Research Briefing

Tackling antimicrobial resistance in Wales

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National Assembly for Wales
Research Service

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Tackling antimicrobial resistance in Wales

An examination of antimicrobial resistance in Wales, including causes, trends, and action taken at a global and local level to address the problem.

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1. Introduction

Antimicrobial resistance (AMR) is an umbrella term that covers drug resistance in any bacteria, virus, parasite or fungi. Within this, antibacterial resistance (ABR) is of particular concern because of its complexity – it involves a widening range of bacteria and large spectrum of diseases, including infections that occur commonly in the community and in healthcare settings. There is also general agreement that there is a greater gap in our knowledge of the scale of the ABR problem, compared to well-established surveillance of resistance in particular diseases such as TB and HIV. The rest of this paper focuses on antibacterial resistance for this reason but will use the general term 'antimicrobial resistance', as is convention.

> **'A post-antibiotic era – in which common infections and minor injuries can kill – is a very real possibility for the 21st century'.**
>
> - The World Health Organisation

Emergence and spread

The emergence of mutations in bacteria (or other microbes) that allow drug resistance is a natural phenomenon, but exposure to drugs creates favourable conditions for drug-resistant bacteria and hence facilitates their growth. Consequently, **anywhere that antimicrobials are used, resistance can occur.**

There are a variety of factors that result in the emergence of resistance across the globe:

- **Use of antimicrobials in humans.** Even in the majority of developed countries where antibiotics are only available on prescription, unnecessary and inappropriate use of antibiotics is still a significant problem.
- **Use of antimicrobials in livestock**. The use of antibiotics for growth promotion is banned in the EU but they are permitted for the prevention and treatment of infections. It is **estimated** that **around 40% of total antibiotic use in the UK is animal use**.
- **Release of antimicrobials into the environment** from hospitals and drug manufacturing sites, and accumulation of antibiotics in waste water treatment. This is a bigger issue in developing countries, which are also the location for many drug manufacturing sites.

These factors do not contribute equally to the growth of the resistance problem in humans. The UK Government's 5 year AMR strategy states that the clinical issues with antimicrobial resistance in human medicine are **primarily the result of use in humans** and the subsequent spread of resistant microbes from person to person. However there is **increasing evidence** (from organisations like the **Soil Association**) **that use in animals does contribute**; microbes carrying resistance genes can be transmitted via the food chain as well as directly to animal handlers. The route of transmission from the environment to humans becomes important when sewage and water treatment is poor and levels of resistant bacteria in water and soil can also have an indirect effect on the problem in humans via the food chain.

A lack of new drugs

The development of new classes of antibiotics to treat drug-resistant infections has stalled in recent decades. The situation is particularly striking when it comes to Gram-negative bacteria, such as E. coli. **There have not been any new classes of antibiotic for use against these bacteria discovered for over 40 years**. Growing resistance to the current major Gram-negative antibiotic classes has resulted in the increased use of carbapenems, a class of antibiotics which has traditionally been held in reserve as a 'last-resort' treatment. The recent emergence of carbapenem-resistance in E. coli and other Enterobacteriaceae is therefore considered to pose a very significant threat to human health.

> **'We know that many common and life-threatening infections, such as E.coli bacteraemia – the commonest organism found in blood tests in the UK - are becoming difficult or even impossible to treat'.**
>
> - Mark Drakeford, Minister for Health and Social Services

Increasing resistance levels without the development of new drugs leads to both a **lack of suitable widely effective first-line treatments**, and a rise in the number of **infections that are untreatable by any drug**. This situation has led the World Health Organisation (WHO), in their **global surveillance report**, to state that "a post-antibiotic era – in which common infections and minor injuries can kill – [is] a very real possibility for the 21st century".

The Welsh resistance problem

The **Welsh Antimicrobial Resistance Programme** (WARP) oversee the surveillance of antimicrobial resistance in Wales. The data they collect and report on includes community and healthcare associated infections and covers resistance to both first-line antibiotics (such as amoxicillin and trimethoprim) and drug classes that are often the last option for hard to treat infections (such as third-generation cephalosporins, carbapenems and fluoroquinolones).

E. coli and Staphylococcus aureus resistance rates

E. coli is **reported** to be the most common cause of both bloodstream infections and urinary tract infections (UTIs). The **latest Point Prevalence Survey** shows that coliform bacteria such as E. coli cause more than 85,000 UTIs a year in the community in Wales, and also comprise around 20% of healthcare associated infections (HCAIs). The general picture is that resistance rates of urinary coliforms have been steadily increasing over the past 10 years. WARP's **Antimicrobial Resistance in Wales** report found that between 2005 and 2014:

- Resistance to amoxicillin, the old first-line treatment, has risen from 51% to 57%, rendering it largely redundant.
- **Resistance to trimethoprim, the first-line treatment recommended under current guidelines, has risen from 27% to 37%.** This would imply that in around a third of cases the first-line treatment is likely to be ineffective and the patient may require a second course of adjusted treatment if they are unable to clear the infection. Resistance rates are even higher in the elderly – as high as 47% in those over 80.
- Resistance to second-line treatments such as fluoroquinolones has also risen from 6% to 10%.

It should be noted that due to sampling bias, these rates are likely to be an overestimate, however the observed trends should not be affected by this.

The resistance rates for E. coli bloodstream infections are even higher and less likely to be subject to bias. Carbapenem resistance in E. coli (isolated from blood cultures) has emerged in Wales over the last few years. However resistance rates remain below 1% and so the number of potentially 'untreatable' infections is still very small.

Increasing resistance to first-line treatments is of particular concern for urinary coliforms. The vast majority of UTIs are managed in the community. Testing samples for the presence of bacteria and establishing drug-susceptibility takes 2-3 days and so **GPs must make a prescribing decision before this information is available.** The fact that UTIs may go on to cause coliform bloodstream infections places additional emphasis on the need for an antimicrobial that can be widely prescribed and will be broadly effective.

Staphylococcus aureus (S. aureus) is consistently the **second most common cause of bloodstream infections** in Wales. It also causes wound infections and surgical site infections. S. aureus bloodstream infections are more commonly acquired in hospital (or other healthcare settings) than E. coli bloodstream infections. The total number of S. aureus bloodstream infections has been roughly stable in recent years, whereas the number of meticillin resistant S. aureus (MRSA) infections has **continued to decline**.

MRSA only accounts for approximately 17% of total S. aureus infections but has received much attention because it is strongly associated with hospital-based cross-infection and therefore indicative of a breakdown in infection control procedures. Since MRSA strains also have higher levels of resistance to other antibiotics, the decline in incidence of MRSA infections also represents a decline in resistance rates of S. aureus in general.

Antibiotic prescribing in Wales

The **2010 Point Prevalence Survey of antimicrobial prescribing in secondary care in Wales** states that **an estimated 20-50% of prescribing, both in the community and in hospitals, is inappropriate.**

WARP, alongside the All Wales Medicines Strategy Group, monitor the use of antimicrobials in both primary and secondary care. According to the **European Centre for Disease Prevention and Control (ECDC)**, **primary care accounts for 80-90% of all antibiotic prescriptions**.

In **primary care**, the unnecessary prescribing of antibiotics to treat viral infections and infections that would clear up without treatment is highly prevalent. For example, a **2014 study** of UK GP practices found that **antibiotics were prescribed for 60% of sore throats though they are only likely to be beneficial in around 10% of cases.** It is evident from the **seasonal variation in total antibiotic prescribing in Wales** that respiratory infections (which occur largely in the winter) account for a significant proportion of all antibiotic prescribing, yet few coughs and colds are bacterial infections. An antibiotic prescription for a respiratory infection can also result in the patient's gut bacteria acquiring resistance which can be detrimental to the patient, increasing the risk of a resistant infection in the future.

Total **antimicrobial use in primary care in Wales** increased between 2005-2013 but showed a slight decrease of 1.5% from 2013 -14. In 2010-11 **National Prescribing Indicators** were introduced to monitor the prescribing of 'restricted antibiotics groups' - particular broad-spectrum antibiotics whose use should be restricted to the few cases where narrow spectrum antibiotics would not be

effective. **Recent data** shows that use of these has decreased since 2011 although it is still above the target in most Health Boards.

The **2014 point prevalence survey of antimicrobial use in secondary care** found that 51% of patients prescribed antibiotics were being treated for a community-acquired infection, 31% for a hospital-acquired infection and 6% for surgical prophylaxis (prevention of infection during surgery). The survey indicates the extent to which prescribing is adhering to guidelines by providing data on the number of infected patients who had consumed systemic antibacterials for more than 7 days, and the number of surgical patients who had been prescribed prophylaxis for more than 1 day. Both of these figures decreased from the previous year, which is considered a positive sign, though it is not possible to tell exactly what proportion of this use is 'appropriate use'.

Only 86% of hospital patients had the reason for the prescription recorded in their notes and **only 48% of prescriptions had a stop/review date recorded** (compared to the target of 95% for both measures).

The reports also show a gradual but consistent increase in the prescribing of carbapenems over the past 6 years.

Variation across Wales and across the UK

The most recent WARP **report on antimicrobial use in primary care** found significant variability between Health Boards in gross annual antimicrobial use in 2014. The dispensing rate ranged from 463 to 648 items/1000 prescribing units per annum. There are significant **differences in resistance rates between Welsh hospitals** for several drug-bug combinations, along with significant **inter-hospital variability in total antibiotic use**, types of antimicrobials used and trends in use over time. Such variation across Wales indicates that improvement in prescribing practices is possible, though variation in use in secondary care will partially be explained by differences in the range of cases at each hospital.

Data shows the total antibiotic use in Wales is high compared to the UK as a whole, and an **ECDC report** shows that in 2014 the UK ranked 16th out of 30 countries in the EU in terms of community prescribing, and 23rd out of 24 in terms of prescribing in secondary care.

Use and resistance in animals

Data on use of antimicrobials in animals is only available on a UK-wide scale. The **UK One Health Report** reports on resistance and use of antibiotics in humans and animals. Data was collected for Salmonella and Campylobacter (which do not cause disease in animals but are the main bacteria transmitted through the food-borne route, causing gastroenteritis in humans) and for E. coli (the organism for which there is the next strongest evidence that farm animals contribute to resistance in humans).

Trends in sales of all antibiotics, 3rd and 4th generation cephalosporins and fluoroquinolones have **shown little change for the past three years**. Antimicrobial use and resistance levels vary depending on livestock type and are **much higher in pigs and poultry**, which constitute only a small fraction of livestock holdings in Wales. The **European Surveillance of Veterinary Antibiotic Consumption (ESVAC) report** in 2013 found that the UK ranked 14th out for 26 countries for antibiotic sales (with 1st being the lowest sales). There was startling variation across Europe – use in Cyprus, Italy and Spain was 20 times higher than that in Sweden, having corrected for size and number of animals.

2. How can antimicrobial resistance be tackled globally and locally?

The **UK Government's 5 year AMR strategy** notes that the problem of antimicrobial resistance 'is not restricted to the UK. It concerns the entire world and requires action at local, national and global level'.

In July 2014, the UK Government commissioned an independent **Review on Antimicrobial Resistance** in collaboration with the Wellcome Trust to analyse the global problem of antimicrobial resistance (AMR) and propose actions to tackle it internationally.

> **'AMR cannot be eradicated but a multi-disciplinary approach involving a wide range of partners will limit the risk of AMR and minimise its impact for health, now and in the future'.**
>
> - UK Government AMR strategy

The **final report from the review** was published **in May 2016**, and set out a 10-point plan for reducing AMR. The report author highlights 4 interventions of particular importance:

- The need for a **global awareness campaign** to educate about the problem of drugs resistance
- The need to tackle the supply problem through the **development of new drugs** to replace the ones which are now ineffective due to resistance
- The need **to use antibiotics more sparingly in humans and animals**, to reduce the unnecessary use that speeds up resistance
- The need to **reduce the extensive and unnecessary use of antibiotics in agriculture**

The **World Health Organisation (WHO)** has produced a global action plan on AMR and are supporting member states to develop national action plans in line with its objectives. The WHO is also leading a global multi-year campaign, ***Antibiotics: Handle with care***, which was launched during the first annual World Antibiotic Awareness week in November 2015.

There are several large **non-governmental organisations** working to tackle the problem of AMR, such as the **Alliance for the Prudent Use of Antibiotics** which conducts large-scale national and international research and educational projects, the results of which have influenced national policy and planning initiatives.

Work to tackle AMR can be broadly summarised under three areas: preventing infection, reducing the unnecessary use of antimicrobials, and finding and developing new drugs or treatments.

Preventing infection

The fewer infections that occur, the less antimicrobials are needed to treat them, reducing the chance of resistance developing. New infections can be prevented by:

- **Encouraging good personal hygiene** through awareness and educational campaigns.
- **Implementing good hygiene practices in hospitals** to limit the spread of healthcare associated infections (HCAIs). Key areas include hand hygiene, decontamination of equipment, isolation procedures and the insertion and management of medical devices. Devices such as catheters and intravenous (IV) lines increase the risk of infection, particularly if they are left inserted for longer periods of time.
- **Facilitating the development and widespread use of vaccines**. The **Review on Antimicrobial Resistance** report ***Vaccines and alternative approaches: reducing our dependence on antimicrobials*** contains three recommendations on this: (1) Use existing products more widely in humans and animals. (2) Renew the impetus for early research. (3) Sustain a viable market for needed products.

Reducing unnecessary use of antibiotics

- **Increasing public understanding** of when antibiotics are necessary and of the risks of inappropriate use. An **English survey in 2009** found that 37% of respondents were unaware that antibiotics do not work on coughs and colds, 28% had asked a GP or nurse for antibiotics in the past year and 8% had taken antibiotics without being told to do so.

  The success of public awareness campaigns has been mixed. Campaigns that have subsequently been reported as successful, in **France** and Belgium, have consisted of multi-year campaigns via mass media, including TV and radio. Though both countries saw a significant reduction in antimicrobial use during and after the campaigns, it is difficult to ascribe causality to this particular intervention.

  Analysis has shown that previous public-facing campaigns in the UK, involving the dissemination of posters and patient information leaflets via GP surgeries and posters in newspapers and magazines have had no demonstrable effect on public understanding or on prescribing rates. It has also been **reported** that national campaigns in Greece, Spain and Australia also failed to show an impact on antibiotic prescriptions.

- **Ensuring prescribing guidelines are in place and adhered to**.

  With regard to primary care, the ECDC state that unnecessary antibiotic prescribing is:

  > *[…] mainly related to factors such as misinterpretation of symptoms, diagnostic uncertainty and perceived patient's expectations.*

  Their **key messages for primary care prescribers** include the importance of effective communication in achieving patient satisfaction, and that there is evidence that prescribing an antibiotic for an upper respiratory tract infection does not decrease the rate of subsequent return visits. Recently, two separate trials, in **England** and in **Wales**, of interventions focused on encouraging and helping GPs to reduce their antibiotic prescribing have achieved small but significant reductions in prescribing.

  In regard to secondary care **the ECDC state that:**

> *[…] multifaceted strategies which include use of ongoing education, use of evidence-based hospital antibiotic guidelines and policies, restrictive measures and consultations from infectious disease physicians, microbiologists and pharmacists, may result in better antibiotic prescribing practices.*

They also recommend monitoring of hospital antibiotic resistance and use.

- **Better and faster diagnosis of resistant infections**. Rapid point-of-care diagnostic tools have the potential to significantly reduce over-use of antibiotics and our dependence on broad-spectrum antibiotics. The Review on AMR's report ***Rapid Diagnostics: Stopping unnecessary use of antibiotics*** concludes that steps towards this will involve putting aside funds to incentivise the development and uptake of diagnostics, investing in early-stage research and development, and supporting and funding large studies that aim to demonstrate clinical cost-effectiveness and the 'public good' of diagnostic use. The development of a new diagnostic tool is not considered to be as far off as the development of a new class of antibiotic drugs.

  This topic is the subject of the **Longitude prize** in the UK – a £10 million prize fund for a diagnostic tool that opened in 2014.

- **Reducing the unnecessary use of antibiotics in farming**. The recent UK **Review on AMR report** recommended that a global target is set to reduce antibiotic use and restrict the use of those drugs deemed important for human medicine. The recommendation has received a mixed reception among stakeholders; while **some have welcomed the recommendations**, others, such as the **British Veterinary Association**, view this approach as potentially detrimental to animal welfare and food production as well as being unlikely to reduce resistance in humans. The AMR Review report cites Denmark and the Netherlands as cases of good practice. In these countries farmers had to move to new farming practices in order to reduce antibiotic use, but have been able to maintain production and profits at the same time. Improved surveillance and monitoring is a common theme between the two case studies.

  The WHO maintains **a list of those antimicrobials that are 'critically important' for human medicine**, for use in guiding policy on veterinary use.

Finding and developing new drugs

The **Review on AMR**, the **Biotechs of Europe innovating in Anti-Microbial Resistance (BEAM) Alliance**, the **Society of Biology** and the **Office of Health Economics** have all recently published reports or position papers on actions that need to be taken to support the development of new drugs and stimulate the antibiotics pipeline. Three key themes emerge in their recommendations:

- **Supporting early-stage research**, potentially through the creation of a specific fund for AMR innovation.

- **Creating a more predictable market** for antibiotics and reducing the financial disincentives that currently exist (as a result of new therapies being held in reserve for a long as possible). Suggestions in this vein are to have a special status for antimicrobial products and for governments to commit together to accept higher price premiums for new antimicrobial drugs, recognising the true value of antimicrobials for the public good. Similar incentives have been discussed or introduced in the past to tackle neglected diseases.

- **Removing regulatory barriers** which slow the development of new antibiotics, for example by giving such treatments automatic fast track status and through governments and health systems more actively facilitating clinical trials.

A positive step was made at the 2016 World Economic Forum in Davos. More than 80 pharmaceutical, biotechnology and diagnostics companies and nine industry associations signed a **Declaration on Combating Antimicrobial Resistance**. They committed to invest in antimicrobial research and improve access to antibiotics around the world in return for governments working with them to develop new market structures and committing funds to make antimicrobial research and development more attractive.

Charities may also have a significant role to play in this area. **Antibiotic Research UK** is a charity aiming to raise an estimated £30m over the next 5 years in order to bring at least one new antibiotic therapy to market, through research that will be carried out in the UK.

3. What action is being taken against antimicrobial resistance in Wales?

In September 2013, the **UK government published their five-year strategy for tackling antimicrobial resistance**.

The first **Welsh Government Delivery Plan** specifically relating to AMR was produced in March 2016. The plan had seven delivery themes, discussed below:

> **The threat from AMR is very real and something must be done – inaction cannot be tolerated.**
>
> - Chief Executive of NHS Wales

Delivery theme 1: Improving infection prevention and control practices

The Welsh Government published a **general strategy for reducing healthcare associated infections** (HCAIs) in 2004. UK-wide point prevalence surveys of HCAIs were conducted in 2006 and 2011 and the prevalence of HCAIs in the acute sector in Wales decreased significantly from 6.4% to 4.4% over that time period. In 2011 **a framework of actions** was produced which shifted the focus towards elimination of HCAIs. The Welsh Government followed this up in 2014 with a **Code of Practice for the prevention and control of HCAIs**, setting out the 'minimum necessary infection prevention and control (IPC) arrangements for NHS healthcare providers in Wales'.

Theme 1 of the new AMR Delivery Plan focuses on ensuring the full implementation of this Code of Practice and compliance with other existing policies. Specific priorities also address the management of patients with carbapenem-resistant infections and rolling out C-reactive point-of-care testing in primary care – a test which reduces diagnostic uncertainty for respiratory tract infections.

Delivery theme 2: Optimising prescribing practice

There is a range of guidance available on the appropriate prescribing of antimicrobials. The Delivery Plan sets out how the implementation of current guidance will be supported and monitored and how new guidance will be developed where it is needed.

For example, ***Start Smart then Focus***, a Public Health England initiative for secondary care, is in use across Wales. The yearly Point Prevalence Survey of antimicrobial prescribing in secondary care already gives an indication of whether its guidelines are being adhered to. The Delivery Plan outlines ways in which compliance will be measured during the next few years.

National Prescribing Indicators have been used to encourage and monitor appropriate prescribing of antibiotics in primary care for several years. The Delivery Plan states that these will be refined and that prescribing indicators for secondary care will be developed.

Delivery theme 3: Improving education, training and engagement

There has not been a specific awareness raising campaign in Wales targeting the general public, but educational and promotional materials such as infographics and leaflets do exist and are available in bilingual form. For example, in 2015 Public Health Wales produced materials to support European Antibiotic Awareness Day, which were available online and advertised to Health Boards via a **Welsh Health Circular**. Researchers at Cardiff University have developed a booklet entitled '**When should I worry?**' intended for use in primary care consultations. **A clinical trial showed that use of the booklet reduced antibiotic prescribing by two thirds**. The interactive **e-bug educational resources** were developed by Public Health England for use in schools and include suggested lesson plans. The November 2015 **Welsh Health Circular** stated that these were being 'commended to schools' by the Welsh Government. It is unclear to what extend the online availability of the materials above has encouraged their use across Wales.

The AMR Delivery Plan states that the Implementation Oversight Group will take responsibility for developing a model for an effective public awareness campaign and submitting it for consideration to the Welsh Government. Public Health Wales will deliver targeted information to schools. The Delivery Plan also contains actions towards training and educating clinicians via issuing feedback to GP clusters on their antimicrobial usage, reviewing the training of prescribers and developing an e-learning module and assessment on prescribing competencies for secondary care.

Delivery themes 4 and 5: Developing new drugs, treatments and diagnostics / Better identification and prioritisation of AMR research needs

Life sciences research in Wales has received significant investment from the Welsh Government over the last few years. In 2013 Ser Cymru and the National Research Networks programme were set up as part of a 5-year programme with £50m investment to attract and support world class researchers. The **Life Sciences Research Network** is part of this program. It includes the **Welsh Antimicrobial Resistance Forum**, which is a consortium of researchers from four Welsh universities conducting research into alternative treatments for bacterial infection, novel therapeutics and novel diagnostics. In 2015 the Welsh Government announced **funding for a £3m Life Sciences bridging fund** which will help turn research projects into viable business ventures. The **second phase of Ser Cymru will receive £60m of funding** from the Welsh Government.

The Delivery Plan states the Welsh Government aims to build on the AMR research currently taking place in Wales by investing in research infrastructure and funding, promoting Welsh research, encouraging and supporting international collaborations and initiatives to create consortia between academia and industry. Other priorities include providing information and support for companies wishing to undertake clinical research in Wales and protecting research time for clinicians as well as improving access of patients to relevant clinical trials.

Delivery theme 6: Better access to and use of surveillance data

Comprehensive surveillance data on resistance rates is currently routinely collected by the Welsh Antimicrobial Resistance Programme (WARP) and yearly reports are published on the **Public Health Wales website**. Prescribing data is collected and analysed by WARP and the All Wales Medicines Strategy Group, as part of the **National Prescribing Indicators**.

The priorities of the Delivery Plan are for resistance and usage data to be available at a finer scale (on a local level and for specific clinical areas) and easily accessible via web-based tools so that they inform

areas for action locally. They also include plans to develop automated trends analyses and a resistance alerts system so that threats can be identified quickly.

Delivery theme 7: Strengthened international collaboration

The Delivery Plan states that currently Public Health Wales collaborates with the European Centre for Disease Prevention and Control networks. It also notes that there are strengthened arrangements in place for collaboration between the relevant Health Boards and NHS Trusts within the UK and between all-Wales networks and English networks.

Animal use

The Delivery Plan largely focuses on human healthcare and notes:

> *The control of veterinary use and prescribing of antimicrobials is not devolved to the Welsh Government and initiatives and actions in this context are being addressed at the UK level.*

However, antimicrobial resistance is one of the priority areas outlined in the **Wales Animal Health and Welfare Framework Implementation Plan for 2015-6**. This states that the Welsh Government and the Wales Animal Health and Welfare Framework Group will work to:

- Increase awareness and education of AMR.
- Increase the promotion of good husbandry and biosecurity practices to control zoonoses, endemic and exotic animal diseases.
- Promote the minimising of routine use of antibiotics.
- Support work at the UK level to develop improved data collection and evidence gathering to ensure a robust evidence base is in place to inform future actions.

Looking ahead

The next Point Prevalence Survey of antimicrobial prescribing in secondary care and healthcare-associated infections will take place in November 2016.

The Welsh Government's AMR Delivery Plan states that it expects to see clear progress demonstrated through annual reports published by Health Boards and NHS Trusts. It states that the Implementation Oversight Group will agree measures of success for:

- Trends in AMR and antibiotics prescribing.
- Improved knowledge and understanding of prudent use of antibiotics.
- Reduction in HCAI rates and improved infection prevention practices.
- Continued year-on-year reductions in other key infections.

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