Biocides – an alternative to antibiotics or an emerging threat to public health and our environment?

Åsa Melhus
Dept. of Clinical Microbiology
Uppsala University Hospital
Sweden

Antimicrobial substances
Definitions

- Biocide: an active chemical molecule to control the growth of or kill bacteria in a biocidal product
- Antibiotic: an active substance of synthetic or natural origin which is used to eradicate bacterial infections in humans or animals

Antibiotics contra biocides

- Antibiotics: the toxic effect is selective, i.e. directed against microorganisms
- Biocides: not selective, toxic to all living organisms – can damage humans, animals, environment

Biocides

- The number/volume of biocides in use is high
- In contrast to antibiotics, not regularly monitored and no demands to document the effects on the environment
- The market for biocides amounted to 10-11 billion euros 2006
- A growth of 4-5% per annum for the previous 15 years

Problem

- Antibiotic resistance has increased worldwide leading to treatment failures in human and animal infections
- There are convincing evidence that antibiotics and biocides share resistance mechanisms developed by bacteria
- **Possible consequence: selection and dissemination of antibiotic resistant bacteria by biocide use**

Types of biocides

- **Disinfectants, antiseptics**
- Conservatives
- Pesticides
- Miscellaneous

Biocides in health care

- The cornerstone of any effective program of prevention and control of health care associated infections

Silver

- Toxic heavy metal with no physiological function
- Used for centuries, disappeared with the introduction of antibiotics
- Reintroduced in the 1960s at burn centers – increased the survival of extensively burnt patients
- 3 forms:
  - metal (close to non-toxic, long-lived)
  - ion (toxic, short-lived)
  - nanoparticle (toxic, long-lived)
    - Can pass through all barriers in the body, including the blood-brain barrier
    - Is easily incorparated into various materials

Silver activity

- Silver ions in contact with water lead to formation of toxic free radicals and oxidative cell damage (cell membranes, DNA)
  - Especially toxic to water-living organisms
  - Carcinogenic
- In sewage treatment works, bacteria purify the water
- By washing clothes with silver, the silver content in sewage has increased in Sweden

Silver – a rising biocidal ”star”

- Introduction of silver-based wound dressings in 2000
- Rapid development of silver products thereafter.
- Nanosilver can be found in almost any type of product – even when its biocidal effects are not needed, ”just in case”
- Nanosilver is today the most commercialized nanoparticle of all

Silver-based dressings started it all – how well do they function in vivo?

- Study at Uppsala University Hospital between november 2006 and september 2007
- 14 patients with chronic leg ulcers:
  - Group 1 (n = 7): Aquacel Ag® (ionized silver, ConvaTec) for 3-5 weeks. Change of dressings 3 times/week. Cultures before and after the silver treatment
  - Group 2 (n = 7): Aquacel Ag®/Acticoat® (nanosilver, Smith&Nephew) for at least 2 months. Culture after the silver treatment

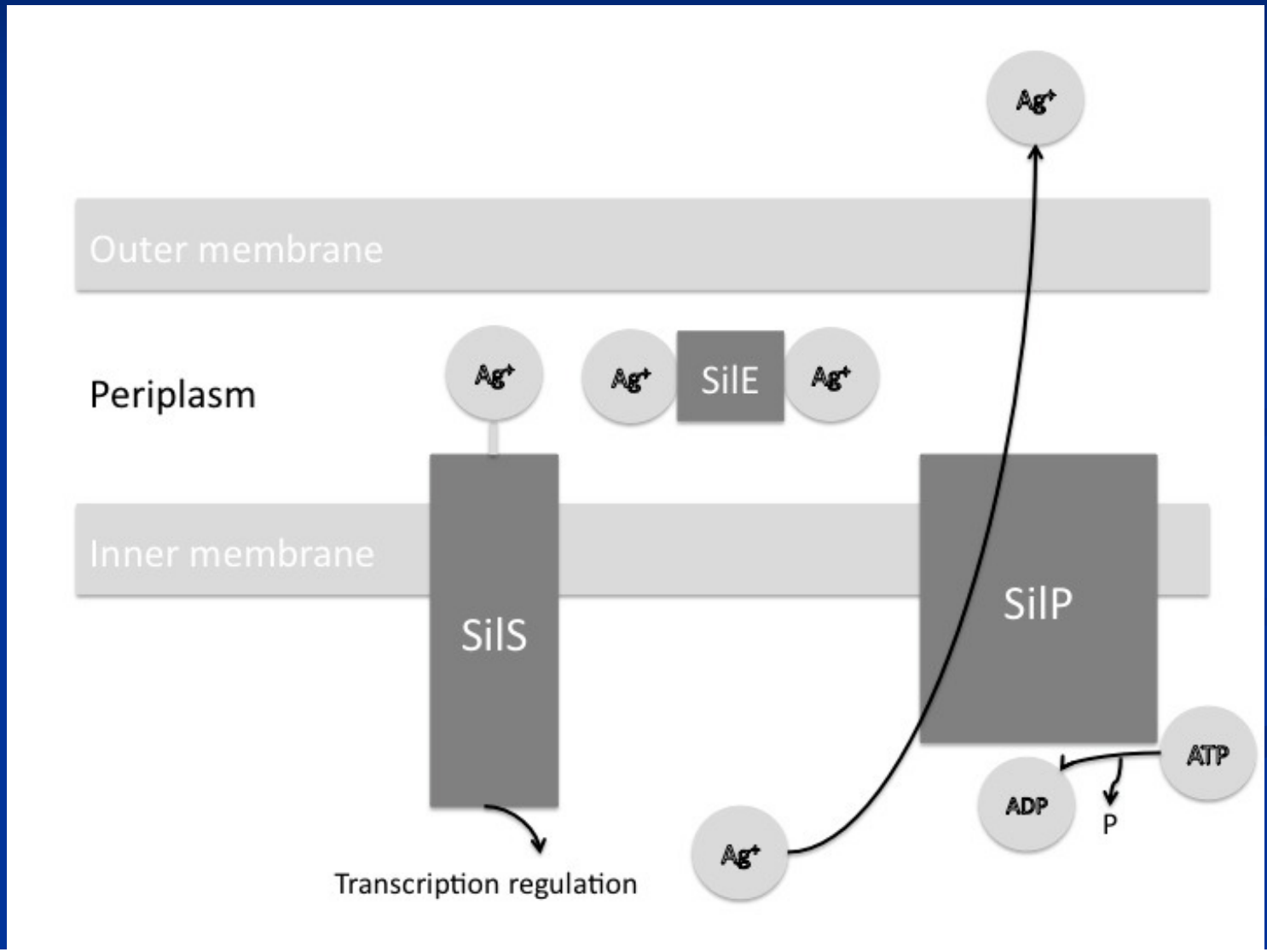
Results

- Cultures yielded 56 isolates
- Primary wound pathogens (Staphylococcus aureus, beta-hemolytic streptococci, Pseudomonas aeruginosa) grew in 79% of the cultures before treatment and in 71% after
- Most common bacterial finding: Staphylococcus aureus
- 3 patients had growth of beta-hemolytic streptococci despite the silver-dressings
- **1 Enterobacter cloacae isolate was silver-resistant (silver nitrate MIC >512 mg/L). More resistant to antibiotics than expected**

Why was silver less active against gram-positive bacteria?

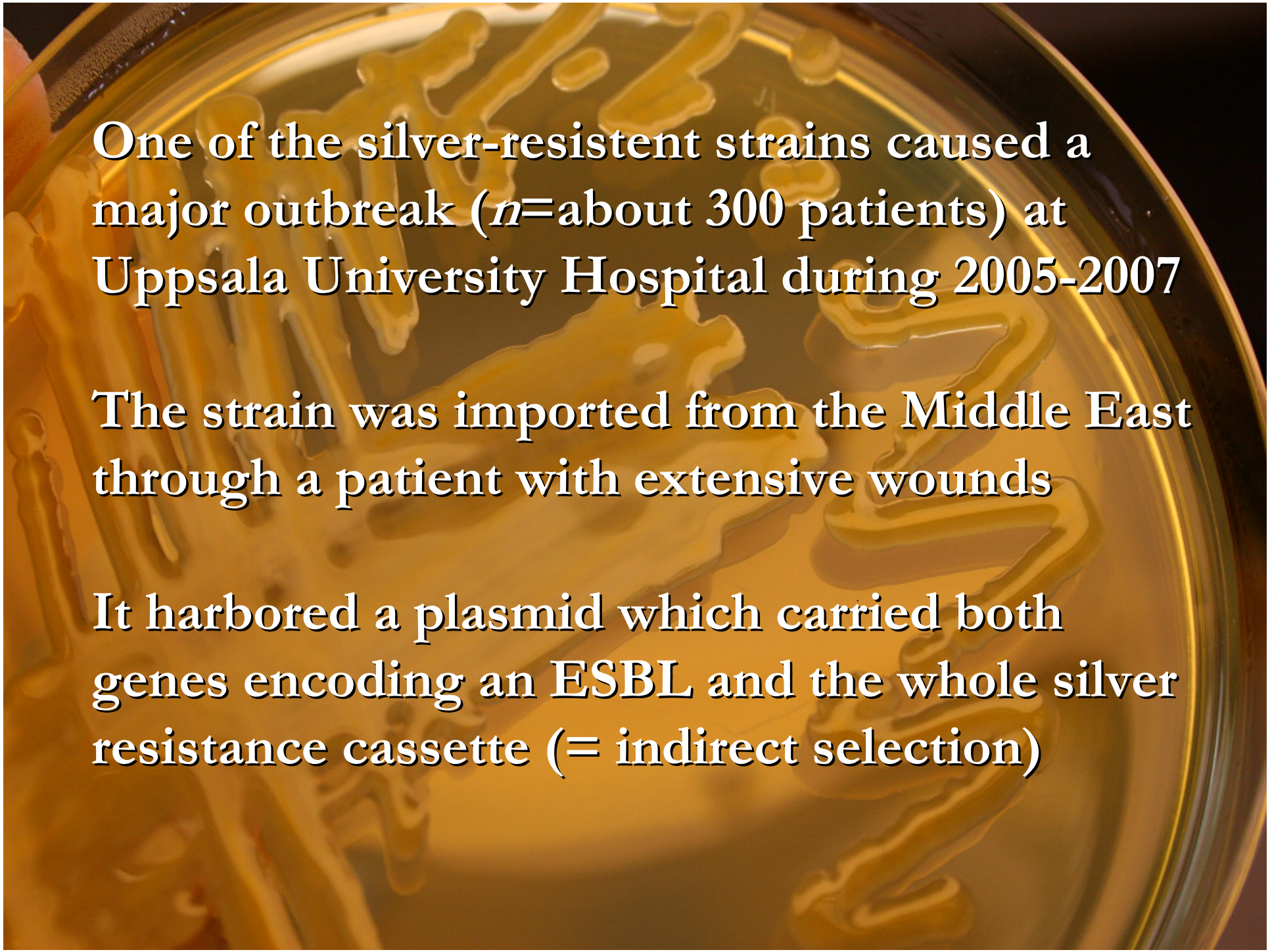
- All S. aureus-strains demanded extremely high silver concentration to be killed; the silver could not kill them, just inhibit their growth
- The gram-negative bacteria were relatively easy to kill. However, one of them was still able to avoid the biocidal effects of silver

How could the E. cloacae strain become silver-resistant?



Further in vitro studies on gram-negative bacteria

- 14 strains (enterobacteria, P.aeruginosa with/without antibiotic resistance)
- 5 strains (36%) developed silver resistance after exposure to silver


One of the silver-resistent strains caused a major outbreak (*n*=about 300 patients) at Uppsala University Hospital during 2005-2007
The strain was imported from the Middle East through a patient with extensive wounds
It harbored a plasmid which carried both genes encoding an ESBL and the whole silver resistance cassette (= indirect selection)

Cross-resistance to antibiotics

- Silver exposure mediated increased resistance to beta-lactams, the most important class of antibiotics
- Most worrying was that 1 strain developed resistance to carbapenems, the last resort for patients with life-threatening infections
- This was due to changes of the cell wall permeability (= direct selection)

A paradox?

- A lot of work is now focused on stopping the development of multiresistant bacteria. The antibiotic consumption has decreased. Not without medical risks
- At the same time the use of biocides is increasing more than ever
- Documented cross-resistance to antibiotics (triclosan, chlorhexidine, silver)
- May act as an indirect selector of multiresistant bacteria (chlorhexidine and MRSA, silver and ESBL)
- The awareness of the risks is quite limited

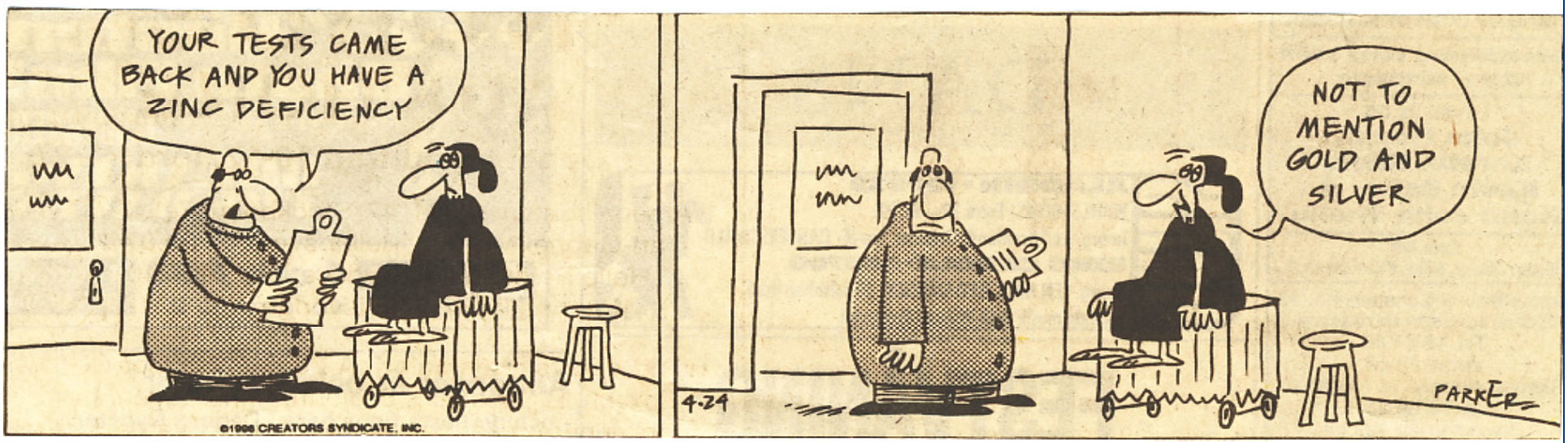
The seriousness is pointed out by WHO

- Antimicrobial resistance was the theme of the World Health Day 2011. ”No action today, no cure tomorrow”
- Identified problems:
  - Lack of research
  - No commitment
  - Weak surveillance
  - Poor drug quality
  - Irrational drug use
  - No infection control

The same problems with biocides

The Scientific Committee on Emerging and Newly Identified Health Risks 2009

- Prudent use guidelines for biocides should be evaluated and harmonized
- Surveillance programs investigating bacterial resistance to biocides are recommended
- Environmental monitoring programs for undesirable substances should include biocides


YOUR TESTS CAME BACK AND YOU HAVE A ZINC DEFICIENCY
©1998 CREATORS SYNDICATE, INC.
4-24
NOT TO MENTION GOLD AND SILVER
PARKER

Thank you!