A GLOBAL PROGRAM FOR THE PRESERVATION OF ANTIBIOTICS

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Intensive Care Specialist
Past President of the French CTIN
(National Committee for Prevention of Nosocomial Infections)
Consultant for WHO
Global program for the preservation of a real treasure: antibiotics

- Hygiene and infection control: key element
- Antibiotic stewardship and control
- Use of diagnostic tests, and new tests to come
- Education programs (Kids +++ E Bug)
- Information programs (TV, radio, web...)
- Research programs. Public-private cooperation
- Development of new AB (protected)
- Change in the rules for development of new AB, with incitative measures for industry, and more simple registration
- Upgrade in vaccination programs
- Surveillance of resistance, and alerts
- Surveillance of consumption
• Efficacy of most programs against MRSA (France, Belgium, Denmark, UK, USA...)
• Efficacy of some national campaigns aimed at reducing antibiotic consumption (France, Belgium, Scotland, South Korea, Japan..)
• Efficacy against carbapenemases (Israel, Poland)
• Strong international « reaction » to resistance (ECDC, IDSA, TATFAR, Biomerieux...).
  International cooperation still rather weak +++++
• Lobbying groups: Wamroo, React, AB action, APUA ....Research EU programs (Mosar...)

THERE ARE SOME VERY GOOD NEWS
- Prevention of cross-transmission (Hands)
- Screening of pts suspect to be carriers
- Cohorting for VRE, Carbapenemases....
- Education of consumers. KIDS ++ E-Bug
- Treatment of hospitals effluents, and epuration stations
- Surveillance of the water used for animals, and agriculture
- Surveillance of drinking water (India)

Hygiene and infection control: key for the success of any program
MRSA bacteremia in Europe, 2008

Legend:
- No Data
- < 1%
- 1 - 5%
- 5 - 10%
- 10 - 25%
- 25 - 50%
- > 50%

Courtesy: Grundmann et al. (EARSS, Sept 2009) and Harbarth for Sarkoleon
Evolution of MRSA prevalence. EARSS-net data ECDC
Counts of MRSA bacteraemia
Oct 2005 to June 2009

Target to halve MRSA cases is met

BBC World news

Courtesy: A. Pearson and colleagues (HPA, Sept 2009)
Taux annuels SARM acquis pour 100 patients admis plus de 24 heures : portage sur tout site et bactériémies  St Joseph hospital

<table>
<thead>
<tr>
<th>Année</th>
<th>SARM acquis tout site/100 admis</th>
<th>Bactériémies à SARM acquises/100 admis</th>
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<tr>
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<td>2004</td>
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Consommation de SHA année 2008

Taux de SARM acquis (novembre 2008)
Before march 2007: 1275 cases in 27 hospitals (175/Million inhabitants)
Mortality before: 55.5 % per 100,000 patients days
Intervention led to a sharp decrease in the Nb of cases (11.7/100,000 Pts days)
Correlation between the number of cases and compliance to the guidelines (P:.02)
SUPERB WORK, excellent news
One hospital’s experience – moving from single room contact to cohorting and dedicated staff

Incidence of KPC-producing *Klebsiella* spp.

P=0.01

Schechner V, unpublished
Looks more easy

Screening, isolation, destruction of the bug in the gut, use of probiotics, or E. coli

....but ESBL outbreak will induce a dramatic increase in carbapenem usage, and the incidence of carbapenemases will uncrease quickly

A global program against both MRSA, VRE, ESBL and carbapenemases is mandatory, but it is a lot of energy

Focusing on carbapenemases ????
QUINOLONES
MRSA per 1000 patient-days
- Efficacious if customized for each hospital
- More difficult in the community, and in LTCF
- Antibiotic referent in each hospital; with precise responsibilities and decision power, and time devoted to this task
- Networks between the university hospitals and small hospitals and the community
Antibiotic stewardship. Rules for antibiotic prescription

- Antibiotics reserved to specialists (IV quinolones, carbapenems, pip/taz, cefta)
- Indication for therapy mentioned in the prescription sheets, and in the dossier, as well as length of therapy
- Systematic re-evaluation at day 2
- Exact quantity delivered by pharmacists
- Use of AB as a quality indicator country wide (ICATB in France)
- Audits
3 notions clés pour bien utiliser les antibiotiques

1. Uniquement pour combattre les infections bactériennes
2. Seulement sur prescription du médecin
3. À condition de suivre l'ordonnance à la lettre

Rhinopharyngites, angines, bronchites : aider son corps à se défendre, ça s'apprend

Parlez-en avec votre médecin

www.antibiotiques.net
ABT prescriptions from 2001-02 to 2006-07 (Oct-March periods) Guillemot et al PLOS medicine 2009
French Campaigns 2002-2007
Outpatient antibiotic use in France in prescriptions per inhabitant – October to March

Sabuncu et al., PLoS Medicine; June 2009
Belgian Campaigns 2002-2010
Outpatient antibiotic use in Belgium in packages per 1,000 inhabitants per day – July – June

-34%

Other J01 classes
Sulfonamides and trimethoprim (J01E)
Quinolones (J01M)
Macrolides, lincosamides and streptogramins (J01F)
Tetracyclines (J01A)
Cephalosporins and other beta-lactams (J01D)
Penicillins (J01C)
National compliance 93% and 7/14 NHS boards achieved target
DG Research funded projects

- ARPAC
- ArMED
- PAR
- GRACE
- MOSAR
- CHAMP
- InTopSens
- TheraEDGE
- TEMPOtest

- SATURN
- HAPPY AUDIT
- R-GNOSIS
- EvoTAR
- ...
- ...
- ...
BAD NEWS, Unfortunately

- Negative experiences
- ESBL increases, in humans, animals, water, soil !!!
- New mechanisms of resistance (NDM-1)
- Extremely high levels of resistance in several countries, very close to us !!
- Asia, Africa ??

- NO new antibiotic active against Gram negatives in the pipe (anti ESBL ?)
- Poor investment of the industry
- No money
- Diagnostic tests poorly used
- Education poorly effective. 53% of consumers: AB work on viruses
• **Strepto test** poorly used in France. It is a real shame!
• **Urinary sticks**, in particular in LTCF
• **Biomarkers**: CRP, PCT, many other to come
• Real time PCR for MRSA, and viruses
• Toxins (C Difficile...)
• New tests more than welcome (start up)
Total outpatient antibiotic use (J01), 32 countries, ESAC network 2009

Cyprus, Lithuania: total use, including the hospital sector.
** Spain: reimbursement data, does not include over-the-counter sales without prescription.
Criticised for not taking into account:

- Differences in dosing between the various substances
- All animals species at risk of being treated (e.g. horses, sheep and goat)
- Biomass animals transported to other countries for fattening or slaughter

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Pre ESVAC data. Published sales data retrieved from national reports for 2007 (Germany 2005) and normalized for biomass at risk.

*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.

Figure 2: The number of new systemic antibiotic agents has declined since 1980, and most (75%) of these drugs are in two classes, beta-lactams and quinolones.
• Negative trials in England or the US
• Recent increase in consumption in France
• RCT in primary medicine Butler BMJ 2012
  34 practices vs 34 controls
  139 clinicians vs 124 controls
• STAR program: practice based seminar, analysis of practices, outline education, practising consulting skills
• Reduction in AB consumption: 4% !
• Reduction in cost: 830 pounds per practice

Negative or poorly positive trials
E coli with ESBL increases everywhere
## Current Status of Antimicrobial Resistance in Asia

### ESBL-producing *E. coli*

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Klebsiella pneumoniae resistant to carbapenems. EARS-net ECDC 2010
Trends in proportion of imipenem-resistant *Klebsiella pneumoniae* isolates in hospitals in Greece, 2000-2006

Vatopoulous A. Eurosurgeryilliance 2008
Eurobact study Tabah A, Timsit JF
20 most frequent pathogens during bacteremia

- Acinetobacter baumannii: 157
- Staphylococcus coagulase-neg: 143
- Klebsiella pneumoniae: 130
- Pseudomonas: 127
- Staphylococcus aureus: 105
- Escherichia coli: 92
- Enterococcus faecium: 68
- Enterococcus faecalis: 60
- Candida albicans: 51
- Enterobacter cloacae: 41
- Candida non albicans: 37
- Staphylococcus sp: 30
- Burkholderia cepacia: 25
- Serratia marcescens: 24
- Streptococcus sp: 22
- Enterobacter aerogenes: 20
- Proteus mirabilis: 17
- Enterobacter sp: 12
- Bacteroides fragilis: 11
- Klebsiella oxytocca: 9
- Enterococcus sp: 8
Rate of incidence (/1,000DHs) of different species of ESBL enterobacteria
38 Univ. hospitals of Paris area 1996-2008

Vincent Jarlier Sept 2009
Assistance publique Paris. Incidence of MRSA (pink) and ESBL (green)
Success with MRSA.....failure with ESBLs....WHY ??

- Low inoculum for MRSA high with ESBL
- Skin, nose for MRSA, GUT for ESBL
- Selection in the gut for ESBL with antibiotics. GUT is the epicenter for R
- Transmission in the community (6% of healthy carriers, MH Nicolas-Chanoine ICAAC 2011)
- ESBLs in food animals. 90% of the sampled chicken Overdevest EID 2011
- ESBLs in water, used and drinking (India)
- Created on April 7th, 2011 (Lancet Paper)
- International (initially French)
- 345 participants
- Supported by 50 societies/professional bodies
- Multi-professional (MDs, veterinarians, pharmacists, environment specialists)
- Multi-disciplinary
- Active participation of consumers (Lien, Ciss, Patients for Patient Safety WHO)

World Alliance Against Multiple-Drug-Resistant Organisms (WAAMDRO)
The main objective is the ACTIVE PROTECTION of antibiotics

The bacterial world must be respected (peace with microbes SB Levy)

Antibiotics: « special » drugs, with specific modalities of prescription

Different ABs in humans and animals

ABs must belong to the UNESCO mondial patrimony
OBJECTIVES

- Develop antibiotic stewardship programs worldwide
- Access to Abs to developing countries
- Upgrade infection control (HRAS)
- Develop rapid diagnostic testing.
- DO NOT treat non-bacterial infections
- Vaccination programs
- Accelerate the development of new compounds
- Anti-virulence agents, non AB agents
- Participation to meetings (French parliament, academy of medicine)
- Papers, citations
- The Barcelona and Porto declaration
- Involvement of consumers (Le LIEN, garance Upham)
- International action, in cooperation with React, Antibiotic action, APUA...
- Studies and RCTs scheduled later
- You are more than welcome to join us
The EU-US Summit Declaration called for the establishment of “…a transatlantic task force on urgent antimicrobial resistance issues focused 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, which could be better addressed by intensified cooperation between us”.
Plus les Français consomment d'antibiotiques, plus les virus résistent.
• An electro-choc is needed to convince people that ABR will be the main pandemia in the next decade
• Some actions worked in several countries. Use the success stories
• A global (many different actions) and worldwide program is mandatory
• Both infection control and antibiotic stewardship. **Antibiotics are special drugs, we need special rules for them**
• Education is key. Kids will save us
P. aeruginosa: ICU St Joseph hospital

Résistance to Ciprofloxacine
P. aeruginosa : ICU St Joseph
Résistance to Amikacine
St JOSEPH  
E. coli : Résistance (I+R)

%  

Années

Ampicilline
Amox / Clav
Pip / Tazo
Cefotaxime
Gentamicine
Ac. Nalidixique
Ciprofloxacine
TMP
Sulfamide


%  

Années
Antibiotic use: specific classes

- Quinolones
- 3rdG Cephalosporins
- Glycopeptides

Year

DDD/1,000 patient-days

1999 2000 2001 2002 2003 2004 2005

Quinolones: decreasing trend, p = 0.01
3rdG Cephalosporins: decreasing trend, p < 0.03
Glycopeptides: no significant trend, NS.
Belgian National Public Campaigns

- **When:** since November 2000, annually during winter season
- **Organised by:** BAPCOC (Belgian Antibiotic Policy Coordination Committee)
- **Budget:**
  - 400,000 EUR/annual campaign
- **Interventions targeting the public:**
  - Ads on TV, radio and newspaper
  - Information booklets
  - Folders
  - Posters
  - Internet campaigns: www.antibiotics-info.be
National compliance 83% and 4/14 NHS boards achieved target 2011 - need to focus on improvement
Why is Europe (partially) successful?

- Bottom up Member States initiatives (e.g. rotating European presidencies) resulting in top down political support and commitment at European level (e.g. surveillance programme);
- Strong leadership with close link between opinion leaders, policy makers and politicians;
- European antibiotic awareness day, built on success stories of countries;
- Support of AMR research projects by EC, providing evidence for public health interventions.
Community-onset bacteremia due to ESBL E coli. Rodriguez-Bano CID 2010

- 95 cases of E coli with ESBL (7.3%)
- From Oct 2004 to Jan 2006
- 87% were CTX-M
- Risk factors: contact with healthcare, urinary cath, previous AB
- Inappropriate AB correlated with ESBL, and with mortality
Klebsiella pneumoniae resistant to carbapenems. EARS-net ECDC 2010
Pseudomonas aeruginosa resistant to carbapenems. EARSS-net  ECDC 2010
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</table>
Distribution of MRSA by Country
2004-6, CA-MRSA and HA-MRSA, Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of isolates (CA-SA, HA-SA)</th>
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<tbody>
<tr>
<td>Sri Lanka</td>
<td>(49/377)</td>
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<tr>
<td>Taiwan</td>
<td>(270/574)</td>
</tr>
<tr>
<td>The Philippines</td>
<td>(93/97)</td>
</tr>
<tr>
<td>VietNam</td>
<td>(654/147)</td>
</tr>
<tr>
<td>Korea</td>
<td>(147/705)</td>
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<td>Hong Kong</td>
<td>(82/345)</td>
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<tr>
<td>India</td>
<td>(46/93)</td>
</tr>
<tr>
<td>Thailand</td>
<td>(122/316)</td>
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Current Status of Antimicrobial Resistance in Asia

ESBL+ K. pneumoniae

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Legend:
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## Current Status of Antimicrobial Resistance in Asia

### Carbapenem R Enterobacteriaceae

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*Indonesia, <1%*
Current Status of Antimicrobial Resistance in Asia

MDR P. aeruginosa

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**Current Status of Antimicrobial Resistance in Asia**

**MDR A. baumannii**

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1st APEC Expert Forum
Can we stop ESBL outbreak?

- ESBL is now endemic: difficult task
- Infection control in hospitals: standard precautions (Star ICU)
- Screening of at risk patients: difficult
- Hygiene in the community: change some habits to prevent fecal transmission: kids
- Treat hospital and animal farms effluents to kill MDRO, and to neutralize antibiotics
- Stop treating animals with AB as growth factors
- Decrease AB usage in therapy, and prophylaxis of animals
Containement of a country-wide outbreak of carbapenem-resistant *K. pneumoniae*  
Schwaber CID 2011

- 2007 national program by ministry health
- Guidelines, with detection of carriers (screening), and dedicated staffing
- Ressources for an extensive audit of IC practices
- Feed back to hospital directors
- Duration: One year
- Outcome: nosocomial cases of CRE
Organized by Biomerrieux
2 days meeting of 70 international experts
Very active meeting, an disposal of 33 posters from 33 countries
Questionnaire on the prevalaged actions for reducing resistance
Publication: Special issue of Antimicrobial resistance and Infection control February 2012

Ready for a world without antibiotics ?? The Pensières antibiotic resistance call to action
- Reserve the most important classes of antibiotics for humans 66%
- Stop over-the-counter sales of AB 51%
- Make the proposal to WHO to develop a chart to be signed by all ministries of health worldwide (including access to Ab, Infection control, and vaccines) 51%
- Change the reimbursement system, rewarding the appropriate usage of Ab, for HCP and pharma companies 36%

**Actions directed toward Health authorities**
Establish standardized, timely, universal surveillance of Ab resistance and consumption 82% of the 70 participants

Educate on AB stewardship and AB resistance, using modern tools 75%

Develop culturally sensitive awareness campaigns for HCP 49%

Provide public with indicators of HAI 36%

Avoid usage of quinolones 15% only

Message to the Health care community
Messages to the general public

- Develop culturally sensitive awareness campaigns targeted to general pub: 75%
- Develop sanitation and hygiene education: 72%
- Include consumers among stakeholders for AB resistance control, including the food chain: 51%
- Balance cost and benefit of antibiotic free food: 15...only
• Develop bedside and rapid testing to better guide AB treatment decisions 63%
• Banish the use of antibiotics as growth promoters in animal food 60%
• Develop new antibiotics 57%
• Develop alternatives to antibiotics 46%

Messages to the industry (pharma, food, diagnostics farming/bio-industry)