EQUITY DEVELOPMENT

Germ Warfare

A Review of Hospital Hygiene

December 2008

Sector: **Healthcare**

Key points

- Infectious diseases are the second leading cause of death worldwide
- If microbial resistance cannot be defeated, can it be kept under control?
- Dealing with Hospital Acquired Infections ('HAI' s) is now a US$ multi billion marketplace

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A Review of Hospital Hygiene

A RESISTANT PLAGUE

At the same time as the risk of transmission of infectious diseases is on the rise, microbial pathogens continue to become more resilient. In addition, the alarming decline in the development of treatments with novel mechanisms of action for antibiotic-resistant infections is driving healthcare organisations worldwide to enforce hygiene protocols. These have become the chief tool in the attempt to protect patients from hospital acquired infections (HAIs) that can result in death. HAIs are second only to medication error as a cause of adverse events in hospitalised patients.

- There is a growing acceptance among scientists that microbial resistance will not be defeated but it *can* be kept under control. However, control requires a continuing, steady development of new antibiotics, immuno-therapeutics, vaccines and diagnostics together with improved targeted therapy. There also needs to be well co-ordinated and funded monitoring, at both domestic and international levels, tracking, plus prevention and control plans put in place;
- An accurate picture of HAIs' incidence, mortality and related costs remains difficult to establish as no standard methodologies have been adopted with many different agencies involved gathering different types of information about different subset of patients, resulting in unclear and fragmented data;
- In recent years large pharmaceutical companies have either pulled out of, or downsized their R&D efforts primarily due to the return on investment and the unclear regulatory guidance available;
- Where there has been the adoption of strict hygiene protocols, this has contributed to a significant reduction in incidence and mortality: going forward one should see further improvements as new decontamination technologies and tools are introduced;
- HAIs market size runs in the order of several tens of US$bn, but the actual size and growth rate is hard to gauge accurately in a global context as antimicrobial agents (ex-antibiotics) are part of the 'consumer products' divisions of vast international organisations, additionally this sector is characterised by the presence of a large number of SMEs or private companies providing an extensive range of products and services.

Facts of concern

- Infectious diseases represent the second-leading cause of death worldwide and the third-leading cause of death in the US;
- Global spread of microbial resistance is the predominant reason why infectious diseases are on the rise;
- Microbes have had *3.5bn years* to adapt to the various environments on our planet and their adaptability is driven by genetic plasticity and rapid replication;
- The sheer quantity of microbes; there are 5-10x more microbes living on and in every human being than there are human cells in our bodies.

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"The future of humanity and microbes will likely evolve as … episodes of our wits vs. their genes"

(Nobel prise winner Dr. Joshua Lederberg)

Since the first hunter-gatherers settled in villages, about 10,000 years ago, infections have killed more people than war and famine. In the 19th century alone two great epidemics typhus and type A influenza, killed over 20m people dwarfing the toll of combat during the First World War.

Over recent decades socio-economic changes, public health initiatives and medical advancements (*antibiotics revolutionised medical care in the 20th century*) have contributed to the improvement of general living conditions, increasing the life span, reducing mortality in infants and small children through the introduction of the polio vaccine, the eradication of smallpox and brought under control diseases like TB (tuberculosis), cholera and syphilis making the Second World War the first major conflict in which epidemics took far fewer casualties than battle. However, to date, infectious diseases remain on the top of the list of deadly diseases representing the **second-leading cause of death globally** and the **third most critical in the US**.

Global spread of microbial resistance is the predominant reason why infection diseases are on the rise. Microbes have had 3.5bn years to adapt to the various environments on our planet and their adaptability is driven by genetic plasticity and rapid replication. It takes between 20 to 30 minutes for many bacteria to replicate, whereas a human being takes on average 20-30 years. Also, the sheer quantity of microbes; there are 5-10x more microbes living on and in every human being than there are human cells in a body. Another point to take into account is that antibiotics were discovered last century while microbes have accumulate survival knowledge for 20m times longer than *Homo sapiens* have known that antibiotics existed, it give us an idea on the complexity behind the development of any sustainable treatment for infectious diseases.

Drastic environmental changes, unprecedented population growth and mobility (i.e. immigration and air travel (1.4bn people travelled in 2003 by air according to a study by the UN Economic and Social Council) have brought about the re-emergence of old diseases considered to be extinguished and the significant increase in the use of antibiotics have caused a number of gram-positive microorganisms such as *staphylococci* (*i.e. Staphylococcus aureus*), *streptococci* and *enterococci* to become resistant to the medicines that are commonly used to treat them, leading to the emergence of more virulent strains.

Although, gram-positive microorganisms account for 70% (Centers for Disease Control and Prevention (CDC)) of the 2m US hospital acquired infections (HAIs), there has been a big increase in multi-drug resistant gram-negative bacteria such as extended-spectrum beta-lactamase (ESBL) producing *E. coli* and *K. pneumoniae* and strains of *P Pseudomonas aeruginosa* (*P. aeruginosa)* and *A. baumannii* resistant to all currently available treatments. Additionally, 70% of the HAIs (hospital acquired infections) are resistant to at least one antibiotic and up to 40% are resistant to three antibiotics (CDC). This provides clear indication that the rate of loss of efficacy of older classes of antibiotics is outstripping the replacement with new ones for many species of pathogenic bacteria.

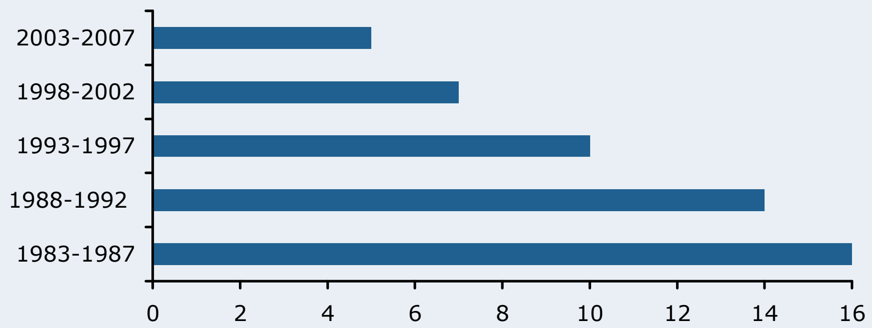
WHO estimated, at the end of 2005, that 5-10% of patients admitted to hospital in developed countries acquired HAIs, this figure increases to over 25% in developing countries. Studies in three OECD countries, one of which is considered to be middle-income, showed that the total economical impact of these infections per year was in the region of US$7-8.2bn.

Additionally, in the past three decades there has been the emergence of Legionnaire's disease, Ebola virus, the human form of 'mad cow disease', West Nile fever, SARS as well as the resurgent cholera, dengue fever and malaria. The prevalence of certain blood-born viruses is growing worldwide along with massive increases in the incidence of Hepatitis C, HIV/AIDS, TB (1 in 3 people infected globally according to WHO (2007) Fact sheet 104), in addition to the growing number of antibiotic-resistant strains being isolated globally, the acquired nosocomial infections like MRSA (Methicillin-Resistant *Staphylococcus aureus* – 60% of most drug resistant microbes worldwide), VRE (Vancomycin-resistant *enterococci*) and *C. difficile* (*Clostridium difficile*) continuing to make the headlines and the imminent threat of a global influenza pandemic, all contributing to the heightened awareness of the health and hygiene risks and responsibilities.

Slow development of new treatments remain a major concern

Although antibiotic development was rapid between the 1950s and 1970s with multiple new drugs being developed, many of the advancements have been eroded over the last 30 years due to the emergence of resistance and making the slow development of new medicines to treat drug-resistant infections a major concern.

Figure 1 : New systemic antibiotics agents approved by the FDA in almost 25 years



Spellberg et al (2008)

Large pharma pulling out or scaling down antibiotic R&D

This decline is multi-factorial and complex, but ultimately the return on investment is the major reason. Antibiotics work so fast (short-course therapies) and well that for pharmaceutical companies there is a disincentive to research and develop new therapies: many large pharma companies (e.g. Abbott Labs, Sanofi-Aventis, Eli Lilly & Co., Roche, Wyeth) are pulling out of or scaling down their efforts, creating opportunities for spin-offs/emerging biotechnologies companies (i.e. two companies were spun off from large pharma: Basilea Pharmaceutica AG from Roche in 2000 and AiCuris from the Anti-infectives Unit of Bayer in 2006). Only five large pharmaceutical companies are still involved in the antibiotic R&D space: GSK, Novartis, Pfizer, AstraZeneca and Merck.

Large pharma overall places more emphasis on so-called 'blockbuster' drugs to treat chronic conditions (i.e. cholesterol, heart disease, diabetes) or life style issues (i.e. Viagra™) with patients taking these drugs for many years and therefore far more profitable than antibiotics that are used for one or two weeks.

In 2001, six antibiotics (Rocephin, Cipro, Levaquin, Zithromax, Biaxin, Augmentin) had blockbuster status. Today only Augmentin and the Levaquin/Floxin franchise (Ortho-McNeil) fall within this category. Other newer antibiotics like Zyvox (Pfizer), Avelox (Bayer), Cubicin and Tygacil (Wyeth) did not make it to the blockbuster status. Patents expirations, generic competition, and the withdrawal due to safety challenges or limited use have fragmented the market.

Table 1 :Some of the New antibiotic approved during the period 1998-2007

Antibiotic	Year	Novel
Rifapentin	1998	No
Quinupristin/dalfopristin	1999	No
Moxifloxacin	1999	No
Gatifloxacin	1999	No
Linezolid	2000	Yes
Cefditoren pivoxil	2001	No
Ertapenem	2001	No
Gemifloxacin	2003	No
Daptomycin	2003	Yes
Telithromycin	2004	No
Tigecycline	2005	No
Doripenem	2007	No

Spellberg et al.

New 'antibiotics'

In the second half of November this year, Basilea Pharmaceutica announced that **ceftobiprole** (Zevtera™), a new anti-MRSA broad spectrum antibiotic belonging to the cephalosporin class, already marketed in Canada, obtained regulatory approval in Switzerland and is expected to be approved in the rest of Europe after the Committee for Medicinal Products for Human Use gave a positive opinion. But in the US, the FDA raised questions about data integrity and has asked additional clinical site audits as well as information on the company's quality assurance programmes. Ceftobiprole's launch in the US is not expected for at least for another 12-18month.

During the same period, the AIDAC (Anti-Infective Drugs Advisory Committee) backed the approval (21 to 5) of Theravance Inc.'s once-daily, injectable, antibiotic designed to treat serious skin infections (*S. aureus* and other gram-positive bacteria) **telavancin**. But narrowly voted against **oritavancin**, a novel semi-synthetic glycopeptide antibiotic, originally discovered and developed by Eli Lilly as a potential replacement for vancomyncin and acquired by Taragant Therapeutics Corp (NASDAQ: TARG), in late 2005. According to the advisory panel oritavancin did not demonstrate sufficient efficacy against the most serious types of infections and at the beginning of December the FDA confirmed the rejection of the NDA (New Drug Application) and asked the company to perform an additional clinical study that should include supplementary information. **Iclaprim**, by Arbida Ltd. (SWX: ARPN), the third being examined on that date was almost unanimously rejected with 17 to 2.

Challenges

Although, the spin-off strategy creates new opportunities some cautious thoughts should be spared on the way some of these companies are capitalised, in the current economic/financial climate and whether they really have the right expertise and experience to develop these treatments.

Additional specific requirements

Antibiotic development has an additional requirement, unique to this therapeutic field: the preparation of microbiological data to support marketing authorisation application that can also be used at a later stage to raise awareness on the product. With the preparation of the microbiological data is increasingly outsourced to microbiological contract research organisations (MiCRO) this sector is enjoying a double digit growth and expected to continue this trend in the coming years. For antibiotics, standard of equivalence is quite strict requiring large number of patients to be enrolled in clinical trials to demonstrate new standard of 'equivalence'. Also, because antibiotic resistance remains an issue, regulatory authorities require prolonged post-marketing surveillance which includes the monitoring of susceptibility of the target pathogens of newly launched antibiotics on an ongoing basis to detect any potential development of resistance.

Unclear guidance on the regulatory path

Biopharmaceutical and pharmaceutical companies have often complained about the lack of available clear guidance on which studies and evidence are considered acceptable to demonstrate safety and efficacy of a new anti-infective drug. **Inconsistencies in protocol requirements** very often arise and can be seen when different companies developing drugs addressing the same pathogen are required a catalogue of different studies and there is uncertainty whether the trial required will be accepted by the regulators at a later stage i.e. when a NDA (new Drug Application) is filed.

Restricting the use of antibiotics

The global antibiotic market long-term growth is also being impacted by increased regulation of their usage, which forces a reduction in prescription (negatively impacting sales), especially for respiratory infections, a major segment of the market, making it the primary growth inhibitor, together with tightening in regulatory approvals and generic competition. The proper use of antibiotics, although is not the answer to drug resistance, is a way to buy time while a real solution to the problem is found. Antibiotic effectiveness can be seen as a precious and limited resource that must be managed carefully.

Despite these challenges, in September 2007, GSK announced the signing of an agreement worth up to **US$41m** over a five-year period, with the US DTRA (Defence Threat Reduction Agency) of the US DOD (Department of Defence), to identify and develop a new class of anti-bacterials targeting both gram-negative bio-threats and conventional gram-negative HAIs. Under this agreement GSK will provide additional staff and cover some of the programme's costs. Astrazeneca, announced earlier in the year, its **US$100m** investment in the development of antibiotics to fight bacteria that are becoming resistant to drug.

There are 21 different classes of antibiotics currently approved with a global market size expected to be in the region of US$25-30bn by 2010 with further growth expected from 2012 onwards when a dozen new products developed by smaller pharmaceutical companies, will enter the market.

Efficient market penetration requires a large, experienced and focused sales force making these smaller companies an attractive target for large pharma so we could see some consolidation among the smaller players (subject to available cash resources or an ability to raise the necessary funding)

Hygiene the chief tool to control and protect patients and population

The market is currently driven by the sale of four leading drug classes that represent 74% of the whole market: chephalosporins (27%), macrolides (20%), quinolones (17%) and penicillins (10%). In the last few years a number of first-in-class antibiotics have been launched: glycylcyclines (Wyeth's tigecycline), oxazolidinones (Pfizer's linezolid) and lipopeptides (Cubist's daptomycin).

With the risk of transmission of infectious diseases on the rise, disease control standards are increasing inexorably, but so are the costs associated with them, making disease control a highly resource intensive field in terms of hospital resources (e.g. increasing length of stay, time of healthcare professionals, consumables and equipment) with an associated financial burden and high rate of morbidity and mortality. Clinical governance requires the adoption of protocols and processes proving that the monitoring, auditing and validation of working practices have been carried out and recorded. Hygiene has become the chief tool in attempts to protect patients and the population at large from deadly infections.

Over a period of 8 years, the US NIAID (National Institute of Allergy and Infectious Diseases) invested more than US$800m to support basic and translational research on antibiotics, more than US$200m of which devoted to understanding the causes, consequences and treatments of antibiotic drug-resistance, but significant clinical results have yet to materialise.

The field of disease prevention and control embraces numerous industries, sectors and subsectors addressing those activities that primarily affect human and animal wellbeing like healthcare, food hygiene (incl. growing and processing), water, waste treatment, air acclimatisation, Health Information Technology (HIT) just to mention a few.

HAIs market size runs in the order of several tens of US$bn, but the actual size and growth rate is hard to gauge accurately in a global context. This is because antimicrobial agents (ex-antibiotics) in the form of disinfectants, hand-washes and scrubs and consumables, including personal preventive equipment (gloves, gowns, masks, eye protection, face shields, cleaning and decontamination equipment) are part of the 'consumer products' divisions of vast international organisations (e.g. Lysol® (Reckitt Benckiser plc); Cidex® (Advanced Sterilisation Products a division of J&J); Ecolab®, Huntington, Mertek brands (Ecolab, Inc.); 3M; Steris Corp; Kimberly-Clark Corp). It is therefore unsurprising that this sector is characterised by the presence of a large number of SMEs or private companies providing an extensive range of products and services, such as: Belimed Sauter AG; Bioquell (BQE:LN); Cantel Medical Corp (CMN:US); Destiny Pharma (UK, unquoted); Getinge AB (GETIB:SS); Proventec Plc (PROV:LN); PuriCore (PURI:LN) Plc; Schülke & Mayr GmbH; Tristel plc (TSTL:LN); Vernon-Carus Ltd (part of Synergy Healthcare since June 2008).

Hospital Acquired Infections (HAIs)

HAIs are infections resulting from treatment at hospitals or healthcare service facilities, but **secondary** to the patient's original condition. The most likely source of HAIs relates to handling and hygiene procedures of healthcare providers.

Three major transmission routes

Within healthcare settings all body fluids including blood, secretions, excretions (except sweat), open wounds and mucous membranes are considered possible vectors for both the acquisition and transmission of infectious diseases. An infection occurs when a microorganism (bacterium, protozoan, virus or fungus) invades a susceptible host. Within hospital settings there are three major transmission routes: **direct contact**, **droplet/airborne** (through coughing, sneezing and talking. Droplets containing germs from the infected person are propelled a short distance through the air) and **waterborne**.

The majority of HAIs are caused by bacteria often isolated on surfaces and hands, making them an important route of indirect contact infection transmission that may occur between patients or from healthcare workers to patients and *vice versa*. As a result meticulous **environmental cleanliness** and particularly **hand washing** is considered to be the single most important procedure to prevent/control the transmission of infections followed by the use of personal preventive equipment (gloves, gowns, masks, eye protection, face shield). Indirect contact transmission includes:

- Hands of healthcare personnel may transmit pathogens after touching an infected or colonised body site(s) on one patient or a contaminated inanimate object, if hand hygiene is not performed before touching another patient;
- Patient care devices and instruments (i.e. electronic thermometers, glucose monitoring devices, endoscopes and/or surgical instruments) may transmit pathogens if they are inadequately disinfected and sterilised between patients treatments; and a clear example is shown in the table below:

Table 2 : Blood Pressure (BP) Cuffs as vector of disease –203 BP Cuffs used in medical, surgical, ICU and emergency units

Type of BP Cuff	Total number	% Contaminated
On nurses' trolleys	35	77%
Individual	41	63%
Wall model	57	53%
Stored	52	17%
Newly cleaned (with disinfecting detergent)	18	0%

University Hospital in Tours - France

- Clothing and fabric in general; when doctors and nurses lean over a patient with MRSA the coat or uniform pick up bacteria 65% of times; MRSA can survive for several hours on fabrics and surfaces;
- Shared toys may become a vehicle for transmitting respiratory viruses (i.e. respiratory syncytial virus or pathogenic bacteria (i.e. *Pseudomonas aeruginosa*) among paediatric patients.

The natural microbial flora of the hand skin and body in general consists of resident (colonising) and transient (contaminating) microorganisms.

- Resident flora includes *coagulase-negative staphylococci*, members of the genus *Corynebacterium* (diphtheroids or coryneforms), *Acinetobacter* species and occasionally members of the *enterobacteriaceae* group. Although, none of the just mentioned microorganisms are usually implicated in nosocomial infections, other than minor skin infections, patients severely immuno-compromised are at risk of acquiring an infection in hospital settings after undergoing invasive procedures like the receiving an implantable device, such as a heart valve or artificial hip.
- Transient flora represents recent contaminants of the hands acquired from colonised or infected patients or contaminated environment or equipment. In contrast to resident flora, the transient microorganisms found on the hands of healthcare personnel are more frequently implicated as the source of nosocomial infections. The most common transient flora includes gram-negative, non-spore forming coliforms and gram-positive *Staphylococcus aureus,* chief culprit behind staph infections.

About MRSA

MRSA is a strain of the *S. aureus*, a bacterium normally found in the noses and on the skin of many healthy people that has become resistant to Methicillin and other commonly used penicillin-related antibiotics. Most *S. aureus* infections in healthy individuals are minor (such as pimples and boils) and can be treated without antibiotics. However, hospitalised patients who are elderly, immuno-compromised, those with an open wound or catheter may become ill from the bacteria.

Additional contributory factors that can put some patients at higher risk for MRSA including prolonged hospital stay, receiving broad-spectrum antibiotics, being hospitalized in an intensive care or burn unit, spending time close to other patients with MRSA, having recent surgery, or carrying MRSA in the nose without developing illness.

HAIs in the US…

According to CDC, HAIs are one of the top ten causes of unnecessary death in the US. According to a study published in November 2007, infections caused by *Staphylococcus aureus* alone have increased by 7% annually from 1998-2003. In 1998, US hospitals reported approximately 250,000 staph infections and five years later that number almost reached 390,000, the equivalent of 1% of hospital in-patient visits.

Data derived from the National Inpatient Sample Database shows that the cost to treat staph infections alone increased from US$8.9bn in 1998 to US$14.5bn in 2003. Of the 2m patients contract infections in hospitals and an estimated **103,000 patients die as a result**. **Overall, HAIs are estimated to add an estimated UD$30.5bn** (*2m x US$15,275 (av. additional hospital costs, when a patient contracts an infection*)) **to the US hospital cost each year**. The US$30.5bn figure does not include doctors' bills, home nursing bills, lost time at work and other non hospital related costs. The CDC reported that MRSA as a percentage of *Staphycoccal* infections in ICUs increased from 2% in 1974, to 22% in 1995 and to 63% in 2006. In a recent article published in the Journal of the American Medical Association, MRSA is responsible for an estimated **94,000** life-threatening conditions and causes **18,650 deaths** annually in the US.

A study completed by the University of Alabama, published in January 2008, utilising data from over 1.3m hospital admissions in 55 hospitals located in urban, suburban and rural communities over a 5-year period (2001-2006), identified 58,381 infections. Out of 99,445 re-admissions of previously hospitalised patients, 7,501 (c.7.5%) were due to an infection acquired during the previous stay. The additional average total cost relating to the infection was US$7,007 in added variable cost, US$12 to fixed costs and 5.4 extra in-patient days. The majority of infections were urinary tract (40%) costing US$3,936, blood (25%) costing US$12,774, respiratory (20%) costing US$24,408 and wound (15%) costing US$7,059.

The Society for Healthcare Epidemiology of America reports that MRSA acquired in the community is increasingly the cause of **infections transferred to hospitals** and adds to MRSA acquired within hospitals settings. There is one in five chances that a patient harbouring MRSA at admission can go on to develop an infection if not identified and treated.

Only high risk patients tested in the US

In Illinois, New Jersey and Pennsylvania, state legislation requires that high risk patients and those in ICUs are to be tested for MRSA. At least eight other state legislatures are contemplating to do the same. Opponents to this initiative believe that testing and isolation will not prevent the spreading of MRSA. Although ICUs account for a relatively small proportion of hospitalised patients, infections acquired in these units accounted in 2003 for >20% of all HAIs (both adults and paediatrics) in the US, according to a study published by CDC in June 2007. Adverse patient outcomes in this setting are more severe and associated with a higher mortality rate.

Widely varied set of stats data

The above figures represent only a tiny snippet of the large amount of computations that have been performed up to now on the subject; all the studies, produced a widely varied set of results as no standard methodologies have been established making it very hard to gain an accurate picture of HAIs' incidence, mortality and costs in the US. The four agencies within the HHS (Health and Human Services Department) gather different types of data about different subset of patients, resulting in unclear and fragmented evidence. At the moment 500 hospitals report data on infection rates, 14 states require the data to be reported to HHS whereas 16 states have legislation pending to do so.

GAO's critical report on HAIs stats

In March 2008, GAO published a very critical report on the way HAIs statistical data is prepared '*Leadership needed from HHS to prioritise prevention practices and improve data on these infections*'. The report concluded that '*HHA could not use its databases to provide reliable national estimates of HAIs rates, even for the selected types of HAIs being monitored, because none of the databases collect data on the incidence of HAIs for a national representative sampling of patients*'. Additionally, GAO identified over 1,200 recommended practices for infection prevention to be followed by hospitals, clinics and long-term care facilities, 500 of which falling within the highly recommended category. GAO found that the huge number of recommendations have slowed down their implementation and suggested that realistic priorities have to be established so that can be followed reasonably.

HAIs are largely preventable

With HAIs being another contributory factor to the continuing soaring healthcare treatment costs and considering that these infections are largely preventable, Medicare, as of October 2008, will not reimburse hospitals for three types of infections, including urinary and vascular catheter and we think that this is going to have a knock-on effect on US healthcare insurance companies as they typically follow the lead of Medicare.

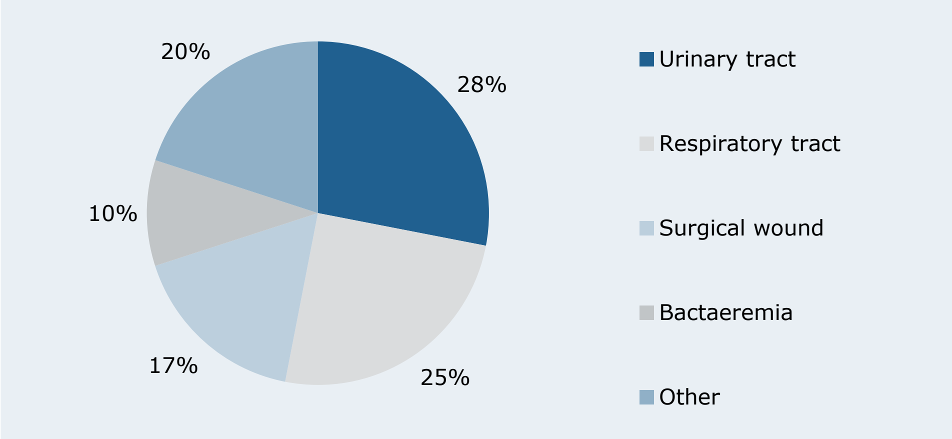
HAIs in Europe

In the EU HAIs are estimated to affect about 3m people each year with a death toll of around 50,000 with one patient out of ten in an EU hospital acquiring such an infection.

The EU faces similar issues as the US with respect to the gathering of data. Laboratories provide the information (to the EARSS (European Antimicrobial Resistance Surveillance System) on a voluntary basis and there is a great variation in countries' participation and large regional differences within these countries. HAIs surveillance protocols are not standardised and reporting compliance in some countries remains 'patchy'. Furthermore, several EU Member States do not have a national surveillance network for nosocomial infections and the setting up such programmes is a slow and costly process as it involves important political decisions, specific legislation and a sizable financial investment especially in hospitals.

HAIs surveillance is highly labour-intensive and therefore targets specific high-risk populations (such as intensive care patients) or infections types (bacteraemias, surgical site infections). The most frequently reported are shown in the graph below.

Figure 2 : EU most frequent HAIs



ECDC

The incidence of MRSA is rising almost everywhere in Europe and is isolated in approximately 5% of all nosocomial infections. Other major nosocomial pathogens are MSSA, *P. aeruginosa, Enterobacteriaceae* (*E. Coli, Enterobacter* sp*, Klebsiella* sp), Enterococci, fungi (*Candida* sp*, Aspergillus* sp), Coagulase-negative staphylococci (e.g. catheterassociated BSI (blood stream infections)), *Acinetobacter* sp. and *C. difficile*.

Denmark, Holland and Finland have managed to bring HAIs under control to ≤1% through 'search and destroy' practices which includes a rigorous hand hygiene and meticulous cleaning of rooms and equipment in between patient use, testing incoming patients for MRSA and other drug resistant bacteria and taking precautions to prevent transmission to other patients.

HAIs in the UK…

In the UK mandatory surveillance of HAIs

In the UK, *S. aureus* and *glycopeptide-resistant enteroccocal* (GRE) blood infections, *C. difficile* (hospital acquired diarrhoea) and general surgical site infections are subject to a mandatory surveillance scheme that has been adopted by all the acute NHS Trusts, but was started at different times (*S. aureus,* since April 2001; *GRE,* since October 2003; *and C. difficile,* since January 2004*)* with different reporting frequencies. Initial data was published annually and then six-monthly and more recently quarterly.

The BMA (British Medical Association) estimates that the NHS spends up to £1bn (BMA) each year to treat and prevent HAIs. Recent statistical data published by the HPA (Health Protection Agency) shows a progressive reduction in MRSA's reported cases in the last four years (FY ending in March), as shown in the tables below, after the staggering rise during the '90s from 5% to 42% at the end of the decade. Concerns about this increase led the health authorities to announce in October 2000 the mandatory reporting for certain types of HAIs. However, MRSA bacteraemia (bacterial infection of the blood-stream) in the UK is thought to be among the highest in Europe.

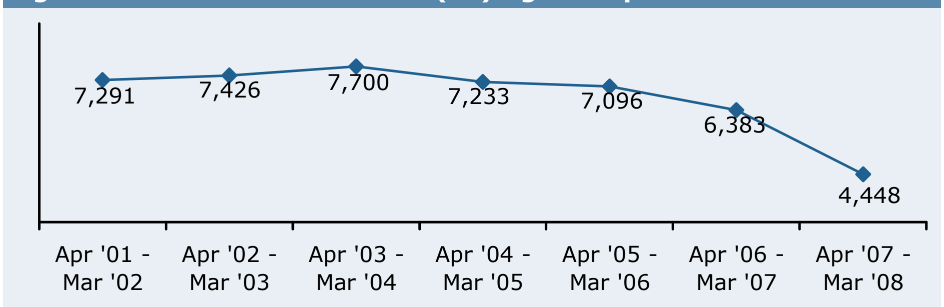
During the last couple FYs the incidence has been decreasing at a rate of 10% and 30% in 2007 and 2008 respectively. At the end of March 2007, of the 17,404 *S. aureus* blood infections reported, 6,383 were due to MRSA, with London being the location with the greatest number of MRSA cases but also the one with the largest improvements and in FY2008 MRSA cases decreased by over 30% to 4,448.

Table 3 : MRSA – Yearly (financial year) figures April 2001 - Mar 2008

Year	No. of cases	y-o-y % chg. in no. of cases	Bacteraemia rate per 10k bed days
Apr '01 -Mar '02	7,291		1.71
Apr '02 -Mar '03	7,426	1.9%	1.78
Apr '03 -Mar '04	7,700	3.7%	1.83
Apr '04 -Mar '05	7,233	-6.1%	1.76
Apr '05 -Mar '06	7,096	-1.9%	1.78
Apr '06 -Mar '07	6,383	-10.0%	1.67
Apr '07 -Mar '08	4,448	-30.3%	1.16

HPA

Figure 3 : MRSA – Semi-annual (FY) figures Apr 2001 – Mar 2008

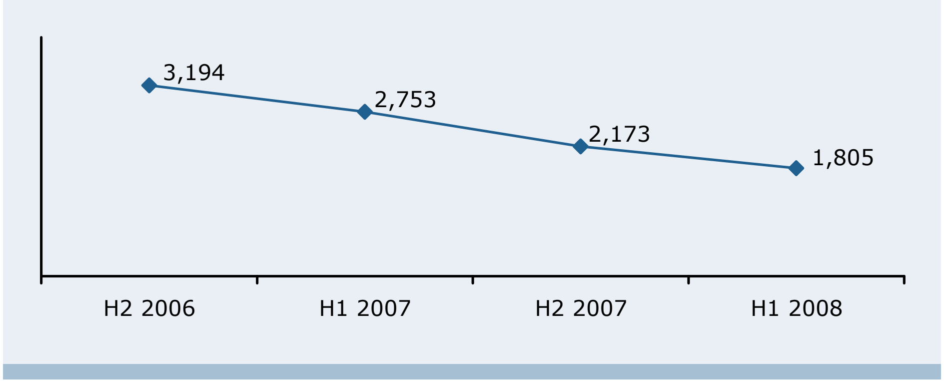


HPA

Whether financial of calendar figures, MRSA cases have been decreasing

The percentage decrease in incidence is even greater if we compare the half-yearly *calendar figures* for the last couple of years. The number of cases in H1 2008 decreased by 52.5% to 1,805 from 2,753 in H1 2007, whereas between H2 2006 and H2 2007 the number of cases decreased by 47%.

Figure 4 : MRSA – Half-yearly calendar figures H2 2006 – H1 2008



HPA

£50m< for the deep cleaning of hospitals

The decreased risk of becoming infected with a MRSA bacteraemia is though to be primarily attributable to higher standards of clinical practice and cleanliness, almost doubled the number of matrons to >5,538 (May 2008) and implemented a £50-57m nationwide hospital deep clean exercise (as of May 2008, 328 trusts completed their deep cleaning programmes), but it is not clear how the achieved cleanliness is going to be maintained. Some of the actions taken during the 'spring cleaning' include:

- Minimise the movements of MRSA-positive patients;
- Use of disposable gowns and aprons when treating MRSA-positive patients;
- Launder privacy curtains or use disposable ones;
- Decontamination of trolleys and wheelchairs after patient use;
- Decolonisation of MRSA-positive patients before surgery; and
- Segregation MRSA-positive patients in the recovery area.

Between 1993 and 2006 the deaths increased from 51 to 1,652. In 2007, deaths certificates mentioning MRSA or *S. aureus* showed a small decrease to 1,593. Most of the deaths were in the older age groups with a higher prevalence in the male patient population (HPA).

MRSA screening will be introduced in April 2009 in the UK

As from April 2009, all elective admissions and most day case patients will be tested for the presence of MRSA on common sites such as nose, armpit, groin, hairline and any superficial clinical lesions on or before admission to hospital. The screening will be then extended to all the admissions, including emergencies by 2010/11. Patients tested positive will receive skin decolonisation treatments before they are admitted.

Improvements have also been made in the fight against *C. difficile.* The mandatory *C. difficile* surveillance programme requires all acute NHS Trusts to report all cases of infection in patients between the ages of 2 and ≥65. Historically the data was prepared on a calendar year basis, but it was changed to financial year from 2007/08.

The number of *C. difficile* cases increased from less than 1,000 in the early 1990s to 22,000 in 2002, 28,000 in 2003, 44,488 in 2004 and almost 56,000 in 2006

(2005 data not found). Some of this was due to improved diagnostic tests and improved reporting by laboratories, but there has clearly been a very significant increase in the number of cases over time.

The data gathered from 170 acute NHS Trusts shows that during the quarter Apr-Jun 2008, 10,866 *C. difficile* cases were reported, a 35.6% reduction when compared to the same period the previous year (16,868 cases) and in particular cases of *C. difficile* in patients ≥65 years decreased by 19%.

Until Q1 2007 data was collected only for patients' ≥65 years of age. In April 2007 acute NHS Trusts started to gather data on patients between the ages of 2 and 64 years old as shown in the table below.

Table 4 : *C. difficile* quarterly figures

Quarter	No. of *C.difficile* cases in patients aged 2-64 years	No. of *C.difficile* cases in patients aged ≥65 years	TOTAL
Jan – Mar 2006		15,349	15,349
Apr - Jun 2006		14,689	14,689
Jul - Sep 2006		12,821	12,821
Oct - Dec 2006		12,776	12,776
Jan – Mar 2007		15,644	15,644
Apr - Jun 2007	2,944	13,924	16,868
Jul - Sep 2007	2,538	10,884	13,422
Oct - Dec 2007	2,239	10,009	12,248
Jan – Mar 2008	2,356	10,608	12,964
Apr - Jun 2008	2,183*	8,683**	10,866

HPA

**From 4 acute NHS Trusts specialised in children care*

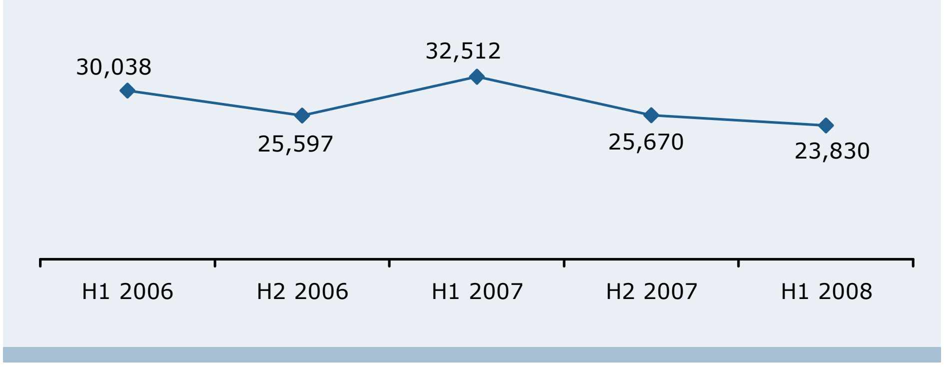
***From 166 acute NHS Trusts*

Figure 5 : *C. difficile* quarterly figures

HPA

Looking at the yearly calendar figures of patients' ≥65 years of age for the years 2006 (55,635 cases) and 2007 (50,461 cases) there has been a decrease in cases of 9.3%.

Figure 6 : *C. difficile* semi-annual calendar figures H1 '06 – H1 '08



HPA

About C. difficile

C. difficile is a spore-forming gram-positive anaerobic bacillus that was first isolated from stools of neonates in 1935 and identified as the most commonly causative agent of antibiotic-associated diarrhoea and pseudomembranous colitis in 1977. This pathogen has been responsible for many large outbreaks in healthcare settings that were extremely difficult to control.

Important factors that contribute to healthcare-associated outbreaks include environmental contamination, persistence of spores for prolonged periods of time, resistance of spores to routinely used disinfectants and antiseptics, hand carriage by healthcare personnel to other patients, and exposure of patients to frequent courses of antimicrobial agents. Antimicrobials most frequently associated with increased risk of *C. difficile* include third generation cephalosporins, clindamycin, vancomycin, and fluoroquinolones.

Since 2001, outbreaks and sporadic cases of *C. difficile* with increased morbidity and mortality have been observed in several US states, Canada, UK and The Netherlands. The control of this pathogen is now even more important than previously given the greater morbidity, mortality, length of stay, and costs associated with patients in both acute care and long term care facilities.

Prevention of transmission focuses on the rigorous application of contact precautions for patients with diarrhoea, accurate identification of patients, environmental measures (i.e. **rigorous cleaning of patient rooms and use of chlorine containing disinfectants**) and consistent hand hygiene. Use of soap and water, rather than alcohol based hand-rubs, for mechanical removal of spores from hands, and a bleach-containing disinfectant (5000 ppm) for environmental disinfection, may be valuable when there is transmission in a healthcare facility.

Hand hygiene

The term "*hand hygiene*" includes both hand-washing with either plain or antiseptic-containing soap and water, and use of alcohol-based products (i.e. gels, rinses, foams) that do not require the use of water.

The link between hand washing and the spread of disease has only been established in the last 200 years. In the mid-1800s, studies conducted in Vienna and Boston established that hospital-acquired diseases were transmitted via the hands of healthcare workers.

The 1980s represented a landmark in the evolution of concepts of hand hygiene in health care when the first national hand hygiene guidelines were published and have been followed by many others in more recent years. These guidelines were essentially issued in countries such as the US and Canada and some European countries.

Hand hygiene concepts have much evolved over the past two decades. In the early '60s the hand washing techniques recommended to wash hands with soap and water for 1 to 2 minutes before and after patient contact. Rinsing hands with an antiseptic agent was believed to be less effective than hand washing and was recommended only in emergencies or in areas where sinks were not available. Twenty years later, the US national guidelines still recommended waterless antiseptic agents (i.e. alcohol-based solutions) only in situations where sinks were not available, and hand washing with soap and water was considered the standard of care.

In 1995 and 1996, the US CDC/Healthcare Infection Control Practices Advisory Committee (HICPAC) recommended that either antimicrobial soap or a waterless antiseptic agent be used for cleansing hands upon leaving the rooms of patients with multidrug-resistant pathogens such as VRE and MRSA. More recently, the CDC/HICPAC guidelines issued in 2002 defined alcohol-based hand rubbing as the standard of care for hand hygiene practices in health-care settings.

Particular attention has been given to the fingernail area of the hand as it is associated with a major portion of the hand flora. The effectiveness of hand hygiene can be reduced by the type and length of fingernails. Hand carriage of gram-negative bacilli and yeasts has been determined to be greater among individuals wearing artificial fingernails, extensions and chipped polished nails both before and after hand washing and have been epidemiologically implicated in multiple outbreaks involving fungal and bacterial infections in ICUs where patients undergo invasive therapeutic support such as mechanical ventilation and often develop a serious and life-threatening lung infections such as Ventilator Associated Pneumonia (VAP) and in the operating theatre. Improved hand hygiene practices have been associated with a sustained decrease in the incidence of HAIs infections especially in ICUs.

Table 5 : Hand hygiene products

Products	Description	Comments
Alcohol based hand rubs	It is not a cleansing agent and is used when rapid hand disinfection is required, such as on a ward round. It is available in all clinical areas and can be found by each bed in intensive care. It can be used after a routine hand wash as an adequate method of decontaminating the hands prior to procedures such as IV drug administration or dressings.	It is **not** effective against *C. difficile* so when caring for a patient with *C. difficile* hands must be washed with soap and water
Antimicrobial medicated soaps	Soap containing an antiseptic agent at a concentration which is sufficient to reduce or inhibit the growth of transient microorganisms	
Antiseptic agents	An antimicrobial substance which reduces or inhibits the growth of transient microorganisms on living tissues.	Examples include alcohols, chlorhexidine gluconate, chlorine derivatives, iodine, chloroxylenol (PCMX), quaternary ammonium compounds, and triclosan
Detergent (surfactant)	Compounds that possess a cleaning action. They are composed of a hydrophilic and a lipophilic part and can be divided into four groups: anionic, cationic, amphoteric, and non-ionic	
Plain soap	Detergents based products that do not contain antimicrobial agents or that contain very low concentrations of antimicrobial agents effective solely as preservatives.	
Waterless antiseptic agents	An antiseptic agent that does not require the use of exogenous water. After application, the individual rubs the hands together until the agent has dried	Hand-rubs (liquid formulations, gels, foams)

WHO

Urinary Tract Infections (UTI)

The urinary tract is the most common infection site acquired in a hospital, or hospital-like setting in both the US (40%) and EU (28%) with most of these infections (66% to 88%) resulting from urinary catheterisation as the catheter surface serves as a platform for the growth of bacteria as biofilm. As the duration of catheterization increases, catheter associated UTI rates approach 100%. Patients who acquire a UTI will stay longer in hospital an average of 6 days longer than those who do not, and will contribute to an extra US$1.8bn in hospital costs in the US.

Recent studies have shown an abundance of evidence that anti-microbial catheters provided benefits when compared to standard uncoated catheters. Furthermore, there is a vast support for the assertion that the increased cost of an effective coated catheter is justified with even a modest reduction in the rate of UTI. To this end the CDC is recommending the use of anti-microbial coated catheters, there is a growing market demand for these types of products. The current $175 million US anti-microbial coating market is forecast to grow to over US$500m by 2012.

There are a limited number of coated urinary catheters in the market today, predominantly made up of those coated with silver. Although, the anti-microbial activity of silver is documented, the use of silver on medical devices is continually debated based on lack of conclusive evidence supporting its ability to reduce infection. According to leading experts, catheter associated UTI are perhaps the prime reservoir for antibiotic resistant pathogens.

APPENDIX

Table 6 : Bacteria commonly found on surfaces of Human bodies

Bacterium	Skin	Conjunctiva	Nose	Pharynx	Mouth	Lower Intestine	Anterior urethra	Vagina
Staphylococcus epidermidis	++	+	++	++	++	+	++	++
Staphylococcus aureus *	+	+/-	+	+	+	++	+/-	+
Streptococcus mitis				+	++	+/-	+	+
Streptococcus salivarius				++	++			
Streptococcus mutans *				+	++			
Enterococcus faecalis *				+/-	+	++	+	+
Streptococcus pneumoniae *		+/-	+/-	+	+			+/-
Streptococcus pyogenes *	+/-	+/-		+	+	+/-		+/-
Neisseria sp.		+	+	++	+		+	+
Neisseria meningitidis *			+	++	+			+
*Enterobacteriaceae (Escherichia coli)**		+/-	+/-	+/-	+	++	+	+
Proteus sp.		+/-	+	+	+	+	+	+
Pseudomonas aeruginosa *				+/-	+/-	+	+/-	
Haemophilus influenzae *		+/-	+	+	+			
*Bacteroides sp.**						++	+	+/-
Bifidobacterium bifidum						++		
Lactobacillus sp.				+	++	++		
*Clostridium sp.**					+/-	++		
Clostridium tetani						+/-		
Corynebacteria	++	+	++	+	+	+	+	+
Mycobacteria	+		+/-	+/-		+	+	
Actinomycetes				+	+			
Spirochetes				+	++	++		
Mycoplasmas				+	+	+	+/-	+

*++ nearly 100% + common (~25%) +/- rare (<5%) * potential pathogen*

Various

Table 7 : Major classes of chemical disinfectants and their relative advantages / disadvantages

Disinfectant	Uses	Advantages	Disadvantages
Quarternary ammonium compounds	**Low** level disinfectant; suitable for hard surfaces and to clean blood spills	Generally non-irritating to hands & have detergent properties	Not suitable for instruments disinfection; narrow microbiocidal spectrum
Phenolics	**Low/intermediate** level disinfectant suitable to clean hard surfaces and equipment that does not touch mucous membranes	Leaves residual film on environmental surfaces; commercially available w/ added detergents to provide one-step cleaning & disinfecting	Not recommended for use on contact surfaces; may be absorbed through skin or by rubber
Alcohols	**Intermediate** level disinfectant; suitable for external surfaces of medical devices (e.g. stethoscopes, thermometers); and home health care equipment; used as a skin antiseptic	Fast acting; no residue or staining	Volatile; evaporation may diminish concentration; inactivated by organic material
Chlorines (hypochlorites)	**Intermediate** level disinfectant; disinfection of hydrotherapy tanks; dialysis equipment; environmental surfaces; suitable following blood spills; home health care equipment	Low cost; fast acting; readily available in non hospital settings	Corrosive to metal; inactivated by organic material; irritant to skin & mucous membranes; shelf-life shortens when diluted
Iodophors	**Intermediate** level disinfectant, suitable to clean hard surface and equipment that does not touch mucous membranes (e.g. IV poles, wheelchairs, beds, call bells, hydrotherapy tanks)	Rapid action	Corrosive to metal unless combined with inhibitors; inactivated by organic materials; may stains fabrics and synthetic materials
Hydrogen peroxide	**High** level disinfectant. Primarily used for the disinfection of environmental surfaces and heat sensitive medical equipment	Fast acting (5 minutes); break down into water and oxygen	Can be corrosive to aluminium, copper, brass or zinc; limited ability to penetrate surfaces
Glutaraldehydes	**High** level disinfectant. Available in liquid & gaseous forms. Primarily used for the disinfection of heat sensitive medical equipment	Non metal corrosive; active in presence of organic material; compatible w/ lensed instruments;	Extremely irritating to skin and mucous membranes; shelf life shortens when diluted; high cost
Formaldehyde	**High** level disinfectant. Available in liquid & gaseous forms; gaseous form primarily used to decontaminate labs	Active in presence of organic material	Carcinogenic; toxic; strong irritant; pungent odour
Peracetic acid	**High** level disinfectant Used for the disinfection of heat sensitive medical devices	Rapid action at low temperature; active in presence of organic materials	Can be corrosive; unstable when diluted

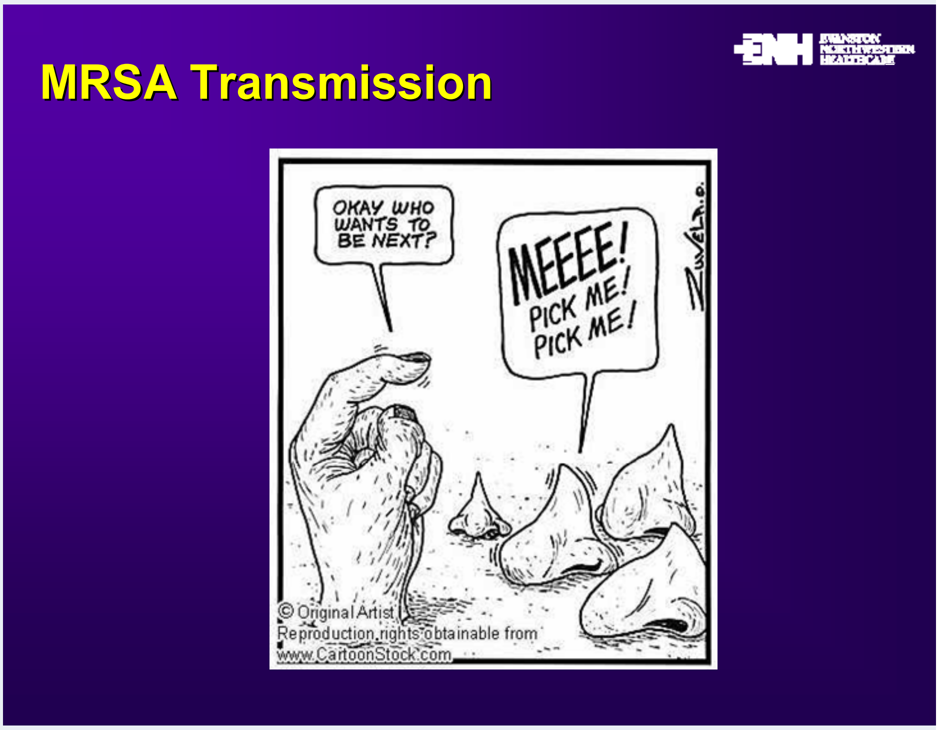
Various

Table 8 :Antibiotics & MRSA emergence timeline

Late 1880s	Scottish surgeon Alexander Ogston identifies *Staphylococcus aureus*
1928	Alexander Fleming discovers the first antibiotic, penicillin
1941	Penicillin becomes available in the US and UK.
1944	Steptomycin was discovered
Late 1940s	25% of *S. aureus* bacteria are penicillin-resistant
1958	Vancomycin is introduced
1959	Methicillin is introduced
1961	First cases of MRSA reported in the UK
1967	The first penicillin-resistant pneunomonococcal bacteria reported in New Guinea
2002	Doctors first identify vancomycin-resistant *S. aureus* in the US
Today	>95% of *S. aureus* worldwide is penicillin-resistant and 60% is methicillin-resistant

Becton Dickinson & Co

Figure 7: No laughing matter?



Evanston Northwestern Healthcare

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