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postnote

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NEW ANTI-INFECTIVES

Infections account for about 10% of all deaths in the UK.[5] The efficacy of all current anti-infectives is threatened by the spread of drug resistance factors, with some already made ineffective. Treatments are also required to tackle emerging diseases such as SARS. As a result, there is a pressing need for new anti-infective drugs. This briefing reviews the UK burden of infectious disease, current anti-infectives research and policy options to stimulate further drug development.

Background

Infectious diseases are caused by bacteria, viruses, fungi, protozoa, parasites, or prions. This POSTnote focuses on bacterial and viral infections prominent in the UK.[1]

Bacterial infections range from life-threatening tuberculosis or healthcare-associated infections (HCAIs) to self-resolving incidents of food poisoning. Bacterial cells differ from human cells, so it is possible to design anti-bacterial drugs that target bacteria but do not harm the patient. Some bacteria (classified as Gram-negatives) are harder to treat than others due to their cell structure. Although there are many effective anti-bacterials, drug resistance is a growing problem (Box 1).

Viral infections can be long-term, life-threatening conditions such as HIV and hepatitis C or short-term, self-resolving conditions like common colds. They are caused by infective particles that use host cells to reproduce. Many viruses are able to evade the immune system and anti-virals, for instance by inserting their DNA into that of their host. Their small genomes (containing their hereditary information) present limited targets for anti-virals. The high genetic mutation rate of many viruses makes it difficult to design effective anti-virals. For this reason preventive measures such as vaccines (where available) are more effective.

The burden of infectious disease

Health burden: illness and death

There is no single analysis of the burden of infectious disease in the UK, but data are available from various sources. There is concern that the incidence of infections is often underestimated, sometimes by a significant margin. World Health Organisation (WHO) figures show that in 2002, infectious diseases caused 70,300 deaths in the UK (12% of all deaths).[3] It is estimated that each year:

- Respiratory infections cause 35,167 deaths.[5]
- There are at least 300,000 HCAIs, implicated in 20,000 deaths.[4]
- There are 5-25,000 deaths due to seasonal flu.[2]
- 35% of GP consultations are due to an infection.[5]
- 20% suffer from an intestinal infectious disease.[5]
- 150,000 are admitted to hospital due to infection.[6]

Data on specific infections are collated by the Health Protection Agency (HPA). In 2006, in England (unless otherwise indicated) there were:[5]

- 55,636 cases of *C. difficile* causing 6,480 deaths;
- 20,007 cases of *E. coli* (mortality data unavailable);
- 17,987 cases of *S. aureus* causing 2,150 deaths;

Box 1. Resistance to anti-infectives

The wide use of anti-infectives in modern medicine means that it is inevitable that drug resistant strains will emerge. A unique tension is created because usage to treat a patient today increases the chance of resistance in the future. Drug resistance is increasing in many (but not all) bacteria and viruses.[5] For instance, after rising rapidly during the 1990s, the rate of methicillin resistance in *Staphyloccus aureus* infections is now falling slowly. Multi-drug-resistant (MDR) TB has also received considerable media attention, but to date, only 1% of cases in England and Wales are MDR.[5] In the 2007/8 European influenza season, 11% of UK infections were caused by viruses resistant to oseltamivir (also known by a trade name Tamiflu), the most common influenza anti-viral.[2]

Resistance drives changes in prescribing practice. One way to combat the emergence of resistant strains is to give multiple doses of different types of anti-infective (combination therapy). Even if drug resistant strains are present in an infection, they may be susceptible to at least one of the drugs used. Currently a combination of four anti-bacterials is required to ensure effective TB treatment and three anti-viral drugs are required for HIV treatment.

- Over 621,000 diagnoses of sexually transmitted infection (UK);
- 8,497 cases of TB, and 359 deaths;
- 8,346 new diagnoses of hepatitis C; a total of 170,000 are chronically infected (England & Wales).

The Department of Health (DH) strategy for tackling infectious diseases was set out in 2002.[6] This identified four areas for action: HCAIs, TB, resistance to anti-infectives, and blood-borne and sexually transmitted viruses (such as HIV/AIDS, and hepatitis B and C).

Economic burden

Infectious diseases cost the NHS ~10% of its budget in England, about £6 billion (2003/04 figures). The largest burden fell on primary care: GP consultations cost £3.5 billion. Other significant costs were HCAIs (£1.4 billion), hospital admissions (£0.9 billion), and HIV/AIDS (£0.3 billion).[5] Costs to the economy as a whole are difficult to calculate as healthcare costs are only part of an overall picture that includes lost productivity. This makes priority setting for health interventions difficult. For instance, only 37% of the estimated £960 million annual cost of intestinal infections is incurred by the NHS.

Anti-infectives research and development

The development of new medicines is a lengthy and expensive process (Box 2). Phase 3 clinical trials are the most costly stage, requiring thousands of patients. For this reason 90% of clinical trials are industry funded.

Box 2. Stages in drug discovery and development

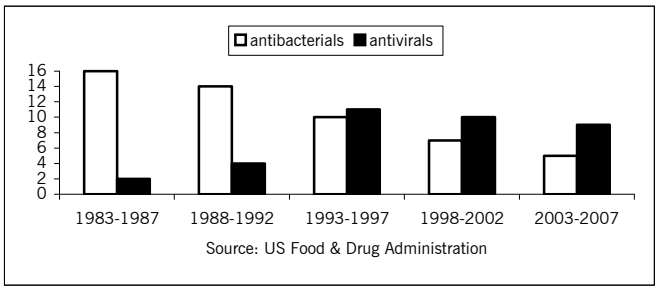
Basic research improves understanding of the causes of disease, how they develop, and possible therapeutic targets. **Translational research** applies basic research to find new potential treatments. Pre-clinical testing then assesses proof-of-concept and toxicity, usually involving animal studies. **Clinical trials** are divided into four phases with increasing numbers of patients and costs. Trials test whether substances are: tolerated in humans (phase 1); safe and effective in small groups with the disease (phase 2); effective compared with a control (phase 3); and safe and effective in the long-term, after the drug has been licensed (phase 4). Regulatory approval can be granted after successful phase 3 trials. It is estimated that this process takes 10-12 years and costs up to £550 million per approved drug.[8] On average, 16 compounds entering clinical trials lead to one approved anti-bacterial.[7]

Pharmaceutical industry research & development (R&D)

Members of the Association of the British Pharmaceutical Industry (ABPI) fund about 60% of all medical R&D, and R&D spend continues to increase.[8] Recent years have seen notable successes in developing new anti-infectives. For instance, there are now 26 anti-virals for HIV which have been developed in just 20 years. Developments in hepatitis C treatment are also promising.

While the number of anti-virals on the market has risen, approvals for anti-bacterials have declined (Figure 1). The ABPI reports that out of a total 951 drugs in pre-registration clinical trials in 2006, 39 (4.1%) were anti-virals including HIV, and only 26 (2.7%) were anti-bacterials.[8] Pharmaceutical Research and Manufacturers of America (PhRMA) report that 118 anti-virals and 83 anti-bacterials are in development,[9] but many of these are reformulations rather than novel medicines. High levels of interest in MRSA over the last decade mean that several new drugs are now available and more are in the pipeline. In contrast, few new treatments against Gram-negative bacteria have been licensed or are in either pre-clinical or clinical testing. In the last 40 years, only two anti-bacterials with a new mode of action have emerged.

Figure 1. Novel anti-infectives approved per five year period.



Public and third sector R&D

Academic research is funded through three major sources (Box 3): UK government; medical charities; and the EU. An analysis of health research funded by UK government bodies and major medical charities found that around two-thirds is basic research, with 7% for developing new drugs and 12% targeted at infectious disease research.[10]

Box 3. Funding sources

EU funding for science and technology

Funding for health research under the 7th Framework Programme (FP7, 2007-2013) is €6.1 billion for medical technologies, healthcare delivery, and translating research for human health. Translational research on infectious disease covers resistance to anti-infectives, HIV/AIDS, malaria, TB, new and re-emerging epidemics, and neglected diseases. There is €20 million for drug resistance research.

UK government research funding

Much underlying basic research is supported by the Biotechnology and Biological Sciences Research Council (BBSRC). Disease-specific research falls within the remit of the Medical Research Council (MRC), whose Infections and Immunology Board spent £86 million in 2006/07 (15% of total spend). As discussed in the text, DH and MRC R&D funding is now combined in a 'Single Health Research Fund' rising to £1.7 billion per year by 2010/11.

Medical charities

The Wellcome Trust's broad remit funds basic, translational, and clinical research worth £520 million per year across all areas. There is limited funding for infectious disease research from other medical charities. Of £64 million spent on health research in 2006, only 3% was on infections.[10]

The need for new anti-infectives

Several high-profile reports have examined infectious diseases and resistance. Many of them emphasised measures such as surveillance, infection control, and better stewardship of existing anti-infectives through 'appropriate use'.[11] For instance, the use of anti-bacterials for growth promotion in animals was banned EU-wide in 2006. Reductions in *S. aureus* infections and rates of methicillin-resistance show such approaches can work. However they are not a panacea; the inevitability

of resistance also necessitates sustained investment in new anti-infectives.[12] The WHO has identified anti-bacterial drug resistance and pandemic influenza as its two highest priority pharmaceutical gaps.[13]

Most current anti-infectives are small molecules which inhibit an essential step in bacterial or viral metabolism. Some researchers argue that problems of resistance will inevitably recur if future anti-infectives work in the same way. As outlined in Box 4, research on a number of completely novel approaches is underway. Increased use of some novel treatments, such as therapeutic antibodies may strain health budgets, as they are expensive.

Barriers to developing new anti-infectives

Scientific barriers: anti-bacterials

The advent of whole-genome sequencing technology in the 1990s appeared to offer new opportunities for drug discovery. Unique bacterial genes not shared with humans could be identified as potential drug targets, and screened against large numbers of compounds to find anti-bacterials. However to date, the strategy has had limited success in finding new targets, and converting candidate compounds into non-toxic drugs also proved difficult. Some new anti-bacterials have been discovered in this way, but none have been commercialised.

Scientific barriers: anti-virals

New techniques are improving prospects for anti-viral drug discovery. However, finding animal models that accurately replicate human viral infection for pre-clinical testing is still challenging. Viral infections such as HIV require life-long treatment, with associated potential for resistance and side-effects. Short-term viral infections require rapid and accurate diagnosis as treatment must start soon after infection to be effective.

Economic barriers

Anti-infectives are the tenth most valuable group of prescription drugs in England, with £220 million sales in 2006. In comparison, sales of drugs for the cardio-vascular system were £1.8 billion.[14] The cost of anti-virals for short-term infections (which are usually self-resolving) can be hard to justify. Drugs for long-term conditions such as HIV are a more attractive economic prospect, as they are taken for life. The following factors make the development of anti-bacterials less attractive:

- The potential market is restricted because there are already many existing drugs, often cheap generics (97% of prescriptions).[14]
- New drugs are held back as 'last resorts', and where a drug *is* used, short treatment courses limit revenue.
- Pressure to reduce anti-bacterial usage to curb rising resistance. Total prescriptions rose by 55% between 1996-2006, but those for anti-bacterials fell 16%.[14]

Regulatory barriers

Current stringent requirements for marketing approval require large and costly clinical trials. Issues include:

- Trials compare a new treatment with the current 'standard of care'. This relies on the historical (and possibly less rigorous) data for the comparator drug.
- Incremental treatment improvements mean it becomes progressively more difficult to demonstrate benefit.
- Strict rules for participant selection can cause recruitment problems for less common, or hard to diagnose conditions.
- Each indication (such as skin and soft tissue infection, or intra-abdominal infection) is trialled separately.
- Trials are conducted for indications where patients can be recruited and regulators satisfied. These indications may not match those a clinician wants to treat.
- Regulatory approval does not guarantee take-up. This may depend on guidance from the National Institute for Health and Clinical Excellence.

Box 4. Novel treatment approaches

- **Bacterial infections** – targeting the ability to cause illness rather than the infection itself is one approach. For instance, drugs to control the diarrhoea-causing toxin produced by *C. difficile* are in advanced clinical trials. Disruption of communication between bacteria is another possibility.
- **Bacteriophages** – these are viruses that infect and kill bacteria, but their clinical efficacy and safety remain unproven despite sustained interest over many years. The use of bacteriophage-derived enzymes to clear infection also holds promise.
- **Viral infections** – most clinically important viruses have a small number of genes, limiting the number of possible drug targets. As understanding of human-virus interactions increases, it is likely that anti-virals directed at human targets (such as the protein receptors viruses use to enter human cells) will become more common. Resistance may be avoided, as these human targets are less likely to mutate. Trials of DNA-based anti-virals are also ongoing, with one approved drug so far.
- **Immunomodulation** - interventions which modulate the immune response hold promise for treatment of infection, with many under investigation, but caution is required to avoid harmful side-effects. The only immunomodulator currently on the market is interferon alpha for hepatitis C. Therapeutic antibodies are another approach: one is already used to prevent a respiratory virus in premature infants.

Policy approaches

Market forces seem more likely to deliver new medicines for long-term viral infections than for either short-term viral infections or resistant bacterial infections. Standard policy approaches such as "orphan" drugs legislation (which encourages investment into drugs for rare diseases) may also be applicable to anti-infectives. The US has recently introduced some relevant measures (see Box 5). However, some researchers argue that a more radical approach is required, perhaps based on the Public-Private Partnerships which have been established to address diseases of developing countries.

Encouraging industry investment

R&D tax credits

Small and medium sized UK companies can claim up to 150% tax credits against qualifying R&D costs (125% for large companies). An additional 50% credit is available for research on HIV, TB or malaria. Proposed US legislation would create a similar (but broader) tax credit covering all infectious diseases.

Box 5. New US legislation on anti-infectives

The Strategies to Address Antimicrobial Resistance (STAAR) Bill was recently introduced into both houses of the US Congress. If passed it would create:

- An Office of Antimicrobial Resistance;
- A Public Health Antimicrobial Advisory Board (similar to the UK Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection).

It aims to strengthen federal resistance surveillance, research activities, infection prevention and control.

The FDA Amendments Act 2007 was signed into law in October 2007. The law requires clarification of which infectious diseases might qualify for "orphan" status. The FDA is also required by the Act to publish guidelines for the conduct of clinical trials for new anti-bacterials.

Intellectual property protection and drug pricing

Extended intellectual property protection might also be considered, for instance replacing time lost through the process of regulatory approval. However, some have argued this would be insufficient incentive where the market is inherently small, and eventual resistance may in any case limit time on the market. Another possibility is 'wild-card' patent extensions granted on another (more profitable) drug from a company's portfolio. These would be more attractive to industry, but the additional costs to the health system may be unacceptably high. Per-company profits are capped by the Pharmaceutical Price Regulation Scheme (PPRS). This is a complex area, recently addressed by the Office of Fair Trading. It recommended pricing based instead on medical value, to encourage investment in areas of high medical need.

Revising the regulatory framework

The European Medicines Agency (EMEA) has identified several targets for addressing the regulatory burden:[15]

- Provide updated guidance for the conduct of clinical trials, and encouraging innovative trial design.
- Increase international harmonisation - EMEA and the Food and Drug Administration have agreed a common procedure for (orphan) drugs for rare diseases.
- Grant two-stage marketing authorisation, with conditional approval after Phase 2 trials. EMEA would consider this only in areas of unmet medical need with exceptionally promising therapeutic results.
- Allow data from animal or lab-based studies to be used when considering extending drug indications.
- Reconsider evidence levels required for Phase 3 trials.
- Encourage greater industry-regulator dialogue.

Initiatives in anti-infectives research

UK government and EU funding

A major reorganisation of publicly funded health research has combined Medical Research Council and DH research budgets into a single fund.[6, 16] The new co-ordinating body, the Office for Strategic Co-ordination of Health Research will publish an overarching health strategy document in 2008, with translational medical research set to receive greater emphasis. It is not yet clear whether anti-infectives will be part of this strategy. The UK Clinical Research Collaboration (UKCRC) and Clinical Research Networks were set up in 2006 to facilitate and encourage high quality clinical trials. In 2007 the UKCRC launched a £16.5 million Translational Infection Research Initiative to foster collaboration and boost capacity for translational research. None of the initial consortia applications have industry involvement.

Framework Programme 7 (Box 3) co-funded a €2 billion Innovative Medicines Initiative (IMI), a project with the European Federation of Pharmaceutical Industries and Associations. The IMI will address bottlenecks in drug development for five areas including infectious diseases.

Other sources

The Wellcome Trust 'Seeding Drug Discovery' initiative has recently supported a number of pharmaceutical companies in pursuing anti-infectives research. It funds a wide variety of drug discovery programmes, including those that may be less profitable. Prolysis received £3.5 million to take an anti-MRSA chemical through to Phase 1 clinical trial; GlaxoSmithKline has £4 million to test part of its current anti-bacterial portfolio in search of a novel class of anti-Gram negative agents; and Novacta was awarded £3.2 million to develop a drug for *C. difficile* infection.

Overview

- Infectious diseases cause 10% of UK deaths and cost 10% of the NHS budget; 7% of drugs in development are new anti-infectives.
- There is a particular shortage of new drugs for Gram-negative bacterial infections.
- There are scientific, economic and regulatory barriers to new anti-infectives development.
- Incentives for pharmaceutical companies to develop commercially unattractive anti-infectives are limited.
- Some progress is being made in bridging the gap between basic and clinical research.

Endnotes

1 POSTnote 241 (2005) discusses diseases of developing countries.
2 www.ecdc.europa.eu/Health_topics/influenza/index.html
3 www.who.int/healthinfo/bod/en/index.html
4 *Improving Patient Care by Reducing the Risk of Hospital Acquired Infection: A Progress Report*, National Audit Office 2004
5 www.hpa.org.uk/web/home
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7 Payne *et al*, *Nature Reviews Drug Discovery*, 6, 29, 2007
8 A to Z medicines research in Britain, ABPI, London, 2007
9 www.phrma.org/fact_sheets/
10 www.ukcrc.org
11 For instance: *Antibiotic Resistance*, STOA 173, 2006
12 *Tackling Antibacterial Resistance in Europe*, EASAC, 2007
13 *Priority Medicine for Europe and the World*, WHO, 2004
14 Prescription Cost Analysis, NHS
15 *Innovative Drug Development Approaches*, EMEA, 2007
16 *The Cooksey Review*, HM Treasury, 2006

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