Fighting the superbugs – turning the tide of antimicrobial resistance
GRENSEN ER NÅDD!
ANTIBIOTIKARESISTENTE BAKTERIER
Human mortality burden

- AVIAN FLU H5N1 449
- EBOLA 11,298
- SWINE FLU H1N1 284,000
- ANTIBIOTIC RESISTANCE > 500,000
AMR is a costly and ticking time bomb...

### Deaths From Drug-Resistant Infections Set To Skyrocket

Deaths from antimicrobial resistant infections and other causes in 2050

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial resistant infections</td>
<td>10.0m</td>
</tr>
<tr>
<td>Cancer</td>
<td>8.2m</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.5m</td>
</tr>
<tr>
<td>Diarrhoeal disease</td>
<td>1.4m</td>
</tr>
<tr>
<td>Road traffic accidents</td>
<td>1.2m</td>
</tr>
<tr>
<td>Measles</td>
<td>130,000</td>
</tr>
<tr>
<td>Cholera</td>
<td>120,000</td>
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<tr>
<td>Tetanus</td>
<td>60,000</td>
</tr>
</tbody>
</table>

Source: Review on Antimicrobial Resistance
The microbiome
- our best friend
Antibiotic consumption

EU
10,500 tons

Human use 52%

Animal use 48%

80 % out-patients

20 % hospital

Björn Wullt, DGU 2015
Selective pressure

Antimicrobial resistance is the sum of all antimicrobial use.

The only weapon we have to not lose the control – is to take the control.
Sharing is everything..

For you!

I LOVE IT!

Bacteria give the most thoughtful gifts.
Horizontal gene transfer → sharing of DNA → Antibiotic resistance

Transformation

DNA

Pili

Bacterium
Horizontal gene transfer → sharing of DNA → Antibiotic resistance

DNA hitch-hikes on retracting pili

Mediating bacterial sex

Skerker & Berg, 2012
http://www.rowland.harvard.edu/labs/bacteria/movies_paeru.html
Transduction
Transfer of bacterial DNA via viruses: bacteriophages inject DNA
Conjugation

Transfer of bacterial DNA by contact between bacteria: “sex pili”, cell-to-cell contact
Can AMR arise without transfer of DNA?

DNA damage events and defects in DNA repair allow chromosomal mutations to arise.
How did we get here?

Selective pressure: Antibiotics
Ex 1: What happened with gonorrhoea?

Registrerte tilfeller med gonróé

Kilde: Folkehelseinstituttet
Gonorrhoea superbug story

- Transformation AND conjugation
- Selective pressure: resistance against both narrow- and broad-spectrum drugs
- AMR required change of clinical guidelines multiple time in the last 2 years
- We’re nearly out of juice
Example 2: Tuberculosis

- *Mycobacterium tuberculosis* colonizes 1/3 of the world’s population
- 9 million new cases yearly
- 1.5 mill deaths yearly
- MDR $\rightarrow$ XDR
- Already in 2012: >10% of Mtb strains in Europe were XDR
How do MDR/XDR Mtb cells arise?

- DNA damage events and defects in DNA repair contribute to mutations arising under selective pressure

- $\rightarrow$ resistance: MDR $\rightarrow$ XDR, no treatment

- Selective pressure, poor hygiene, poor compliance, migration, travel, alarming reduction in development of novel drug candidates – filling up biosafety facilities
How do we solve the AMR problem?
Turning the tide of AMR = TTA
From the patient to global health

1. Clinical Disease (Ng)
   - Ng AMR Basic Research
     - Diagnostics
     - New Treatment
   - Knowledge

3. Global Health Aspects
   - Health Economy
   - Policy Making
   - Global Ethics
Structure-function analysis:
- Construction and *in vivo* expression of complex-components/mutants
- Large-scale complex purification
- 3D cryoEM and single particle averaging
Big data generated in the –omics era

Genomics: The origin!

Transcriptomics: What’s happening?

Proteomics: What happened!

PTMs: How are proteins decorated?
Big data → require large internal memory and vast storage capacity

eInfrastructure for handling large data sets:
All scientists involved can share and analyse large data-sets at the same time
Novel diagnostics

Diagnostics and surveillance of AMR:
New and improved diagnostics of AMR and antibiotics on a chip
New drugs for super-bugs

Therapeutics:
Novel antibiotics / new principles for treatment
Novel prevention and intervention

New vaccines
Block transmission and DNA transfer pathways
Surveillance is intervention
Impact of the microbiomes and probiotics/fecal transplantation
TURNING THE TIDE OF ANTIMICROBIAL RESISTANCE

- turn your tide!