The Role of Vaccines to Combat Antimicrobial Resistance (AMR)

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Disclosure

Employed by GSK where I am a vaccine research physician scientist

Presentation at the invitation of Dr. Meera Varman, Professor, Pediatric Infectious Diseases, Creighton University School of Medicine

Presentation is for educational purposes only; this is not a sales, marketing or promotional presentation

Content of presentation will not include unapproved or investigational uses of products or devices
The value of vaccines

Only clean drinking water rivals vaccination in its ability to save lives¹

2–3m² deaths prevented every year by vaccination

$150bn³ the benefit of vaccines to low and middle-income countries over the next 10 years

750,000² children saved from disability every year

x44⁴ is the estimated return on Investment of the cost of immunization

Driving the potential of new vaccines to transform human health

Scientific knowledge advances and modern vaccine technologies offer great potential for new vaccine development:

- uncommon and/or emerging diseases imparting significant morbidity & mortality
- patient populations small in number yet at risk of clinically important medical and healthcare-associated infections
- personalized vaccines based on subpopulation or individual genetic information
- AMR-relevant vaccines aimed at preventing target pathogens likely to drive antimicrobial use and resistance

New vaccines need to be discovered, developed through to commercialization, and implemented through evidence-based vaccination policy recommendations
Need for comprehensive approach to realize full potential and impact

Discovering innovative technologies and developing new vaccines:
  time, human, capital resource intensive, risky

Formulating vaccine policy decisions:
  broad view, beyond direct health and economic benefits

Evaluate:
  – Moral, social, ethical impact of vaccines, integrated alongside other societal health interventions and programmatic synergies
  – Health equity, justice, community health gains, improved healthcare system function, societal economic health
  – Impacts related to reduced antibiotic use and antibiotic resistance.
For 99.9% of the history of mankind, life expectancy was <40 years
Average life expectancy of early *Homo sapiens* was apparently 25-40 years

**Improved health and increased life expectancy: an achievement of civilization**

In the last 2 centuries things have changed beyond recognition. Pills, injections and sophisticated operations save us from a spate of illnesses that once dealt an inescapable death sentence. The average life expectancy jumped from around 25-40 years, to 67 in the entire world, and to around 80 in the developed world.
## Top 10 Causes of Death

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No deaths/100,000</th>
<th>Etiology</th>
<th>No deaths/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia or influenza</td>
<td>202.2</td>
<td>Heart disease</td>
<td>192.9</td>
</tr>
<tr>
<td>TB</td>
<td>194.4</td>
<td>Cancer</td>
<td>185.9</td>
</tr>
<tr>
<td>GI infections</td>
<td>142.7</td>
<td>Noninfectious airway dis</td>
<td>44.6</td>
</tr>
<tr>
<td>Heart disease</td>
<td>137.4</td>
<td>Cerebrovascular dis</td>
<td>41.8</td>
</tr>
<tr>
<td>Cerebrovascular dis</td>
<td>106.9</td>
<td>Accidents</td>
<td>38.2</td>
</tr>
<tr>
<td>Nephropathies</td>
<td>88.6</td>
<td>Alzheimer’s dis</td>
<td>27.0</td>
</tr>
<tr>
<td>Accidents</td>
<td>72.3</td>
<td>Diabetes</td>
<td>22.3</td>
</tr>
<tr>
<td>Cancer</td>
<td>64.0</td>
<td>Nephropathies</td>
<td>16.3</td>
</tr>
<tr>
<td>Senility</td>
<td>50.2</td>
<td>Pneumonia or influenza</td>
<td>16.2</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>40.3</td>
<td>Suicide</td>
<td>12.2</td>
</tr>
</tbody>
</table>

Data are from the Centers for Disease Control and Prevention

NEJM 2012:366;2333-2338
Antibiotics

The discovery of antibiotics is one of the greatest medical advances of the 20th century.

Modern medicine is made possible by our ability to treat, and prevent, infection: transplantation, neonatal care, complex surgeries, joint replacement, caesarian sections, oncology treatment, ...
Antibiotics

Unfortunately, their use has created an evolutionary response from microbes, and these gains in healthcare are under threat from AMR.
### Timeline: Some Key Events of Antibiotic Resistance Development

<table>
<thead>
<tr>
<th>Antibiotic Resistance Identified</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin-R <em>Staphylococcus</em></td>
<td>1940</td>
</tr>
<tr>
<td>Tetracycline-R <em>Shigella</em></td>
<td>1959</td>
</tr>
<tr>
<td>Methicillin-R <em>Staphylococcus</em></td>
<td>1962</td>
</tr>
<tr>
<td>Ceftazidime-R <em>Enterobacteriaceae</em></td>
<td>1987</td>
</tr>
<tr>
<td>Imipenem-R <em>Enterobacteriaceae</em></td>
<td>1998</td>
</tr>
<tr>
<td>Ceftaroline-R <em>Staphylococcus</em></td>
<td>2011</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic Introduced</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1943</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1950</td>
</tr>
<tr>
<td>Methicillin</td>
<td>1960</td>
</tr>
<tr>
<td>Imipenem &amp; Ceftazidime</td>
<td>1985</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>2010</td>
</tr>
</tbody>
</table>

Adapted from Ventola CL. P&T 2015; 40: 277-83
These events were predicted

Stanley Falkow (1934-2018) discovered the molecular mechanisms through which bacteria cause disease and predicted the rise of multidrug-resistant bacteria.

By the 1970s he predicted that overuse of antibiotics would soon lead to drug resistance and the loss of their utility.

Falkow already had plenty of evidence to base his predictions on.

His recommendation to stop the use of antibiotics in animals was not implemented by the US authorities.
The Issue
Antimicrobial Resistance (AMR)

- Multidrug resistant organisms increasingly common, extremely difficult to treat
- Now encountering infections that are untreatable
- Major contributor: over-prescription of current antibiotics in animals and humans
TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:
FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE
CHAIR BY JIM O’NEILL
MAY 2016
Overuse of antibiotics is prevalent

Even when access to antibiotics is restricted by a prescription system, much of the use is unnecessary

Partly, this is because it is hard to know what’s necessary at the time prescribing happens

Misuse of antibiotics is also prevalent

But it is important to understand that even if used appropriately, antibiotic resistance will arise

It is a natural and predictable consequence of actually using antibiotics

All we can do is slow it down

AMR: an imperative for all stakeholders

Serious, growing threat to public health and economy

Deaths annually global, current:

- Tetanus (60,000)
- Cholera (120,000)
- Measles (130,000)
- Road accidents (1.2M)
- Diarrheal dis (1.4M)
- Diabetes (1.5M)
- Cancer (8.2M)
- Drug resistant infections (700,000)

Drug resistant infections:
- 50,000 US/EU
- globally >700,000

If current trend holds:
by 2050, ~10 million AMR deaths globally, world GDP reduced up to 2-3.5%

Predictions of possible future risks

“A problem so serious that it threatens the achievements of modern medicine” – WHO

Antimicrobial use is rising across the world, with global consumption of antibiotics increasing by nearly 40% between 2000 and 2010

“We have reached a critical point and must act now on a global scale to slow down antimicrobial resistance” – Professor Dame Sally Davies, UK Chief Medical Officer

International travel has created new opportunities for antimicrobial-resistant diseases to be spread globally

1. WHO: http://apps.who.int/iris/bitstream/handle/10665/112642/9789241564748_eng.pdf;jsessionid=40BECF8DD7E6DA5F7BB23C7585D88E2A?sequence=1
2. https://amr-review.org
Worst case scenario: “post antimicrobial era”

– Problem attracting global attention
– Most proposed solutions focus on development of new technologies:
  • Antibiotics
  • Rapid diagnostic tests
  • Vaccines
AMR is difficult for antibiotics alone

Bloom, Black Salisbury and Rappuoli. PNAS 2018:115;12869
The number of new antibiotics developed and approved has decreased over the past decades.

Number of new antibiotics

Adapted from Ventola CL. P&T 2015; 40: 277-83
WHO list of bacteria for which new antibiotics are urgently needed (2017)

CDC - Antibiotic resistance threats in the United States (2019)
https://www.cdc.gov/drugresistance/biggest-threats.html
Worst case scenario: “post antimicrobial era”

- Problem attracting global attention; most proposed solutions focus on development of new technologies: antibiotics, rapid diagnostic tests, and vaccines
- Role of vaccination in controlling AMR frequently acknowledged, yet not led to concrete changes in policy or resourcing
Vaccines combat AMR in two ways

1. Prevent infection, carriage and spread of resistant organisms
2. Reduce antibiotic use and therefore selective pressure
Preventing infections to reduce society’s dependence on ABX

Bacterial infections are major drivers of antibiotic prescribing

Vaccines to prevent bacterial infections reduce antibiotic use
– vaccines for diphtheria, meningitis, pneumonia and pertussis have protected tens of millions of individuals from these bacterial infections

Non-bacterial infections can trigger inappropriate use of antibiotics
– vaccines for non-bacterial infections, such as influenza and rotavirus, avoid diseases that can trigger inappropriate use of antibiotics
Haemophilus influenzae type b vaccines (Hib)

Before Hib introduction

Global incidence of disease:
3.5-601 cases/100,000 children ≤5 yo

Canada: 2.6 cases/100,000 (1987-88)

Global prevalence of β-lactamase positive strains:
16.6 %

After Hib introduction

Decrease of global incidence of disease and of nasopharyngeal carriage

Canada: 0.08 cases/100,000 (2011-15)

Rapid decrease of β-lactamase positive strains

Hib: Haemophilus influenzae type b

Impact of pneumococcal conjugate vaccine on incidence of Penicillin-nonsusceptible IPD (USA)

Incidence of penicillin-nonsusceptible S. pneumoniae strains associated with invasive pneumococcal disease by age group, USA

Cases per 100,000 population

- Reduction on penicillin nonsusceptible IPD in children < 2 years

IPD: invasive pneumococcal disease. PCV7 vaccine was introduced in 2000.

Impact of pneumococcal conjugate vaccine on antibiotic prescription in USA

35% Reduction of antibiotic use after PCV introduction

1.4 million antibiotic prescriptions/year are preventable with PCV in USA

Impact of universal influenza vaccination on antibiotic prescription

3-9% of antibiotic courses are attributable to influenza

64% decrease in influenza-associated respiratory antibiotic prescriptions after UIIP* in Ontario

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* UIIP: universal influenza immunization program (offered to everyone ≥ 6 months of age). Overall vaccine uptake in Ontario: 38%.

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* Children, USA.
“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
- Prevent infections quickly and over time

Source: Kennedy DA and Read A. Why the evolution of vaccine resistance is less of a concern than the evolution of drug resistance. PNAS 2018 115:51 12879. Adapted with permission of the authors. *Quote from Andrew Reed.
Increase awareness of role of vaccines in addressing AMR

Requires collaborative global response from all stakeholders:
- scientific community
- pharmaceutical sector
- policy-makers
- healthcare funders
Developing innovative AMR-relevant vaccines

Develop innovative AMR-relevant vaccines aimed at preventing infections where target pathogens are likely to drive antimicrobial use and resistance (e.g. Shigellosis, Tuberculosis, Malaria, Meningococcus, Pneumococcus, COPD, RSV, Flu Universal, MRSA, Gonorrhea, HSV, candidiasis, C. difficile, Klebsiella, Pseudomonas)

New, global initiatives for R&D of new drugs and vaccines being deployed
1950-70 golden period for antibiotics
1980-today golden period for vaccines

Bloom, Black Salisbury and Rappuoli. PNAS 2018:115;12870
Vaccine technology has been revolutionised in the past 30 years

Waves of new technologies have enabled the development of vaccines that were previously not possible and led to improvements in vaccine safety.

Adapted by permission from Macmillan Publishers Ltd: Nat Rev Immunol, Rappuoli R et al., Nov 4;11(12):865-72. doi: 10.1038/nri3085, copyright 2011
Potential vaccine game-changing technology

- Adjuvant Systems
- Synthetic vaccines (DNA/RNA)
- Adenoviral vectors
- Reverse vaccinology
- Structural vaccinology
- Platform Technologies
The pipeline for AMR vaccines is thin

<table>
<thead>
<tr>
<th>Pathogen name</th>
<th>Research / Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Marketed</th>
<th>Total</th>
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<tr>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Enterococcus faecium</td>
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<td>Escherichia coli (enteric)</td>
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<td>3</td>
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<td>1</td>
<td>18</td>
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<td>Escherichia coli (urinary)</td>
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<td>1</td>
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<td>Mycobacterium tuberculosis</td>
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<td>4</td>
<td>8</td>
<td>2</td>
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<td>52</td>
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<tr>
<td>Neisseria gonorrhoeae</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
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<td>Pseudomonas aeruginosa</td>
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<td>Salmonella (non-typhoidal)</td>
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<td>Salmonella Paratyphi</td>
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<td>Salmonella Typhi</td>
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<td>2</td>
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<td>2</td>
<td>20</td>
<td>32</td>
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<td>Shigella</td>
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<td>Staphylococcus aureus</td>
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<td>27</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>31</td>
<td>7</td>
<td>8</td>
<td>3</td>
<td>7</td>
<td>56</td>
</tr>
</tbody>
</table>

Technologies to develop vaccines for AMR: Not the major challenge

Sustainability of vaccine development for AMR: The major challenge
Call to action:

Increase Uptake of Today’s Vaccines
- Increase funding, broaden points of access
- Encourage greater use existing vaccines
- Increase AMR education, awareness

Incentivize Development of New AMR Vaccines
- Attribute AMR-related value in regulatory submissions
- Consider market-based incentives where needed

Build the Evidence Base
- Surveillance, research inform policy maker decision-making
- AMR-sensitive economic models for vaccines
The role of vaccines to combat AMR

- AMR is difficult for antibiotics alone

- Vaccines and Antibiotics together have a better chance to control AMR

- By joining forces we can control AMR

Source: Bloom et al, Antimicrobial resistance and the role of vaccines. PNAS 2018 115:51 12869. Adapted with permission of the authors.
Discussion

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