ReAct facts

Burden of Antibiotic Resistance

Antibiotic resistance (ABR) poses an increasing threat to human health across the world. No country can escape from the medical and economic impacts from this serious problem.

Certain bacteria such as multi-resistant Gram-negative bacteria are particularly worrisome.[1] In the US, two thirds of deaths due to bacterial infections are caused by Gram-negative bacteria.[2]

Common diseases resulting from these bacteria are e.g. blood stream infections, urinary tract infections, post-operative wound infections and intra-abdominal infections.

The lack of effective antibiotics for treating these infections will increasingly lead to serious health problems and premature deaths.

The consequences of antibiotic resistance affects patients' lives but also reaches far beyond the individual patient affecting health care systems and societies across the world.

Within just a few years, we may very well be faced with unimaginable setbacks, medically, socially and economically unless we react now.

The ongoing pandemic spread of resistant bacteria illustrates that the problem can only be addressed through international cooperation.

The studies in this fact sheet were published between 2005 and 2012.

PATIENT GROUPS ESPECIALLY AFFECTED BY ABR

Newborns and children

- ESBL-producing bacteria are frequently causing infections in newborns. In an Indian hospital, *Klebsiella* and *E. coli* were the most common Gram-negative bacteria among infants with BSIs. About 33% of ESBL-infections were deadly in spite of available newer antibiotics and other supportive care.[3]

- In a study from Pakistan, 37 of 78 newborns (less than 6 days old) with infections due to *Acinetobacter* died within a short time frame. 71% of the bacteria were resistant to all antibiotics except polymyxin.[4]

- In an outbreak in India caused by NDM-1 *E. coli*, 4 newborn babies contracted blood stream infections (BSIs). All four died.[5]

- Three premature babies in a German neonatal ward died due to an outbreak of ESBL-producing *Klebsiella pneumoniae* from an unknown source.[6]

- In a study of Tanzanian children, the BSI rate was as high as 13.9%. One third of these children died. The death rate from Gram-negative BSI (43.5%) was more than double that of malaria (20.2%). One

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significant risk factor for death was treatment with ineffective antibiotics due to antibiotic resistance.[7]

Transplantation and cancer patients

- In Spain, among 416 patients undergoing transplantations of kidneys, 58 were infected with multi drug resistant (MDR) bacteria, most often Gram-negative. BSIs occurred in 14% of those. Death or graft loss was significantly more frequent among those with MDR infections (19% vs. 8 %).[8]

- In the US, an outbreak of *K. pneumoniae* carbapenemase-producing infections among liver transplant recipients killed two patients. A larger outbreak involving 24 patients soon followed the two initial cases in the ward.[9]

- In another study from the US, recent organ

or stem-cell transplantations were associated with a higher risk of infection with resistant bacteria. Patients were significantly more likely than control patients to die during hospitalization (48% vs 20%) and to die from the infection (38% vs 12%). [10]

- An outbreak of a carbapenem-resistant *K. pneumoniae* (CRKP) bacteria occurred in a German hospital. Five patients treated in the ICU after transplantations or cancer treatment were infected with the resistant bacteria and died; in four of the cases, death was directly related to the infection. [11]

- In Egypt, children contracting a BSI while treated for cancer were followed. Among 239 episodes of BSI, 38% were MDR. Twenty-five children died and among those, 72% were infected with MDR bacteria. [12]

ECONOMICAL AND SOCIETAL IMPACT OF ABR

The table below summarises examples of studies regarding additional costs as well as additional days in hospital due to treatment of resistant bacteria.

Location	Description	Additional treatment costs for ABR per individual	Additional hospital days due to ABR per individual
US	MRSA/MSSA infections[14]	$21 000 – 25 000	
US	ABR/Non-ABR infections[15]	$29 000	6.4-12.7 additional days
US	Health-care associated infections caused by Gram-negative resistant bacteria[16]	29% higher costs for patients with ABR infections	24% longer stay
US	MRSA/MSSA (SSI infections)[17]	$24 0000	6 additional days
Israel	ESBL-producing bacteria[18]	57% higher costs for patients with ESBL	56% longer stay
Spain	Resistant *K. pneumoniae*[20]		29 additional days

Table 1: Summary of calculated additional costs as well as additional days in hospital due to treatment of resistant bacteria.

- In the EU, the economic burden associated with antibiotic resistant infections weighs heavily on the individual, the health care system and society. Infections due to resistant infections resulted in approximately 2.5 million extra hospital days in 2007 and the overall societal costs are estimated to about 1.5 billion € per year. [13]

- A study from the US found the mean cost per patient for the hospitals to be $ 51 252 - 84 436 for MRSA infections compared with $ 30 158 – 59 245 for MSSA. [14]

- In another US study, the medical and societal costs for resistant infections were measured. Among 1391 patients, 188 had resistant infections incurring considerable medical costs. The mean cost difference between study cases and controls was $ 29,069. Excess duration of hospital stay was 6.4 -12.7 days. The societal costs were $10.7-15.0 million. If effective interventions could have been applied and decreased the rate of resistant infections from 13.5% to 10%, such a reduction could have saved $ 2.7 million for this group of 1391 patients, or $1948 per patient. [15]

- A US study involved 662 patients admitted from 2000 to 2008 that all developed health-care associated infections (HAIs) caused by Gram-negative bacteria. Resistant bacteria caused 29% of the HAIs, and almost 16% involved MDR bacteria. The total hospital costs,

The minimum total attributable medical and societal cost for antimicrobial-resistant infections in 188 patients in a single hospital was 13,35 million USD. [15]

attributable to HAIs, caused by antibiotic-resistant Gram-negative bacteria were 29.3% higher than those attributable to HAIs caused by non-resistant Gram-negative bacteria. Length of stay was 23.8% longer. [16]

- A multi-center study from the US regarding surgical site infections (SSI) due to MRSA noted no difference in mortality compared with patients with MSSA. However, length of stay in the hospital was increased by approximately 6 days and costs increased with more than $24 000 per patient. [17]

- A study from Israel on BSIs with ESBL-producing bacteria showed that ESBL production increased length of stay 1.56-fold. Also, costs increased 1.57-fold giving a mean increase in cost attributable to ESBL- producing bacteria of $9,620. [18]

- In Spain, an ICU had to be totally refurbished due to a large outbreak of multi-resistant *A. baumannii.* [19]

- Patients in Spain infected or carrying resistant *K. pneumoniae* had a much longer total length of stay than controls: median stay, 36 versus 7 days. [20]

- The bacteria *Neisseria gonorrhoeae* has an ability to develop rapid resistance to antibiotics. Already in 2005, there were 3 million estimated cases of treatment failure globally, which translates into a treatment cost of $500 million per year. If left without effective treatment, gonorrheal infections can cause great suffering such as infertility, extra-uterine pregnancies with fatal complications, and blindness in newborns. The risk of transmitting HIV is significantly increased if a gonococcal infection is left untreated. [21]

ABR AND INCREASED RISK OF DEATH

- In the European Union alone, infections with only a subset of all multi-resistant bacteria cause around 25 000 deaths per year. [13]

Below is a table summarising available data on differences in death rates (mortality) between resistant and sensitive bacteria.

Bacteria	Death rate *resistant* strain	Death rate *sensitive* strain
E. coli[23]	32%	17%
A. baumannii[25]	16.4%	5.4%
A. baumannii[19]	53.8%	31.0%*
K. pneumoniae[26]	42.9% (CRKP)	18.9%
K. pneumoniae[27]	43.8% (CRKP)	12.5%
K. pneumoniae[10]	38%	12%
S. aureus[28]	36.4% (MRSA)	27.0%
S. aureus[14]	23.6% (MRSA)	11.5%

Table 2: Comparison of death rates (mortality) in patients with resistant or sensitive strains of bacteria. *=not fully sensitive.

Blood Stream Infections (BSIs)

- *E. coli* and *S. aureus* are the most common causes of BSIs worldwide. Data from Europe show that 150 000 cases of BSI were caused by *E. coli* and among those 9.3% were resistant to third generation of cephalosporins, G3CREC. More than 100 000 cases of BSI caused by *S. aureus* were reported and among those 25.6% were MRSA. An estimated 5503 additional BSI-deaths were attributed to MRSA and 2712 to G3CREC. [22]

- In another, prospective study from 13 European countries, the impact of BSIs caused by G3CREC was evaluated. The death rate at 30 days increased 2.5 times. [23]

- A retrospective study from Israel on BSIs showed that infection with ESBL producing bacteria was a strong predictor of increased risk of death. [18]

Acinetobacter baumannii (A. baumannii)

- *A. baumannii* was earlier regarded as not being particularly dangerous but it has recently emerged as a threat especially in Intensive Care Units (ICUs). It is often multi-resistant and may cause a number of different infections.

- Mortality caused by carbapenem-resistant *A. baumannii* in a number of European countries ranged from 3-67% during the years 2003-2011. [24]

- In the UK, multi-resistant *A. baumannii* has been circulating since 2001. Carbapenem resistance, rose from 0% in 2000 to 55% in 2006 among patients with BSIs. 16.4% of patients with carbapenem resistant *A. baumannii* died compared to 5.4% among those with BSIs caused by non-resistant bacteria. [25]

- In a Spanish hospital, more than 370 patients were infected with or carried multi-drug resistant *A. baumannii*. The death rate was 53.8% in this group compared to 31.0% among patients infected by another *A. baumannii* clone. [19]

Carbapenem-resistant Klebsiella pneumoniae (CRKP)

- CRKP is an emerging hospital acquired bacteria In a study from Greece on BSIs caused by *K. pneumoniae*, 6 out of 14 (42.9%) patients with carbapenem resistant bacteria died compared to 10 of 53 (18.9%) among those with non-resistant bacteria. [26]

- A study from Israel assessed death rates in three groups of patients: Patients with CRKP, that had a very high death rate (44%) in comparison to patients infected with carbapenem-susceptible *Klebsiella* (12.5%) and non-infected patients (2%). [27]

- A large increase of carbapenem-resistant *K. pneumoniae* was noted in a hospital in Spain. 55 patients infected with or carrying resistant *K. pneumoniae* had a significantly higher death rate than control patients, 45.5% vs. 30.9%. [20]

Pan-resistant Acinetobacter infections is life-threatening in neonates, particularly in premature babies and those with low birth weight. Struggling as we are with a neonatal mortality rate as high as 54/1000, minimizing poor hospital outcomes due to neonatal nosocomial infections is imperative. [4]

Methicillin-resistant Staphylococcus aureus (MRSA)

- A large study investigated the role of methicillin resistance in survival of patients with *S. aureus* infections. Data were collected for 13 796 adult patients in 1265 participating ICUs from 75 countries. ICU death rates were 29.1% for MRSA and 20.5% for MSSA-infections and corresponding hospital death rates were 36.4% and 27.0%. [28]

- In another study, from the US, patients with MRSA infection were also significantly more likely to die than were patients with MSSA; 23.6% vs 11.5%. [14]

Salmonella typhi (Enteric fever)

- A report from WHO SEARO states: shortly after the emergence of multi-drug resistant *S. typhi* in this region, death rates approaching 10% (close to 12.8% recorded in the pre-antibiotic era) were reported. [29]

CONCLUDING REMARKS

The numbers and figures presented in this document clearly indicate the seriousness of antibiotic resistance. It is today not possible to present a full picture of the spread of antibiotic resistance and its health and economic burden due to the lack of a global data. Thus, the information presented here is very likely just the tip of the iceberg. Some countries and regions do have surveillance systems in place; others have no system at all for collecting data.

The lack of global data on antibiotic resistance and its burden makes it almost impossible to track and contain emerging outbreaks in particular and resistance challenges in general. It also makes it impossible to evaluate the effects of national and regional initiatives to contain antibiotic resistance.

ReAct works to promote the development of a global surveillance system.

List of abbreviations

ABR	Antibiotic Resistance
BSI	Blood Stream Infection
CRKP	Carbapenem-Resistant *Klebsiella pneumoniae*
ESBL	Extended-Spectrum β-Lactamase
G3CREC	Third generation Cephalosporin-resistant *Escherichia coli*
HAI	Health Care Associated Infections
ICU	Intensive Care Unit
MDR	Multi Drug Resistant
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Sensitive *Staphylococcus aureus*
SSI	Surgical Site Infection
WHO	World Health Organization
SEARO	WHO South-East Asia Regional Office

ReAct

Action on Antibiotic Resistance

- ReAct is an independent global network for concerted action on antibiotic resistance.

- ReAct aims for profound change in awareness and action to manage the interacting social, political, ecological and technical forces that drive the rising rate of resistant human and animal infection and the rapid spread of resistance within and between communities and countries.

- Our vision is that current and future generations of people around the globe will have access to effective prevention and treatment of bacterial infections as part of their right to health.

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