Antimicrobial resistance – the silent epidemic

Global challenges needs global solutions

John-Arne Røttingen

Nordic Summit for Deans of Medical Faculties and Hospital Directors

Bergen
May 5, 2015
Historical Ebola outbreaks 1976-2014

- Died
- Survived

(Bar chart showing the number of deaths and survivors in each year from 1976 to 2014.)
Ebola cases (per week)
Guinea, Sierra Leone, Liberia, and Nigeria (per 28/9/2014)

Number of cases

UN security council
WHO declares PHEIC
Guinea report to WHO

Country
Guinea
Liberia
Sierra Leone

Jan 05 Jan 12 Jan 19 Jan 26 Jan 02 Feb 09 Feb 16 Feb 23 Mar 02 Mar 09 Mar 16 Mar 23 Mar 30 Apr 06 Apr 13 Apr 20 Apr 27 May 04 May 11 May 18 Jun 01 Jun 08 Jun 15 Jun 22 Jun 29 Jul 06 Jul 13 Jul 20 Jul 27 Aug 03 Aug 10 Aug 17 Aug 24 Sep 07 Sep 14 Sep 21 Sep 28
PUBLIC INTEREST VS. EBOLA CASES

No. of New Cases

Google search traffic*

Sources: Google Trends / The New England Journal of Medicine

*Reflecting how many searches have been done for a particular term, relative to the total number of searches done on Google over time. Data is normalized and presented on a scale from 0-100.
RESISTANCE
Global Burden of Disease

Global, DALYs
Both sexes, All ages, 2010

DALY 2010

Annual % change 2005 to 2010 DALYs/100,000
Norway’s BOD
Maternal and child health

Modern medicine

Basic health care
Impact of AMR

• The clinical burden of disease
  Every year in the US, at least 2 million people acquire infections with antibiotics resistant bacteria

• The economic burden of disease
  In the US, antibiotic resistant infections account for USD 20 billion in direct healthcare costs, and USD 35 billion when including societal costs

Costs of resistance

Figure 2 Cost ratio of alternative drugs to first-line antimicrobials for common acute infections

Source: WHO Policy Perspectives 2005
Estimates of burden of ABR

European Union
population 500m

25,000 deaths per year
2.5m extra hospital days

Overall societal costs
(€ 900 million, hosp. days)
Approx. €1.5 billion per year

Source: ECDC 2007

Global information is insufficient to show complete disease burden impact and costs

Source: WHO Global Report on Surveillance 2014
Deaths attributable to AMR every year compared to other major causes of death

AMR in 2050
10 million

- Tetanus
  60,000

- Cancer
  8.2 million

- Road traffic accidents
  1.2 million

- Measles
  130,000

- Cholera
  100,000–120,000

- Diarrhoeal disease
  1.4 million

- Diabetes
  1.5 million

Amri: The Review on Antimicrobial Resistance
Tackling a crisis for the health and wealth of nations

Chaired by Jim O’Neill
December 2016
Total GDP loss
$100.2 trillion
AMR – A Global Collective Problem

Movement of two strains of Carbapenem-resistant *Klebsiella pneumoniae*
2000 - 2008

**KPC**
- **2000**: First found in North Carolina
- **2003**: Isolates spread rapidly through New York
- **2005**: Found to be widespread throughout Israel
- **After 2005**: Spreads to Italy, Colombia and Sweden

**NDM**
- **Before 2008**: Resistance first identified in India
- **2009**: Discovered in Sweden
- **2010**: Discovered in the UK
- **2010**: Discovered in Canada

1 New-Delhi Metallobetalactamase

SOURCE: Nature 13th July 2013
The report is the most comprehensive picture to date, with data provided by 114 countries.

Looking at 7 common bacteria that cause serious diseases from bloodstream infections to gonorrhoea.

High levels of resistance found in all regions of the world.

Significant gaps exist in tracking of antibiotic resistance.
Quinolone resistant *Neisseria gonorrhoeae* – GASP 2012
Proportion of 3rd generation cephalosporins (R+I) resistant *Escherichia coli* isolates in participating countries in 2012

ECDC, EARS-Net
ESBL prevalence in gut microbiome

Nasjonal strategi for forebygging av infeksjoner i helsetjenesten og antibiotikaresistens (2008–2012)

The evolving threat of antimicrobial resistance
Options for action

Chief Medical Officer Dame Sally Davies: Resistance to antibiotics risks health 'catastrophe' to rank with terrorism and climate change

The bacterial challenge: time to react
A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents
Correlation between penicillin use and prevalence of penicillin non-susceptible *S pneumoniae*

AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK, England only

Norway Total use 16.9 DDD (no 11) a very high use of methenamine (a urine antiseptic), almost 20% of total antibiotic use. Excluding methenamine: 13.6 DDD (no 6).
Quinolone use
2012
ESAC report,
ECDC Stockholm
2014
Tetracycline use
2012
ESAC report,
ECDC Stockholm
2014
Figur 3. Gjennomsnittsbruk over siste 5 år av alle antibiotika i ATC gruppe J01 (systemiske antibakterielle midler) utenom metenamin i alle fylker. Antall resepter/1000 innbygger/år (røde kolonner) og DDD/1000 innbygger/år (blå linje).
Figure 1. Amounts, in mg, of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data. **The substances included vary from country to country.


Norge 20 mg/kg biomasse
Danmark 50 mg/kg biomasse (2,5 x mer)
Holland 180 mg/kg biomasse (9 x mer)
Aktuelle tiltak
FoU & innovasjon
Overvåkning
Fornuftig bruk
Oppmerksomhet & forebygging
Antibiotikaretningslinjer
Raskere diagnostikk
Regulering (salg, forskrivning)
Ikke bruk som vekstfremmer
Begrenset 'flokk'-behandling

From Gunnar Skov Simonsen
Children with suspected pneumonia receiving antibiotics

Share of children under age 5 with suspected pneumonia receiving antibiotics, by region, 2006–2011 (per cent)

- South Asia: 18
- Sub-Saharan Africa: 30
- East Asia and Pacific: 50
- Middle East and North Africa: 62

Lack of access to effective antibiotics

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

Orphanage in Bamako, Mali
**ESBL colonized 100% of the children and 63%, of the adult staff studied.**


Mumhibili hospital, Tanzania
**Tanzania**

**The paediatric mortality rate from Gram-negative infections were more than 40%.** Antibiotic resistance were a significant risk factor for a fatal outcome

*Blomberg et al. BMC Infect Dis. 2007 May 22;7:43.*
A «bath tub problem»
A «bath tub problem»
AB development - the status quo

- Lack of incentives for pharma cause companies to close down their AB R&D departments
- Reasons for the antibiotic market failure:
  - **Science:** AB R&D have become more complex and resource intensive
  - **Economics:** ABs have poor return on investments relative to other classes of drugs (e.g. drugs for chronic diseases)
  - **Regulations:** Pre/post market regulations deter AB development
- Only three of top 50 pharma companies develop ABs

The traditional pharmaceutical commercial model

David J. Payne et al. Phil. Trans. R. Soc. B
2015;370:20140086

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Application of traditional commercial model to antibacterials

(b)

limited opportunity for re-investment into AB R&D

increasing investment
decreasing return

— decreasing peak sales (price x volume)
— decreasing speed of product uptake
— decreasing duration of life cycle

— increasing investment cost
— increasing development time

David J. Payne et al. Phil. Trans. R. Soc. B
2015;370:20140086
Commercial model does not incentivize future potential unmet needs

David J. Payne et al. Phil. Trans. R. Soc. B
2015;370:20140086
Principles of a de-linked model

(d)

- ‘series of payments’
- ‘lump sum’

- no marketing
- provide agreed no. doses/year or stockpile

David J. Payne et al. Phil. Trans. R. Soc. B
2015;370:20140086
Recent proposals

• Könberg report (Nordic countries, 2014)
  – Nordic countries to take the lead in an international initiative
  – Total 5 year investments around 75 mSEK or 0.005 % of annual global GDP

• O’Neil review (UK, in progress)
  – Global innovation fund
  – Total investments of 0.003% of annual global GDP, i.e. around $25 billion over 10 years

• Leaders of global health funding and research organizations (PloS Med, next week)
  – A global biomedical R&D mechanism for public health emergencies
  – $10 billion annually for infectious disease threats - AMR, emerging infections (incl Ebola), poverty related/neglected diseases
Access for the millions of people without antimicrobials

Conservation of effectiveness of existing drugs

Innovation towards creating new antimicrobials

Hoffman et al. (2015)
Worldwide country situation analysis
WHO - 2015

• Few countries reported having a national plan
• Lack of laboratories with sufficient competent technical staff, weak infrastructure, poor data management and lack of standards are impediments to effective laboratory surveillance
• Counterfeit medicines have been reported to be a problem in many regions
Policy framework for Sustainable Access to Effective Antimicrobials

One Health

Surveillance and Monitoring

Infection prevention

Universal Access

Innovation and R&D (Knowledge Base)

Human Health

Animal Health

need

demand

supply

Responsible use
The Global Health System – Four functions

- Global Public Goods (GPGs)
- Solidarity/Assistance
- Managing Externalities

Leadership/stewardship
AMR - Interconnectedness

Global Public Goods (GPGs)

Innovation of Antimicrobials

Solidarity/Assistance

Universal Access to Antimicrobials

Managing Externalities

Conservation of Antimicrobials
Global policy options – in WHO Global Action Plan

Global Public Goods (GPGs)

Guidelines, Standards and Norms

Solidarity/Assistance

Technical support

Surveillance and Response System

Managing Externalities
Global policy options – still on the drawing board

Global Public Goods (GPGs)

- Partnership based innovation models
- Capacity building and Access
- Managed markets and utilization
- Managing Externalities
- Solidarity/Assistance

Norwegian Institute of Public Health
Five levels of international collaboration

Position in Hierarchy

V. Collective action

IV. Collaborative decisions

III. Coordination

II. Communication

I. Common norms, principles and goals

Description

To what extent does the policy require binding multi-national decisions i.e. through joint institutional arrangements or pooled financing

To what extent does the policy require multi-national collaborative decision-making through i.e. joint strategies

To what extent does the policy require coordination of individual country decision-making

To what extent does the policy require sharing of information and data to be effective

To what extent does the policy require common norms, principles and goals shared and agreed across organisations and governments
International Collaboration on AMR

1. Common norms, principles and goals
2. Communication and information sharing
3. Coordination
4. Collaborative decision making
5. Collective action

WHO
JPI-AMR
GAVI Global Fund
UNITAID

IMI-ND4BB (BARDA)
WHO Global Action Plan

*Half-full or half-empty?*
What is needed – for a full glass?

• Financial and technical assistance
• International or harmonized standards and regulations
  – Licensing, sales, trade, marketing
• Professional leadership – technical agency
• Pooled funding (or strongly aligned)
  – Innovation
  – Capacity building for National plans
• Monitoring and accountability
What is needed – *for a full glass*?

- **Instruments**
  - International law
  - Institutional arrangements
  - Political initiative

- **How?**
Access  Innovation
Sustainable  effectiveness
Conservation
Thanks!

Contributions from
Martin Steinbakk, Jørgen Bjørnholt, Gunnar Skov Simonsen, Steven Hoffman and Otto Cars