Vaccination as an approach to reducing antimicrobial resistance

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Agenda

• Prevention versus cure
  – Major features of antibiotics and vaccines
• Vaccines to reduce antibiotic resistance
  – Pneumococcal conjugate vaccine
• Even vaccines with relatively low efficacy may be useful
  – *Staphylococcus aureus*
• Future approaches
# Major features of antibiotics and vaccines

<table>
<thead>
<tr>
<th>Relevant Feature</th>
<th>Antibiotics</th>
<th>Vaccines</th>
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<tbody>
<tr>
<td>Therapeutic/prophylactic</td>
<td>Mostly therapeutic</td>
<td>Mostly prophylactic</td>
</tr>
<tr>
<td>Coverage and specificity</td>
<td>Broad, indiscriminate</td>
<td>Narrow, specific</td>
</tr>
<tr>
<td>Resistance emergence</td>
<td>Common</td>
<td>Not observed</td>
</tr>
<tr>
<td>Selective pressure</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Time to develop resistant strains</td>
<td>Short</td>
<td>Not observed</td>
</tr>
<tr>
<td>Durability</td>
<td>Restricted to the time of treatment</td>
<td>Duration of protection persists from several months to life-long</td>
</tr>
<tr>
<td>Treatment/prevention of viral infections</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Herd or community effect</td>
<td>No</td>
<td>Yes (maternal immunity)</td>
</tr>
<tr>
<td>Prevention of perinatal infections</td>
<td>Yes</td>
<td>Yes (HBV, HPV)</td>
</tr>
<tr>
<td>Prevention of cancer</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cost</td>
<td>Few $s to $1000s</td>
<td>Few $s to &lt;$200</td>
</tr>
</tbody>
</table>

The use of vaccines to reduce antibiotic resistance

- Vaccines are a key component in the fight against antibiotic resistance both directly and indirectly.
- By targeting bacterial pathogens, vaccines directly reduce the need for the use of antibiotics.
- However, even vaccines created against non-bacterial pathogens can also have an indirect effect on pathogenic bacteria by reducing complications associated to *super-infections* that routinely require antibiotic use.
- Vaccines also contribute to the reduction of antibiotic usage through the establishment of herd immunity.
- One of the best documented examples of this effect is the use of pneumococcal conjugate vaccine (PCV) that targets the most virulent, serotypes linked to invasive pneumococcal disease (IPD) and that are also associated with antibiotic resistance.
Penicillin resistance children *over two and adults*
Impact of pneumococcal conjugate vaccine

Kyaw *et al*, NEJM 2006; 354:1455-63
The change in prevalence of PCV13 serotypes (43.4 to 27.1%) was primarily due to a decrease in serotype 19A strains, i.e., 22% of all strains in 2008-09 to 10% of all strains in 2012-13.
A high incidence of pneumococcal infections is combined with a constantly growing antibiotic resistance of this pathogen. The growing resistance is thought to be associated with misuse of antibiotics and emerging of resistant clones that may spread throughout the entire population. Pneumococcal polysaccharide conjugate vaccines (PCV) contain an assortment of pneumococcal capsular polysaccharides (from 7 to 13) that produce serotype-specific protective antibodies. Since the early 2000s, the introduction of PCV into national immunization programs has been shown substantially to decrease the incidence of invasive pneumococcal disease and pneumococcal carriage associated with vaccine-type pneumococci in many countries. In 2014, PCV vaccination was included in the Russian national calendar of prophylactic vaccination……
Even vaccines with relatively low efficacy may be useful tools against antimicrobial resistance

- The growing prevalence of antimicrobial resistance in major pathogens is outpacing discovery of new antimicrobial classes
- Vaccines mitigate the effect of antimicrobial resistance by reducing the need for treatment, but vaccines for many drug-resistant pathogens remain undiscovered or have limited efficacy, in part because some vaccines selectively favor pathogen strains that escape vaccine-induced immunity
- A strain with even a modest advantage in vaccinated hosts can have high fitness in a population with high vaccine coverage, which can offset a strong selection pressure such as antimicrobial use that occurs in a small fraction of hosts
- Joice and Lipsitch propose a strategy to target vaccines against drug-resistant pathogens, by using resistance-conferring proteins as antigens in multicomponent vaccines
- Resistance determinants may be weakly immunogenic, offering only modest specific protection against resistant strains
- Therefore, if such vaccines confer even slightly higher protection (additional efficacy between 1% and 8%) against resistant variants than sensitive ones, they may be an effective tool in controlling the rise of resistant strains, given current levels of use for many antimicrobial agents

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0068940
Figure 1. Modeling a vaccine with increased efficacy against drug-resistance determinants for an endemic colonizing pathogen (*S. pneumoniae*).


http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0068940
Figure 2. Modeling a vaccine against drug-resistance determinants for an endemic colonizing pathogen for which no vaccine currently exists (S. aureus).

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0068940

- There are several potential reasons behind the disappointing results of clinical trials. Some, which are common to all the trials, determined their downfall
  - First of all, preclinical results obtained with antigens tested in clinical trials were likely overestimated by vaccine manufacturers
  - Furthermore, vaccines tested in humans to date, since they all targeted single antigens, were probably disproportionate to the complex pathogenic mechanisms of the bacterium
  - In addition, the lack of known correlates of protection in humans has severely limited the ability to interpret both preclinical and clinical data
  - Finally, the vaccines did not contain new generation adjuvants, which may be critical in augmenting antibody production and steering the T-cell response toward the proper profile of cytokine production

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3417391/
A model to generate protective immunity against S. aureus infections through vaccination (Bagnoli et al. 2012)

Protective vaccines should be able to elicit three major immune responses:
(i) antibodies to directly inhibit bacterial viability and/or toxicity;
(ii) antibodies to mediate opsonophagocytosis; and
(iii) cell-mediated immunity to stimulate recruitment of phagocytes (eg neutrophils) at site of infection
Conclusions

• Antibiotics differ from vaccines in many ways
• The uptake of vaccines has contributed in a positive way to antibiotic prescribing and to antibiotic resistance
  – Pneumococcal conjugate vaccine
• Even vaccines with relatively low efficacy may be useful
• *S. aureus* vaccine trials to date have been disappointing
• New approaches needed, such as a better understanding of immune responses, adjuvants and reverse vaccinology