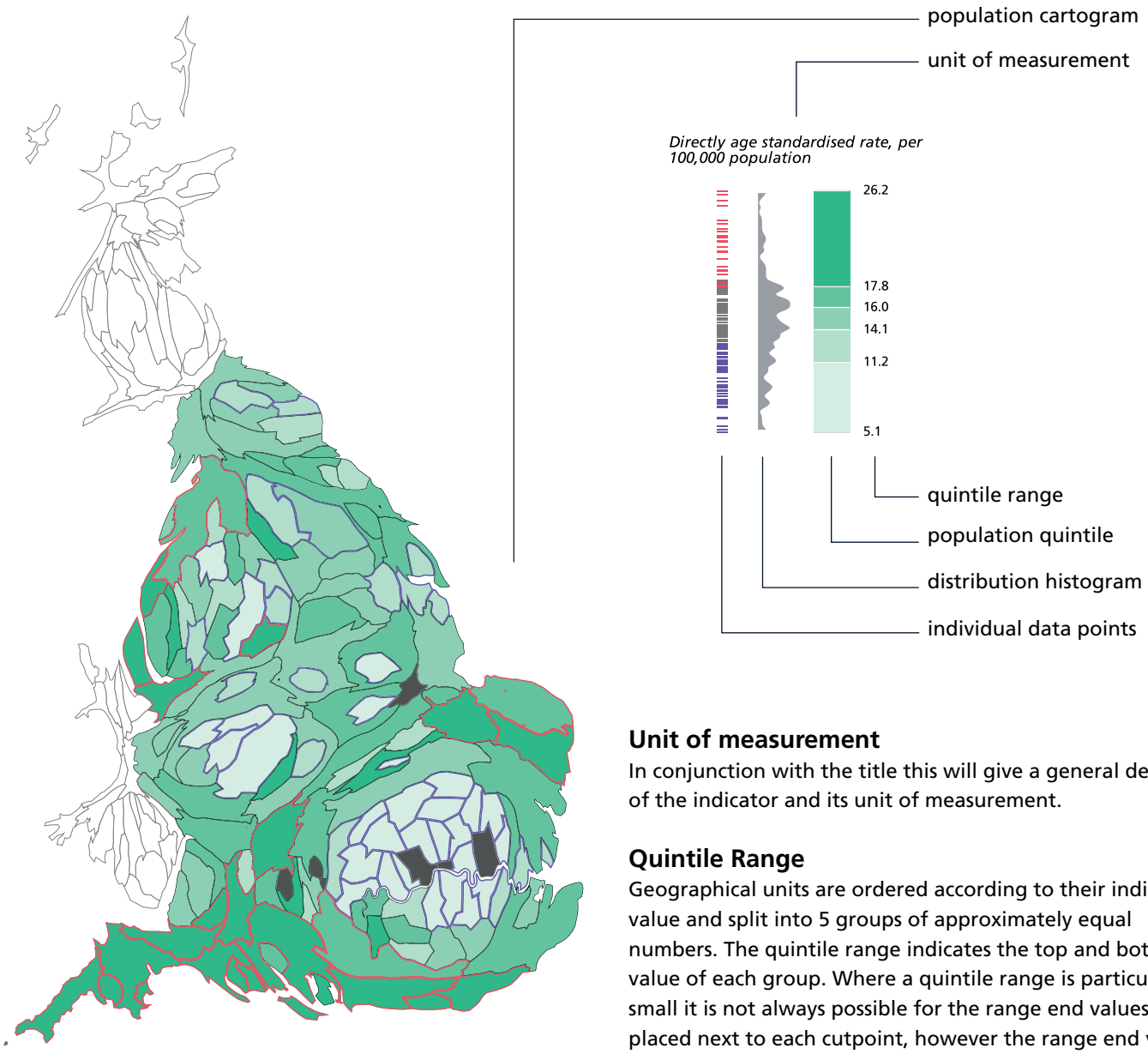
The Annual Report of the Chief Medical Officer Volume One 2011 is available for download at http://www.dh.gov.uk/health/2012/11/cmo-data/

The following pages have been extracted from the section "How to use this report" in Volume One to describe how to read the maps in this volume.

Data provision

Chapter authors were responsible for the provision of data displayed in individual chapters. The Department of Health will make the underlying data available via data.gov.uk, in a standardised format, for public use.

How to read the maps



Population Cartograms

All maps in this report are population cartograms. A population cartogram, or *isodemographic map* is where each geographical unit has been scaled so that it is approximately proportional to the size of the resident population in that area, with minor size adjustments for areas with especially high or low population or density. Map keys for the different geographical units used are provided here.

Where analysis has been undertaken to determine which geographical units are significantly ($p<0.05$) greater or less than the national average, significantly different indicator values are identified by the boundary of the geographical unit being coloured red or blue.

Where no data is available, or data has been suppressed due to small numbers, geographical units are coloured dark grey.

Unit of measurement

In conjunction with the title this will give a general definition of the indicator and its unit of measurement.

Quintile Range

Geographical units are ordered according to their indicator value and split into 5 groups of approximately equal numbers. The quintile range indicates the top and bottom value of each group. Where a quintile range is particularly small it is not always possible for the range end values to be placed next to each cutpoint, however the range end values given and the order in which they appear is correct.

Population Quintile

This is the key to the map. It identifies which quintile a geographical unit is part of and illustrates the range of each quintile.

Distribution Histogram

This is a smoothed histogram displaying the distribution of the underlying indicator values for the different geographical units.

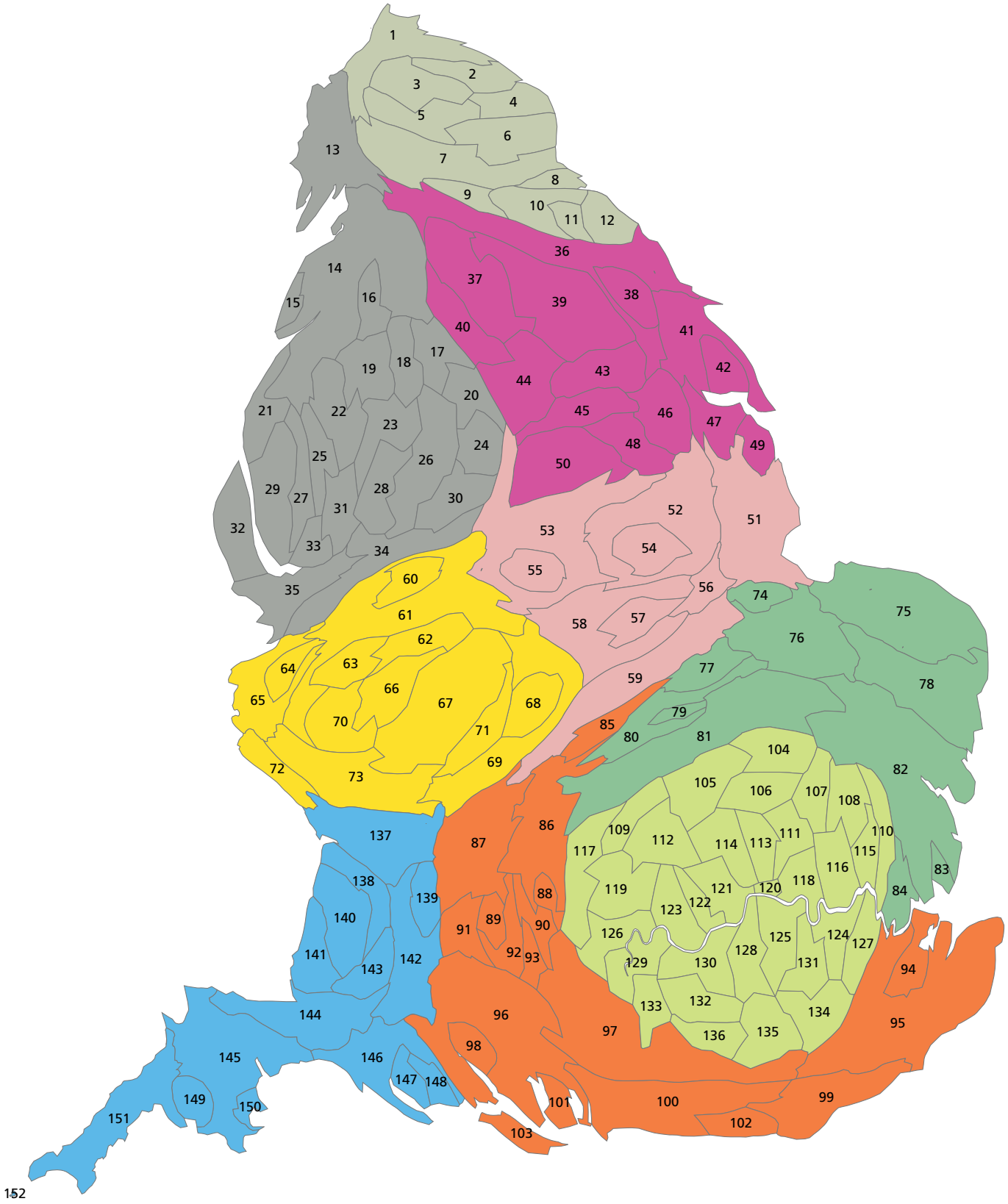
Individual data points

This is a plot of the indicator value for each of the geographical units. Where analysis has been undertaken to determine which geographical units are significantly ($p>0.05$) greater or less than the national average, significantly different indicator values are identified by being coloured red or blue.

Upper Tier Local Authorities

UA = Unitary Authority
MD = Metropolitan District
CC = County Council
LB = London Borough

This map shows each Upper Tier Local Authority, scaled to be proportional to the size of its resident population. This is the default geographical unit used in the report.



1. Northumberland UA
2. North Tyneside MD
3. Newcastle upon Tyne MD
4. South Tyneside MD
5. Gateshead MD
6. Sunderland MD
7. County Durham UA
8. Hartlepool UA
9. Darlington UA
10. Stockton-on-Tees UA
11. Middlesbrough UA
12. Redcar and Cleveland UA

13. Cumbria CC
14. Lancashire CC
15. Blackpool UA
16. Blackburn with Darwen UA
17. Rochdale MD
18. Bury MD
19. Bolton MD
20. Oldham MD
21. Sefton MD
22. Wigan MD
23. Salford MD
24. Tameside MD
25. St Helens MD
26. Manchester MD
27. Knowsley MD
28. Trafford MD
29. Liverpool MD
30. Stockport MD
31. Warrington UA
32. Wirral MD
33. Halton UA
34. Cheshire East UA
35. Cheshire West and Chester UA

36. North Yorkshire CC
37. Bradford MD
38. York UA
39. Leeds MD
40. Calderdale MD
41. East Riding of Yorkshire UA
42. Kingston upon Hull UA
43. Wakefield MD
44. Kirklees MD
45. Barnsley MD
46. Doncaster MD
47. North Lincolnshire UA
48. Rotherham MD
49. North East Lincolnshire UA
50. Sheffield MD

51. Lincolnshire CC
52. Nottinghamshire CC
53. Derbyshire CC
54. Nottingham UA
55. Derby UA
56. Rutland UA
57. Leicester UA
58. Leicestershire CC
59. Northamptonshire CC

60. Stoke-on-Trent UA
61. Staffordshire CC
62. Walsall MD
63. Wolverhampton MD
64. Telford and Wrekin UA
65. Shropshire UA
66. Sandwell MD
67. Birmingham MD
68. Coventry MD
69. Warwickshire CC
70. Dudley MD
71. Solihull MD
72. Herefordshire County UA
73. Worcestershire CC

74. Peterborough UA
75. Norfolk CC
76. Cambridgeshire CC
77. Bedford UA
78. Suffolk CC
79. Luton UA
80. Central Bedfordshire UA
81. Hertfordshire CC
82. Essex CC
83. Southend-on-Sea UA
84. Thurrock UA

85. Milton Keynes UA
86. Buckinghamshire CC
87. Oxfordshire CC
88. Slough UA
89. Reading UA
90. Windsor and Maidenhead UA
91. West Berkshire UA
92. Wokingham UA
93. Bracknell Forest UA
94. Medway UA
95. Kent CC
96. Hampshire CC
97. Surrey CC
98. Southampton UA
99. East Sussex CC
100. West Sussex CC

101. Portsmouth UA
102. Brighton and Hove UA
103. Isle of Wight UA

104. Enfield LB
105. Barnet LB
106. Haringey LB
107. Waltham Forest LB
108. Redbridge LB
109. Harrow LB
110. Havering LB
111. Hackney LB
112. Brent LB
113. Islington LB
114. Camden LB
115. Barking and Dagenham LB
116. Newham LB
117. Hillingdon LB
118. Tower Hamlets LB
119. Ealing LB
120. City of London LB
121. Westminster LB
122. Kensington and Chelsea LB
123. Hammersmith and Fulham LB
124. Greenwich LB
125. Southwark LB
126. Hounslow LB
127. Bexley LB
128. Lambeth LB
129. Richmond upon Thames LB
130. Wandsworth LB
131. Lewisham LB
132. Merton LB
133. Kingston upon Thames LB
134. Bromley LB
135. Croydon LB
136. Sutton LB

137. Gloucestershire CC
138. South Gloucestershire UA
139. Swindon UA
140. Bristol UA
141. North Somerset UA
142. Wiltshire UA
143. Bath and North East Somerset UA
144. Somerset CC
145. Devon CC
146. Dorset CC
147. Poole UA
148. Bournemouth UA
149. Plymouth UA
150. Torbay UA
151. Cornwall UA
152. Isles of Scilly UA

Postscript

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Authors

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Anne M Johnson, University College London
Anthony Kessel, Health Protection Agency
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Ibrahim Abubakar, University College London and Health Protection Agency
Robert W Aldridge, University College London and London Deanery
Gayatri Amirthalingam, Health Protection Agency
Ellen Bloomer, University College London
Alex Bottle, Imperial College London
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Paul Cleary, Health Protection Agency North West
Christopher P Conlon, University of Oxford
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Elizabeth Koshy, Imperial College London
Shamez Ladhani, St George's University London
David M Livermore, University of East Anglia, Norwich
Nicola Lovett, Oxford University Hospitals NHS Trust
Jo Murray, Imperial College London
Lily O'Connor, Oxford University Hospitals NHS Trust and University of Oxford
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'Future challenges' chapter contributors

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