The need for global access to effective antibiotics– bridging the gap between science and policy

Birmingham 2013

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Executive Director, ReAct (www.reactgroup.org)
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As it effects antibiotics, this problem is of exceptional magnitude.....
We should seek a more **peaceful coexistence** with pathogens.....

Antibiotics that are used as prophylaxis or as "**growth factors**" would allow antibiotic resistance and new diseases to breed.....

**Hospitals** are bacteriologically **dirty places**....

The relative protection from disease afforded by antibiotics is bought at the cost of a **huge ransom**.....
The gap between science and policy

Number of entries in PubMed
Search term: Antibiotic

Knowledge
The gap between science and policy

Number of entries in PubMed
Search term: Antibiotic

Global policy & governance
Social mobilization
Research and drug development
Numbers of unique β-lactamase enzymes identified since introduction of first β-lactam antibiotics

Generating data…
Publishing data…
Presenting data…
Why the global complacency?

- ABR has no disease or economic face
- Scarce data on global antibiotic use, global resistance levels and trends
- Inadequate data on the global health and economic burden
- The global self-deception: There will always be new antibiotics
No of laboratory confirmed cases of MRSA in blood

And the number of death certificates mentioning MRSA

England & Wales 1993-2003
Strama-The Swedish Strategic Programme Against Antibiotic Resistance

- Political level
- Professional organizations
- Swedish Institute for Communicable Disease Control
- Medical Products Agency
- European Centre for Disease Prevention and Control
- Swedish Medical Association
- National Board of Health and Welfare
- Swedish Veterinary Institute
- Swedish Association of County Councils
- The Dental and Pharmaceutical Benefits Agency

Network of local Strama groups
Antibiotic sale on prescriptions in Sweden 1987-2012 – age groups
Regional differences within the country-range from 410 to 290- national target at 250 prescriptions/1000 inhabitants
Patients diagnosed acute bronchitis and received antibiotics at health care centers.
Opinion of the Economic & Social Committee of the European Communities on
Resistance to Antibiotics as a Threat to Public Health
(own initiative opinion)

July 1998
Proving the obvious

Correlation between antibiotic use and resistance
Sales of different classes of antibiotics expressed as DDD/1000 inhabitants and day to outpatients 1997 in the 15 EU countries.
EMEA, ECDC, ReAct, Report, September 2009:
The bacterial challenge: time to react

Activities during the Swedish EU presidency 2009
Burden of multidrug-resistant bacteria in the EU

Human burden of antibiotic resistance

- Attributable deaths: approx. 25,000 / year
- Extra hospital days: approx. 2.5 million / year
- Total costs: approx. €1.5 billion / year

Source: ECDC, 09
USA

2 million resistant bacterial infections per year

23,000 deaths
Health Burden of AMR Infections in Thailand 2010

• Total number of AMR infections: 87,751 episodes

• The total number of deaths due to AMR infections: 38,481.

• The total additional length of stay (LOS) in hospitals for patients with AMR infections: >3,200,000

Professor Visanu Thamlikitkul
Thamlikitkul, MD
Health Systems Research & Development Program
Faculty of Medicine Siriraj Hospital Mahidol University, Bangkok, Thailand
How large is the unknown?

The tip of the iceberg
In Dar es Salaam, Tanzania, the paediatric mortality rate from gram-negative infections were more than 43%. Antibiotic resistance were a significant risk factor for a fatal outcome.

Blomberg et al. BMC Infect Dis 2007
Antibiotic resistance is causing significant mortality

Tanzania, 2000’s:
Gramnegative (ESBL) is causing a decrease the chance of a 14-day survival from ~ 70% to 20%

Severe neonatal bacterial infections

Adapted from Blomberg, BMC Infect Dis 2007
The amazing power of penicillin

USA 1950's:

Antibiotic treatment increased the chance of a 14 day survival from ~25% to 85%

Pneumonia with bacteria in blood

Sepsis in newborns in five countries in South Asia (India, Pakistan, Afghanistan, Nepal, Bangladesh)

- The contribution of antibiotic resistance (ABR) to major causes of newborn and under 5 bacterial infections and mortality is grossly under-estimated and possibly increasing

- Crude estimates indicate that an excess 96,000 neonatal infection deaths occur due to ABR infections in South Asia alone

- Conservative estimates based on etiological fractions indicate that treating these infections alone with appropriate second line antibiotics would cost in excess of $110 million

Zulfiqar Bhutta presentation at ReAct conference Sep. 2010
Available at www.reactgroup.org
One child dies every five minutes because the antibiotics given are not effective due to bacterial resistance.

Zulfiqar Bhutta presentation at ReAct conference Sep. 2010
China: Intravenous antibiotics for common colds

Annual antibiotic use per capita
Sweden: 7 grams  China: 138 grams
Illegal OTC antibiotic sale in the EU

Athens, Greece 2008 (174 pharmacies):

- 100% of all visited pharmacies sold Amoxicillin/clavulanate acid OTC
- 53% sold Ciprofloxacin OTC, despite extra restrictions for fluoroquinolone prescriptions

Plachouras et al. Euro Surveill. 2010
Modern medicine is built on access to effective antibiotics.....
### Antibiotic Sensitivity

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC mg/L (S/I/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pip/Tazo</td>
<td>&gt;128 R</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&gt;64 R</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;64 R</td>
</tr>
<tr>
<td>Cefepime</td>
<td>&gt;64 R</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>&gt;32 R</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&gt;32 R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&gt;32 R</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt;64 R</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&gt;64 R</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>16 R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;16 R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;4 R</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&gt;8 R</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>1.5 I</td>
</tr>
<tr>
<td>Colistin</td>
<td>0.5 S</td>
</tr>
</tbody>
</table>

#### Clinical Case

62-year old patient with hospital acquired pneumonia caused by *Klebsiella Pneumoniae*.
As a deadly infection, untreatable by nearly every antibiotic, spread through the National Institutes of Health’s Clinical Center last year, The staff resorted to extreme measures. They built a wall to isolate patients, gassed rooms with vaporized disinfectant and even ripped out plumbing.

‘Superbug’ stalked NIH hospital last year, killing six
“On the thinnest of ice”
Resistance in E coli for UTIs in patients in a rural Indian hospital

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole</td>
<td>94%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>91%</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; gen. cephalosporin</td>
<td>97%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>68%</td>
</tr>
<tr>
<td>Amikacin</td>
<td>25%</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; generation ceph.</td>
<td>72%</td>
</tr>
</tbody>
</table>

Anurag Bhargava M.D. et al
Health Centre: District Bilaspur, Chhattisgarh India
Polymyxins – Brazil

- Definitive, only when susceptibilities were known until 2004

- Epidemics of OXA-23 A. baumannii: polymyxins → empirically prescribed in many hospitals

- Emergence of KPC-2 Enterobacteriaceae: polymyxins → empirically prescribed in most hospitals

- Polymycin resistance increasing in some centers, especially in CRE 10-15%

Alexandre P. Zavascki
Infectious Diseases Service, Hospital de Clínicas de Porto Alegre Medical School, Federal University of Rio Grande do Sul - Brazil
The Current Crisis
Who is responsible?

Antibiotic Resistance

Morbidity
Mortality
Costs

Drug Development
“The issue is comparable to that of climate change in the sense that both phenomena involve non-renewable global resources, both are caused by human activity and are intrinsically linked to our behavior. The problem can only be addressed through international cooperation.”

Elinor Ostrom, 2009 Nobel Laureate in Economic Sciences,
Tercentenary Linnaeus Honorary Doctor of Uppsala University.
Improving the containment of antimicrobial resistance

The Fifty-eighth World Health Assembly,

Having considered the report on rational use of medicines by prescribers and patients,

Acknowledging that the containment of antimicrobial resistance is a prerequisite for stemming several of the internationally agreed health-related goals contained in the United Nations Millennium Declaration,

Recalling the recommendations of the Second International Conference on Improving Use of Medicines (Chiang Mai, Thailand, 2004);

Recalling also the findings of relevant WHO reports, including “Priority medicines for Europe and the world”1 and the Copenhagen Re-Recommendation from the European Union conference on “The Microbial Threat” (Copenhagen, 1999);

Aware that the spread of antimicrobial resistance recognizes no national boundaries and has reached proportions that require urgent action at national, regional and global levels, especially in view of the decreasing development of new antimicrobial agents;

Recalling previous resolutions WHA49.21 and WHA47.13 on the rational use of drugs, WHA51.17 on antimicrobial resistance, and WHA54.14 on global health security;

Recognizing the efforts of WHO in collaboration with governments, universities, the private sector and non-governmental organizations to combat antimicrobial resistance, thereby contributing to prevention of the spread of infectious diseases;

Noting that, despite some progress, the strategy for containment of antimicrobial resistance has not been widely implemented;

Wishing to sustain efforts to contain antimicrobial resistance and to promote rational use of antimicrobial agents by providers and consumers in order to improve global health security;

__________________________

1 Document WHO/HQ/99.222
2 Document WHO/CD/GUM/2001.2
Global strategies against antibiotic resistance
Disease treatments and medical procedures under serious threat

- Antibiotic Resistance
  - Blood infections
  - Surgical infections
  - Transplantations
  - Pneumonia
  - Cancer treatment
  - Typhoid fever
  - Care of preterm children
  - Safe child deliveries
  - Gonorrhea
  - Major surgical procedures
An independent international network to improve the management of antibiotic resistance

Vision

” A world free from fear of untreatable infections ”

www.reactgroup.org
ReAct: Main areas of action

• Increasing the visibility of antibiotic resistance in the global health dialogue

• Promoting evidence generation on the burden of antibiotic resistance

• Catalyzing action towards regional and national coordinated policies against antibiotic resistance

• Promoting needs-driven research and development for new antibiotics while securing their global access, affordability and rational use.
Political Opportunities

Social Mobilization

Evidence Generation
Network building

ReAct arranca sus actividades en Latinoamérica

El investigador sueco Otto Caro, coordinador global de ReAct (Acción Contra la Resistencia Bacteriana), ofreció ayer una conferencia en las que destacó la importancia de combatir la resistencia antibiótica. "Las actuales y futuras generaciones deben tener acceso a una prevención y un tratamiento efectivo contra las infecciones bacterianas, como parte de su derecho a la salud", destacó el investigador sueco.
Reframing the issue

Access to effective antibiotics

- Essential for any health system
- Health security
- Universal health coverage
- Sustainable development
- Ecology/environment/Onehealth
- Away from the war metaphor
Earlier today the World Economic Forum published their Global Risks 2013 report developed from an annual survey of over 1000 experts from industry and government.
Chief Medical Officer adds antibiotic resistance to national risk register

Posted on April 8, 2013 by chill

In 2003 there were only three confirmed laboratory reports of antibiotic-resistant bacteria. By 2012 this had increased to 800.

Antibiotic-resistant bacteria are bacteria that have mutated to become resistant to certain types of antibiotic medicines. This makes any infection caused by these bacteria more difficult to treat. Even if an infection has been treated effectively with an antibiotic in the past it may not be able to in the future.
Antibiotic resistance: A health systems failure

- Infection: Inadequate prevention leading to avoidable infections
- Resistance: Inappropriate use leading to premature development of resistance
- Innovation failure: Inadequate market incentives
- Clinical failure: No effective treatment for serious bacterial infections

Antibiotic resistance: A health systems failure
The consequences of antibiotic resistance reaches far beyond the health sector

Productivity
Labour supply
Household income
Government transfers
Tax revenues
Unemployment
Social services
Real GDP

R.D. Smith et al. / Journal of Health Economics
24 (2005) 1055–1075
Challenges in low-income countries

• High background mortality and morbidity of bacterial disease, competing challenges
• Many patients do not have access to effective antibiotics, but simultaneously in some areas there is uncontrolled excess use
• Poor sanitation and hygiene
• Increasing levels of resistance to first line drugs
• Second line drugs may be unaffordable
According to the United Nations, four products could greatly assist health workers in saving many newborn lives.

One of these products are:

injectable antibiotics (to treat newborn sepsis and pneumonia).

“Sepsis can kill quickly, but low-cost injectable antibiotics – such as procaine benzylpenicillin, gentamicin… can save lives if administered by a skilled health professional or a community health worker in some setting”s.
Some parts of the world have already run out of effective antibiotics

About 70% of neonatal systemic infections can not be treated with the antibiotics recommended by WHO….

Realigning incentives

Volume sales → Rational Use
Prescriptions → Controlled access
Dispensing → Rationing
Changing Policies to Meet the Challenge of Antibiotic Resistance in China

Yonghong Xiao, MD, PhD

State Key Laboratory for Diagnosis & Treatment of Infectious Diseases
The First Affiliated Hospital, School of Medicine
Zhejiang University
Major G(-) resistance bacteria
ASP Special Campaign from 2011

Initiation in May 2011 by vice-minister of China

Local healthcare authority promotion

Institute inspection

MOH promotion
Indicators for AMR campaign

– General hospitals:

• AB prescription in inpatients: <60%
• AB prescription in outpatients: <20%
• AB prescription in emergency patients: <40%
• AB utilization for inpatients: <40DDDs/100
• Microbiological examination rate for AB therapy: ≥ 50%/80%
Achievement of ASP campaign in 2011

Adopted from MOH China press report
Antibiotics Smart Use Program: Thailand’s experiences in promoting rational use of antibiotics

Present by Dr. Nithima Sumpradit$^{1,2}$
On behalf of the ASU partners and networks
1. Food and Drug Administration  2. International Health Policy Program
Interventions for prescribers

Interventions for patients – to reduce expectations on antibiotics
Don’t be surprised, if doctors, nurses, pharmacists and health professionals did not give you antibiotics.

97% of 1,200 patients with common cold-sore throat were recovered and felt better without taking antibiotics.
Pay-for-performance (P4P) on ASU practice

- 2009 – P4P for ASU is based on process evaluation for district hospitals
  - Score 1 – hospital policy on ASU …. 3 = training …. 5 = result dissemination

- 2012 – Output/outcome evaluation for all hospitals
  - Antibiotics prescribed for URI and acute diarrhea
    - Not more than 20% : Score = 5
    - 21 – 30% : Score = 3
    - 31- 40% : Score = 1
    - More than 40% : Score = 0
Patients’ health outcomes and satisfaction

Of 1,200 patients who did not receive antibiotics,
• almost all (97.1%) recovered and felt better within 7-10 days after the medical visits.

• 80-90% of patients felt satisfied and would return to this healthcare facilities for next medical visits.
The failing machinery....

More than 70 years of antibiotic use

Millions of tons....

- Resistance
- New antibiotics
- Over-consumtion
- Marketing
There have been numerous initiatives to promote action to stimulate R&D for novel antibacterial drugs in the EU.
In the US.....
Few Novel Classes of Antibiotics Discovered in Recent Decades

**Antibiotic Discovery Void:**
discovery dates of distinct classes of antibiotics. No new classes have been discovered since 1987.

Source: World Economic Forum, adapted from Silver
Drugs for bad bugs: confronting the challenges of antibacterial discovery
David J. Payne, Michael N. Gwynn, David J. Holmes & David L. Pompliano

The sequencing of the first complete bacterial genome in 1995 heralded a new era of hope for antibacterial drug discoverers, who now had the tools to search entire genomes for new antibacterial targets. Several companies, including GlaxoSmithKline, moved back into the antibacterials area and embraced a genomics-derived, target-based approach to screen for new classes of drugs with novel modes of action. Here, we share our experience of evaluating more than 300 genes and 70 high-throughput screening campaigns over a period of 7 years, and look at what we learned and how that has influenced GlaxoSmithKline's antibacterials strategy going forward.
Pipeline of ‘HTS to drug’ for antibacterials is not delivering

Number of milestones needed for 1 Launch (AB compared with industry average)

<table>
<thead>
<tr>
<th></th>
<th>HTS</th>
<th>Leads</th>
<th>Development Candidates</th>
<th>Ph1 starts</th>
<th>Ph2 starts</th>
<th>Phase 3 starts</th>
<th>Files</th>
<th>Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibacterials</td>
<td>2066</td>
<td>145</td>
<td>72</td>
<td>36</td>
<td>12</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Other areas</td>
<td>24</td>
<td>14.6</td>
<td>12.4</td>
<td>8.6</td>
<td>4.6</td>
<td>1.6</td>
<td>1.1</td>
<td>1</td>
</tr>
</tbody>
</table>

From David J Payne, GlaxoSmithKline, Collegeville, PA, USA with permission
Innovative Incentives for Effective Antibacterials

A conference during the Swedish Presidency of the EU 2009 focusing on the need to reinvigorate research and development of new antibiotics

Governments
Academia
Pharmaceutical and biotech industry
Civil society
Innovative Incentives for Effective Antibacterials

Council Conclusions on innovative incentives for effective antibiotics

2980th EMPLOYMENT, SOCIAL POLICY, HEALTH AND CONSUMER AFFAIRS Council meeting
Brussels, 1 December 2009

The Council adopted the following conclusions:

Note bene: In this document, the term "antibiotics" encompasses medicinal products produced either synthetically or naturally used to kill or inhibit the growth of bacteria as well as those with alternative mechanisms of action e.g., effect on bacterial virulence. In this context, alternative methods for prevention and control of infections should also be taken into account.

2. RECALLS the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine.
3. RECALLS the Council Conclusions on antimicrobial resistance of 10 June 2008.
4. RECALLS the Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections.

2 9837/08
Communication from the Commission to the European Parliament and the Council
Action plan against the rising threats from Antimicrobial Resistance

- Action n° 6: Promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antimicrobials to patients.

NewDrugs4BadBugs (ND4BB)
A summary diagram of the ND4BB programme is presented below.

ND4BB cross-topic collaboration and dissemination

**Topic 1: COMBACTE**
- Enabling Clinical Collaboration and refining clinical trial design
- Clinical Development of GSK1322322

**Subtopic 1C:** Clinical development of MEDI4893

**Topic 2: TRANSLOCATION**
- Research penetration and efflux Gram-negatives
- Data Hub & Learning from R&D experience

**Subtopic 3A:** Management and Resource Hub

**Subtopic 3B:** Hit-to-Lead and Lead-to-Candidate Portfolio

**Topic 3: Development of new drugs combatting Gram-negative infections**

**Topic 4: Driving reinvestment in R&D and Responsible use of Antibiotics**

**Topic 5: Clinical development of antibacterial agents for Gram-negative antibiotic resistant pathogens**

93 M€

16 M€

58.9 M€

6.3 M€

30.55 M€

All numbers are only IMI JU contribution (in-kind EFPIA contributions are in addition)
Reengineering R&D Value Chain
The 3Rs

Compound Library Access
Crossing the Valley of Death
Discovery
Pre-Clinical
Clinical
Development
Post-marketing
Microbiology
Medicinal Chemistry
Regulatory Approval
Rational Use

Towards a new business logic for R&D of novel antibiotics

• Needs driven - based on analysis of pipeline vs resistance and its burden

• Solving the scientific challenges

• Collaboration and knowledge sharing

• Incentives that stimulates R&D of priority antibiotics

• De-linking return of investment from sales

• Controlled use and distribution

• Equitable global access and affordability
R&D Pipelines 11/2013

Small molecules in clinical development Phase 1-3, NDA/MAA

Focus of activity

- Gram-pos. old
- Gram-pos. novel
- Staph. only
- Gram-neg. old
- Gram-neg. novel
- Pseud. only

Old: Analog of used antibacterial class
Novel: New antibacterial class

Submitted
Ph 3
Ph 2
Ph 1

Treatment options: The new kids on the block?

Thanks to Magnus Gottfredsson for the slide.
The implications of widespread resistant strains of gonorrhoea: Are we heading towards a postantibiotic era?

106 million new cases of gonorrhoea yearly—many of which are not treatable with available drugs
Framing Technology Options

- Decrease need for antibacterial use
  - Vaccines
- Improve the rational use of antibacterials
  - Diagnostics
- Accelerate the development of alternatives to antibiotics
  - Drugs
Time to effective treatment for sepsis is critical

Children with Acute Lower respiratory Infections in Africa, Asia, Latin America

404 Million antibiotic prescriptions could be avoided with a rapid test for bacterial infections

Selected Declarations on AMR/ABR

• Guadalajara Declaration (2001)
• Cuenca Declaration (2008)
• Jaipur Declaration (2011)
• New Delhi Call to Action (2011)
• Barcelona Declaration of WAAMRO (2012)
• Chennai Declaration (2012)
• U.S. Joint Statement from Health Organizations and CDC (2012)
• Statement of the Academies of Science (2013)
• G8 Science Ministers (2013)
• Paris Declaration of WAAAR (2013)
The Current Crisis
Who is responsible?

Antibiotic Resistance
Morbidity
Mortality
Costs

Drug Development
The evolving threat of antimicrobial resistance
Options for action
POLICY PACKAGE TO COMBAT ANTIMICROBIAL RESISTANCE

1. COMMIT TO A COMPREHENSIVE, FINANCED NATIONAL PLAN WITH ACCOUNTABILITY AND CIVIL SOCIETY ENGAGEMENT

2. STRENGTHEN SURVEILLANCE AND LABORATORY CAPACITY

3. ENSURE UNINTERRUPTED ACCESS TO ESSENTIAL MEDICINES OF ASSURED QUALITY

4. REGULATE AND PROMOTE RATIONAL USE OF MEDICINES, INCLUDING IN ANIMAL HUSBANDRY, AND ENSURE PROPER PATIENT CARE

5. ENHANCE INFECTION PREVENTION AND CONTROL (IPC)

6. FOSTER INNOVATIONS AND RESEARCH & DEVELOPMENT FOR NEW TOOLS
We need a strong governmental alliance that move this issue to a global (UN) antibiotic commission, panel or treaty on antibiotic resistance which should agree on a global code of conduct and collaborative actions in an antibiotic survival plan.
Health policy agenda
Partnership for global action
National governments

International org. and donors

Civil society org.
The inequitable and non-sustainable use of a scarce global resource
1. Support countries in developing national coordinated policies

including

- educational and regulatory interventions in the health care system for rational prescribing of antibiotics

- major changes in knowledge, understanding and perception of antibiotics to reduce demand
2. Minimize morbidity and mortality from bacterial infection through massive implementation of simple interventions to reduce spread of bacterial infections e.g. clean water, basic hygienic rules soap and alcoholic hand rub. Make access to effective antibiotics an issue for development aid like access to drugs for TB, malaria and HIV.
3. Develop a new business model and a global regulatory framework for antibiotic development with incentives that de-links return of investment from sales and where new antibiotics are made globally accessible and affordable and with ways to secure their controlled distribution and rational use.
“Prediction is very difficult, especially about the future”.

Niels Bohr
1885-1962
To the Congress in 1969:

The time has come to close the book on infectious diseases.....

William H. Stewart
Surgeon General 1965-69
Sir Frank Mac-Farlane Burnet, Director of the Walter and Eliza Hall Institute of Medical Research and co-winner of the Nobel Prize in Medicine in 1960 (along with Sir Peter Medawar) for the discovery of immunological tolerance.

“One can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of the infectious diseases a significant factor in social life”
Are we reaching the tipping point?

Falling back to a pre-antibiotic era?

Moving towards a sustainable collaboration to preserve effective treatment for bacterial infections?
Ljuset i tunneln....

The light in the tunnel......
Never Give Up, Faith moves Mountains!
Back up slides
New strains of superbug hit hospitals

im-seekers
nger protest
Is of Zimbabwean
seekers in detention
began a hunger strike
aim's decision to send
2k to face torture
bert Mugabe's regime.
age 3

cellar's call
Brown called on the
ight to end its
nits ambitions and
radical economic
needed to turn it from
sock into a global force.
age 2

Hospitals fear over superbug epidemic
Vulnerable patients in danger from
deadly bacteria running riot on wards

At 65, she's the world's
most beautiful woman
The incredible Sophia Loren • See Page 15

£10

travel to
europe
from only

only this dog knows
the truth about
Geri's ginger romance
exclusive interview • see page 3

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HOSPITALS FEAR OVER SUPERBUG EPIDEMIC

Vulnerable patients in danger from deadly bacteria running riot on wards

EXCLUSIVE BY ANTHONY DEVINS
AND RACHEL ELLIS

The spread of a deadly superbug in British hospitals is reaching epidemic proportions, a leading scientist warned yesterday.

Over the past nine years, there has been a 15-fold increase in the incidence of the bug known as MRSA, which is resistant to all but the most powerful antibiotics. In Scotland, Wales and the West Midlands, increases have been even more dramatic. Dr David Livermore, of the Public Health Laboratory Service, told The Express that the soaring number of cases was due to epidemic strains 13 and 15, particularly virulent forms of the bacteria which can be transmitted from patient to patient simply by touching one patient’s faeces.

Hospitals have been warned to step up infection control measures. Doctors and nurses are being reminded to wash their hands between patients, and GPs have been told to slash their prescribing of antibiotics, which only helps the bugs develop resistance. MRSA can be fatal, particularly to seriously ill and elderly patients, but there are no official figures on the number of deaths caused by the bug and it is rarely identified as the cause on death certificates.

Potentially fatal blood poisoning caused by MRSA has increased from less than three per cent before 1992 to 37 per cent so far in 1999, Dr Livermore said.

"What we are talking about is this hospital bacteria that can cause serious infection, sometimes fatal, deaths mostly in those who’ve got very severe underlying disease."

TURN TO PAGE 4, COLUMN 2

WEATHER 2 • OPINION 10 • LETTERS 39 • DIARY 41 • LIFE 43-48 • CROSSWORD 58 • TV 61-65 • CITY 72-75
Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study


Summary

Background Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo-β-lactamase 1 (NDM-1) are potentially a major global health problem. We investigated the prevalence of NDM-1, in multidrug-resistant Enterobacteriaceae in India, Pakistan, and the UK.

Methods Enterobacteriaceae isolates were studied from two major centres in India—Chennai (south India), Haryana (north India)—and those referred to the UK’s national reference laboratory. Antibiotic susceptibilities were assessed, and the presence of the carbapenem resistance gene \( \text{bla}_{\text{NDM-1}} \) was established by PCR. Isolates were typed by pulsed-field gel electrophoresis of XbaI-restricted genomic DNA. Plasmids were analysed by S1 nuclease digestion and PCR typing. Case data for UK patients were reviewed for evidence of travel and recent admission to hospitals in India or Pakistan.

Findings We identified 44 isolates with NDM-1 in Chennai, 26 in Haryana, 37 in the UK, and 73 in other sites in India and Pakistan. NDM-1 was mostly found among \( \text{Escherichia coli} \) (36) and \( \text{Klebsiella pneumoniae} \) (111), which were highly resistant to all antibiotics except to tigecycline and colistin. \( \text{K pneumoniae} \) isolates from Haryana were clonal but NDM-1 producers from the UK and Chennai were clonally diverse. Most isolates carried the NDM-1 gene on plasmids: those from UK and Chennai were readily transferable whereas those from Haryana were not conjugative. Many of the UK NDM-1 positive patients had travelled to India or Pakistan within the past year, or had links with these countries.

Interpretation The potential of NDM-1 to be a worldwide public health problem is great, and co-ordinated international surveillance is needed.
According to the United Nations, four products could greatly assist health workers in saving many newborn lives. The products are:

- **steroid injections for women in preterm labor** (to reduce deaths due to premature babies’ breathing problems);
- **resuscitation devices** (to save babies who do not breathe at birth);
- **chlorhexidine cord cleansing** (to prevent umbilical cord infections); and
- **injectable antibiotics** (to treat newborn sepsis and pneumonia).

“Sepsis can kill quickly, but low-cost injectable antibiotics – such as procaine benzylpenicillin, gentamicin... can save lives if administered by a skilled health professional or a community health worker in some setting”s.
Imagine this scene between doctor and patient. The doctor: “I’ve got good news and bad news”. “Gimme the good news, doc”. “I’ve found you a bed in a hospital”. “Great! What’s the bad news?” “It’s in the Hospitals for incurables.”
NHS TRUST
HOSPITAL FOR THE
TREATMENT OF INFECTIOUS
DISEASES CAUGHT IN
HOSPITALS
”We may look back at the antibiotic era as just a passing phase in the history of medicine, an era when a great natural resource was squandered, and the bugs proved smarter than the scientists”

Cannon G. 1995
Antibiotic Resistance
The interface between science, politics and people
MRSA kan dyka upp var som helst!
Antibiotic resistance costs lives, money and public confidence.
Figure 3.2. Consumption of antibacterials for systemic use (ATC group J01) at ATC group level 3 in the community, EU/EEA countries, 2010, expressed as DDD per 1 000 inhabitants and per day.

(a) Greece and Iceland provided total care data, i.e. including the hospital sector. On average, 90% of total care data correspond to consumption in the community.

(b) Spain provided reimbursement data, i.e. not including consumption of antibiotics obtained without a prescription and other non-reimbursed courses.
We need guidelines!

And they must be implemented!
1850

….mortality caused by soiled bed linen that was not changed between deliveries nor properly sterilized because the hospital outsourced the cleaning of linen to the cheapest contractor…..

End private cleaning in NHS call

Nurses have called for hospital cleaning to be brought back in-house to tackle hospital infections.

The Royal College of Nursing conference overwhelmingly voted for a motion proposing an end to contracting out cleaning to private firms.

Many hospitals use private cleaning.
The Royal College of Nursing conference overwhelmingly voted for a motion proposing an end to contracting out cleaning to private firms. Cleaning contracts have been outsourced since the 1980s and about 40% of hospitals now use the private sector. Nurses at the Bournemouth conference said it had led to a drop in standards and a rise in infections’
Γεωγραφικός διαχωρισμός αποικισμένων ασθενών σε ΘΑΛΑΜΟ - Cohorting
Squeezing the balloon: When science to policy did not work

The Effect of Changes in the Consumption of Macrolide Antibiotics on Erythromycin Resistance in Group A Streptococci in Finland
Macrolide consumption and resistance in Streptococci Group A in Finland

Seppälä et al. NEJM 337:441, 1997
Macrolide consumption and resistance in Streptococci Group A in Finland

- **Klaritromycin**
- **Azitromycin**
- **Roxitromycin**
- **Erytromycin**

**DDD/1000inh/d**

**% resistance**

- **Klaritromycin**
- **Azitromycin**
- **Roxitromycin**
- **Erytromycin**

**Resistance**

- 1990
- 1991
- 1992
- 1993
- 1994
- 1995
- 1996
- 1997
- 1998
- 1999
- 2000
- 2001
Reversibility of trimethoprim resistance in E coli following a drastic 2-year reduction in trimethoprim use

Trimethoprim and trimethoprim-sulfamethoxazole use
(prescriptions /1000 inh), 2000-2006

Kronoberg
Sweden

(Resistance defined as nonsusceptibles using epidemiological cut-offs)
Access vs. Excess

• Fewer than a third of children with suspected pneumonia received antibiotics.
• Fewer than four in ten children receive appropriate treatment with oral rehydration therapy and continued feeding.
AMR Strategies in Thailand

AMR Containment Package, 2013 - 2016

- Implementation of AMR Containment Bundle
- Fundamental Systems Development such as
  - Legislation of banning over-the-counter sale of selected ATB and non-therapeutic use of ATB in animals
  - Develop laboratory and IT systems for surveillance of AMR and antibiotic use
  - Develop manuals/media for infection control and rational use of antibiotics for responsible human & animal health personnel, patients and public
  - Raise awareness and campaign on AMR
  - Incorporate AMR & RUD in health and non-health educational curriculum
  - Propose AMR containment & RUD as major criteria for hospital accreditation, pay-for-performance and quality of care audit
Initiative during the Swedish Presidency of the EU 2009

Establishment of a transatlantic taskforce on urgent antimicrobial resistance issues
Agreed at the EU-US Summit on the 3rd of November. The task force is to focus on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs.
Collaboration for Innovation
The Urgent Need for New Antibiotics

ReAct policy seminar, Brussels, 23 May 2011
Inadequate Antibiotic Treatment of Infections
A Risk Factor for Hospital Mortality Among Critically Ill Patients

Prospective study on 655 patient with infections in intensive care

- Inadequate antimicrobial therapy: 22.5% of patients
  - Mortality 42%

- Adequate antimicrobial therapy
  - Mortality 17.7%

From Kollef et al. Chest, 2000