Antimicrobial Resistance in a planet floating in an antibiotic solution

Rino Rappuoli

A European Tribute to the Life and Career of Stanley Falkow

Paris May 28th 2019
Impact on the planet

131,000 tons of antibiotics used for animal food in 2013

61,279 tons up to May 28 in 2019
The journey of antibiotics from land to oceans

Town: households, hospitals to animal feed etc.

Wastewater treatment plants

Rivers & lakes
0.06*10^{21} L

Sea & oceans
1.34*10^{21} L

1.3*10^5 tons/y globally

5.0 pg/mL

0.2 pg/mL

Antibiotic resistance

Selection of antibiotic-resistant bacteria

0.2 pg/mL
“we owe to chemotherapy (antibiotics) the debt of reducing the high mortality rate of many bacterial infections” and to hygiene and vaccines the debt of preventing them, however “in helping to solve some of the problems of infectious diseases, chemotherapy has created some problems of its own”

The problem he was talking about was AMR
Economics of AMR

Impact comparable to climate change

Predicted impact equal to 2 °C raise above preindustrial level of average surface temperature

Rope et al. Science 364, eaau4679, 2019

Antimicrobial resistance is a global crisis that threatens a century of progress in health and achievement of the Sustainable Development Goals.

NO TIME TO WAIT: SECURING THE FUTURE FROM DRUG-RESISTANT INFECTIONS

REPORT TO THE SECRETARY-GENERAL OF THE UNITED NATIONS

APRIL 2019

There is no time to wait. Unless the world acts urgently, antimicrobial resistance will have disastrous impact within a generation.
Vaccines for AMR
A Special PNAS Feature dedicated to Stanley

- No resistant pathogens to vaccines
- Vaccines avoid microbiome disruption
- Vaccines bring greater return on investment for society
The problem of antimicrobial resistance
Economics of AMR
impact comparable to climate change
(Rope et al. Science 364, eaau4679, 2019)

• **Global tragedy of commons** (individuals acting rationally and according to their self-interest, collectively damage public goods)

• 100 trillion the cost of AMR up to 2050

• 3.4 trillion impact on GDP by 2030 (predicted impact of 2 °C raise above preindustrial level of average surface temperature is 3 trillion)

• So important to be discussed by the United Nations General Assembly

• Carbon tax for social cost of carbon (SCC) is being discussed, what about a tax for the social cost of antibiotics (SCA)
Impact on the planet

Infectious multiresistant plasmids colonizing the world, replacing the global microbiota...

...THE GLOBAL MICROBIOME IS BECOMING AMR

what is the consequence of living in a world where all microbes in water, soil, air, animals are antibiotic resistant? how close are we to the point of no return?

- **Bystander selection** of microbes that are not target of treatment is above 80%
  - (PNAS 115, e11988-95, 2019)

- **Wastewater treatment plants in Europe**: 70-100% of samples contain AMR genes against most common antibiotics (Science advances 2019 eaau9124)

- **Vibrio Cholerae in the Bay of Bengal**: 100% resistant to 2 antibiotics,
  - 17.2% resistant to 10 or more antibiotics (PNAS, 116, 6226-31, 2019)
Medical consequences

- 700,000 deaths now, 10 M in 2050 (Cancer 8.2M)
- Death from infection could follow from something as minor as a scratch
- Cesarean sections, Joint replacement surgery, Chemotherapy, Organ transplant (4% of global GDP) more dangerous or prohibitive
- Hospital infections untreatable
Human Evolution
and Infectious Diseases
Improved health and increase of life expectancy is an achievement of civilization.

55 years gained since 1700
35 years gained since 1900
In 1900 in the USA people died of infectious diseases

Infectious Diseases
- Diphtheria (40 million prevented)
- Measles (35 million prevented)
- Smallpox...

Non Communicable Diseases
- Ischemic Heart Disease
- Stroke
- Cancer
- Diabetes
- Alzheimer
- ....
Conquest of Infectious Diseases
Antibiotics generate resistance, become obsolete and need new antibiotics to control diseases

Antibiotics

Vaccines control diseases quickly and for very long time, without generating major resistance

Vaccines

Hygiene

It works, however the time to introduce good hygiene and clean water in a low income country is several decades (40-50 years)
vaccines are evolution proof, drugs are not
Andrew Read

Antimalarials

Antibiotics

Vaccines

1920 1940 1960 1980 2000 2020
vaccines are evolution proof, drugs are not

• Drugs
  – one target
  – work on a big bacterial population with high numbers to generate diversity and resistance

• Vaccines
  – many targets /epitopes
  – control a small bacterial population
  – Resistance when the above rules are violated
1950-70 golden period for antibiotics 1980-today golden period for vaccines

Various advances in molecular biology have spurred vaccine development.
Licensed vaccines and antibiotics since 1980’s

**Vaccines**
- Zoster
- Malaria
- Meningococcus B
- Pneumococcus 13
- Human papillomavirus
- Meningococcus ACYW
- Rotavirus
- Pneumococcus 7
- Meningococcus C
- Adjuvanted influenza
- Acellular pertussis
- Varicella
- Hemophilus influenzae
- Hepatitis B

**Antibiotics**
- Diarylquinolones
- Fidaxomicin
- Mutilins
- Lipopeptide
- Oxazolidinone
Antimicrobial resistance (AMR)
700,000 deaths now, 10 M in 2050 (Cancer 8.2M)
Infectious multiresistant plasmids colonizing the world, replacing the global microbiota...

Vaccines can have an effect on antimicrobial resistance by reducing the number of ill people and avoiding unnecessary antibiotic prescriptions.

Deploy vaccines to fight superbugs

Immunizations combined with antibiotics could be our best shot at combating drug-resistant microbes, argue Rino Rappuoli, David E. Bloom and Steve Black.
Vaccines for AMR

- No resistant pathogens to vaccines
- Vaccines avoid microbiome disruption
- Vaccines bring greater return on investment for society
### Diphtheria Venezuela

**Emerg Infect Dis 25 (4) April 2019**

<table>
<thead>
<tr>
<th>2016 vaccination rates</th>
<th>DTP3 84%</th>
<th>DTP4 60%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1990 – 2015</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>• 2016</td>
<td>324</td>
<td>17</td>
</tr>
<tr>
<td>• 2017</td>
<td>1040</td>
<td>103</td>
</tr>
<tr>
<td>• 2018</td>
<td>806</td>
<td>287</td>
</tr>
</tbody>
</table>

| **Mortality**          |          |          |
| Case/Case              | 0        |
|                        | 0        |
|                        | 5.5%     |
|                        | 9.9%     |
|                        | 35.6%    |
Vaccines
Vaccines

New technologies led to the development of new vaccines and to conquer new diseases.
Capsular polysaccharides & Conjugates

- Haemophilus influenzae type B (Hib)
- Pneumococcus
- Meningococcus
- Group B streptococcus

Capsule → Polysaccharide → Conjugate

Neisseria meningitidis bacteria
Effect of Pneumo 10 Vaccine in Iceland

- P = penicillin
- E = erythromycin
- TE = tetracycline
- C = chloramphenicol
- SXT = sulpha-trimethoprim
Reverse Vaccinology 2.0: human immunology instructs vaccine antigen design
Rappuoli, Bottomley, D'Oro, Finco, De Gregorio JEM April 2016

GENOMICS / PROTEOMICS

HUMAN MONOCLONALS
antigen discovery
epidemiology
antigen conservation/expression
human genome homology
tumor neoantigens

X RAY, CRYO-EM, NMR

protective epitopes
structure-based antigen design

structure/antigen/antibody complex
protective conformation

Reverse Vaccinology
information-based vaccine design
New Zealand experience
In 2004 an OMV vaccine was used in New Zealand

- Global vaccination campaign (5 wks-18yrs)
- Outer Membrane Vesicles successfully eliminated the MenB epidemic in New Zealand and reduced gonococcal infection by 30%

---

Holst et al Human Vaccines and Immunotherapeutics 9 (6), 1241-53, 2013
• Many potent vaccine adjuvants have failed, due to safety concerns
• MF59 was a key innovation, first novel adjuvant in 70 years
• Alum and MPL (AS04®) are the only adjuvants currently approved in US
M72/AS01\textsubscript{E} candidate vaccine (M72)

To induce a robust Th1 CD4+ T cell response against Mtb antigens

**Mtb antigens**
- PepA (Mtb32A)
- PPE18 (Mtb39A)

**Adjuvant system**
- AS01\textsubscript{E}

**Antigens selection**
[Skeiky, 1999; Dillon, 1999; Al-Attiyah 2004]
- Lymphoproliferation - IFN-γ production
  - Healthy PPD +
  - TB patients
  - PPD -
- No IL-10 production in TB patients

*QS-21: Quillaja saponaria Molina, fraction 21; Licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation.*
A promising TB vaccine

<table>
<thead>
<tr>
<th>Time</th>
<th>VE (case definition 1, ATP)</th>
<th>%</th>
<th>LL 90%CI</th>
<th>UL 90%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 1 (≤ 1.12 years)</td>
<td>39.0</td>
<td></td>
<td>-42.5</td>
<td>73.9</td>
</tr>
<tr>
<td>Period 2 (&gt; 1.12 years)</td>
<td>66.5</td>
<td></td>
<td>13.3</td>
<td>87.0</td>
</tr>
</tbody>
</table>

Kaplan-Meier (ATP cohort for efficacy)
Van Der Meeren NEJM. 25 Sep 2018; DOI: 10.1056/NEJMoa1803484

Figure adapted from Van Der Meeren et al, presented at IDWeek, October 2018, San Francisco CA, Abstract 70677 http://www.idweek.org
Vaccines against poverty, an Institute to address the gaps in vaccine development

In the recent past, no mechanism was in place to develop vaccines needed only in developing countries.

**Novartis Vaccines Institute for Global Health (NVGH)**

*New name:* **GSK Vaccine Institute for Global Health (GVGH)**

A new non-profit initiative to develop effective and affordable vaccines for neglected infectious diseases of developing countries.

- Located in Siena, Italy
- Legal entity started in Feb 2007
- Allan Saul hired as CEO Sept 2007
  - Inauguration Feb 22, 2008
- Typhoid vaccine licensed to BioE successful Phase III
- Shighella vaccine Phase I 2014
- iNTS Phase I 2020
AMR is difficult for antibiotics alone

This figure was inspired by an early version of a manuscript by Elizabeth J Klemm, Vanessa K Wong, and Gordon Dougan
Vaccines and Antibiotics together have a better chance to control AMR

This figure was inspired by an early version of a manuscript by Elizabeth J Klemm, Vanessa K Wong, and Gordon Dougan.
By joining forces we can control AMR

This figure was inspired by an early version of a manuscript by Elizabeth J Klemm, Vanessa K Wong, and Gordon Dougan
Thank you