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

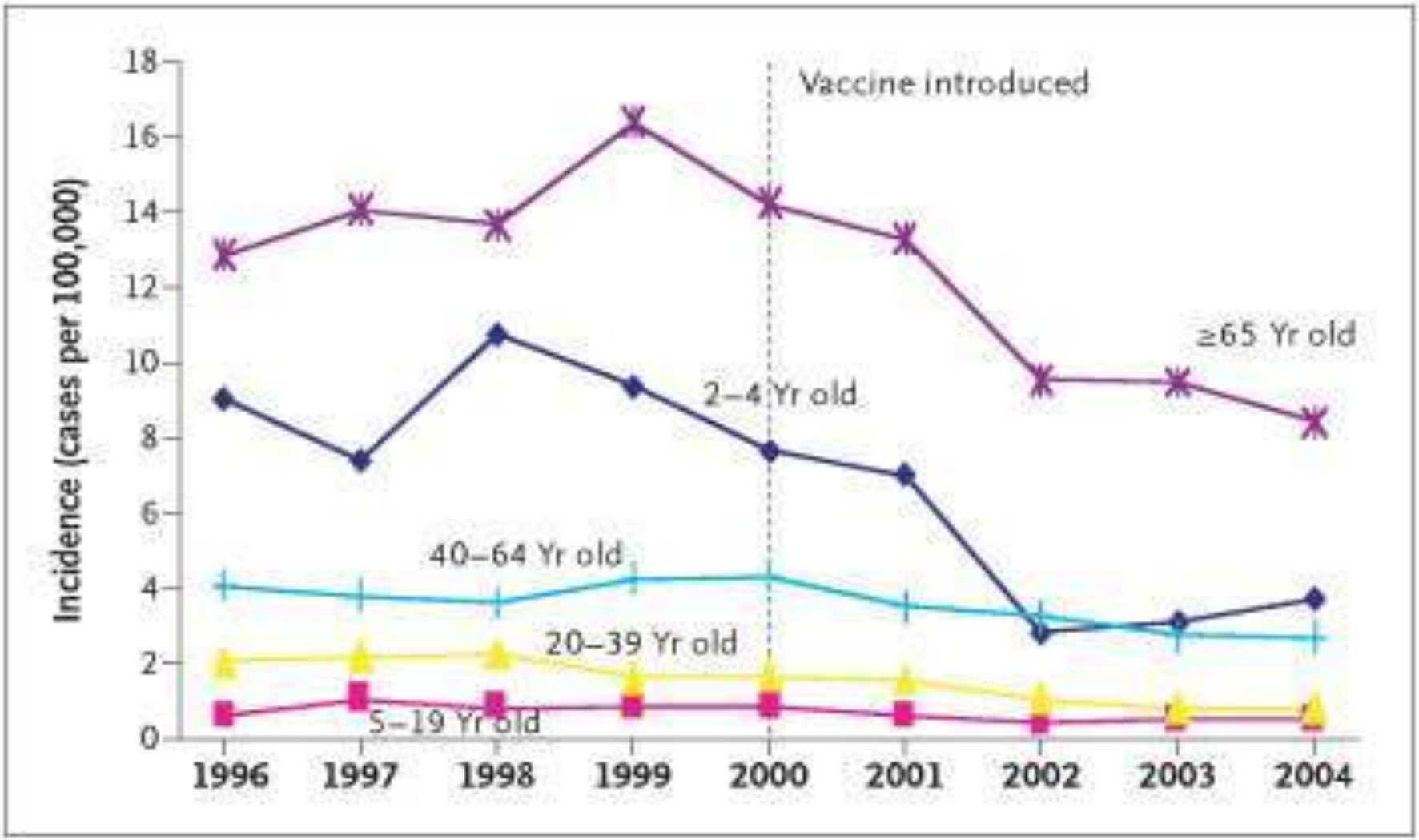
Relevant Feature	Antibiotics	Vaccines
Therapeutic/prophylactic	Mostly therapeutic	Mostly prophylactic
Coverage and specificity	Broad, indiscriminate	Narrow, specific
Resistance emergence	Common	Not observed
Selective pressure	High	Low
Time to develop resistant strains	Short	Not observed
Durability	Restricted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

Mishra *et al*. Vaccines and antibiotic resistance. Current Opinion in Microbiology 2012; 15 (5): 596 - 602

The use of vaccines to reduce antibiotic resistance

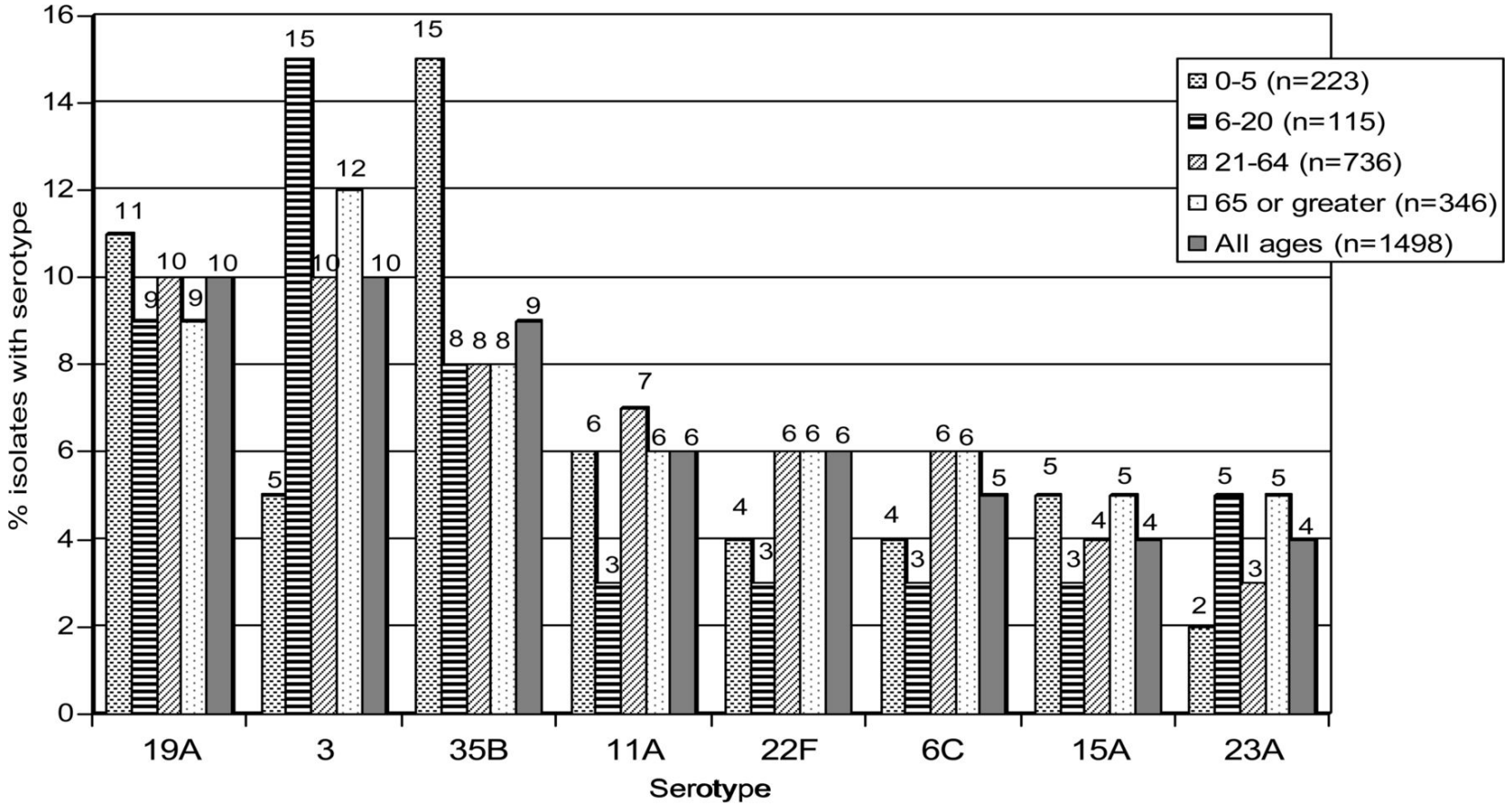
- Vaccines are a key component in the fight against antibiotic resistance both directly and indirectly.
- By targeting bacterial pathogens, vaccines directly reduce the need for the use of antibiotics.
- However, even vaccines created against non-bacterial pathogens can also have an indirect effect on 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

Distribution of predominant serotypes by patient age for 1,498 pneumococcal isolates recovered in 2012-13 in the USA



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.

Sandra S. Richter et al. Antimicrob. Agents Chemother. 2014;58:6484-6489

Antimicrobial Agents and Chemotherapy

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Серотиповое разнообразие и резистентность пневмококков

Пневмококк (Streptococcus pneumoniae) входит в число главных возбудителей острых бактериальных инфекций у детей, особенно в возрасте до 5 лет. Пневмококковые инфекции могут быть мукозальными (например, острый средний отит, синусит, неинвазивная пневмония) и инвазивными, которые включают тяжелые, нередко жизнеугрожающие заболевания (менингит, сепсис). Высокая заболеваемость пневмококковыми инфекциями сочетается с неуклонным ростом резистентности пневмококка к антибактериальным препаратам, наиболее широко используемым в клинической практике. В популяции резистентных пневмококков доминирует небольшое число клонов, которые имеют глобальное распространение, поэтому понимание молекулярных механизмов устойчивости к различным классам антибиотиков помогает прогнозировать вероятность экспансии резистентных генов на конкретной территории. Широкое использование пневмококковых конъюгированных вакцин (ПКВ) для профилактики пневмококковых инфекций оказало существенное влияние на сероэпидемиологию пневмококка в тех странах, где они включены в национальные календари иммунизации. Эти вакцины содержат полисахариды нескольких капсульных вариантов — серотипов — пневмококка (от 7 до 13), в ответ на которые вырабатываются серотипспецифические антитела. ПКВ показали свою высокую эффективность, резко снизив циркуляцию вакцинных пневмококков как среди пациентов с инвазивными инфекциями, так и у носителей. В 2014 г. вакцинация ПКВ была включена в российский календарь профилактических прививок, поэтому современные мировые и российские данные о распространенности серотипов, антибиотикорезистентности и влиянии вакцинации на эволюцию пневмококков, представленные в настоящем обзоре, приобретают особую актуальность.

Ключевые слова: пневмококк, серотип, сиквенс-тип, антибиотикорезистентность, полисахаридные конъюгированные вакцины.

(Вестник РАМН. 2014; 7–8: 38–45)

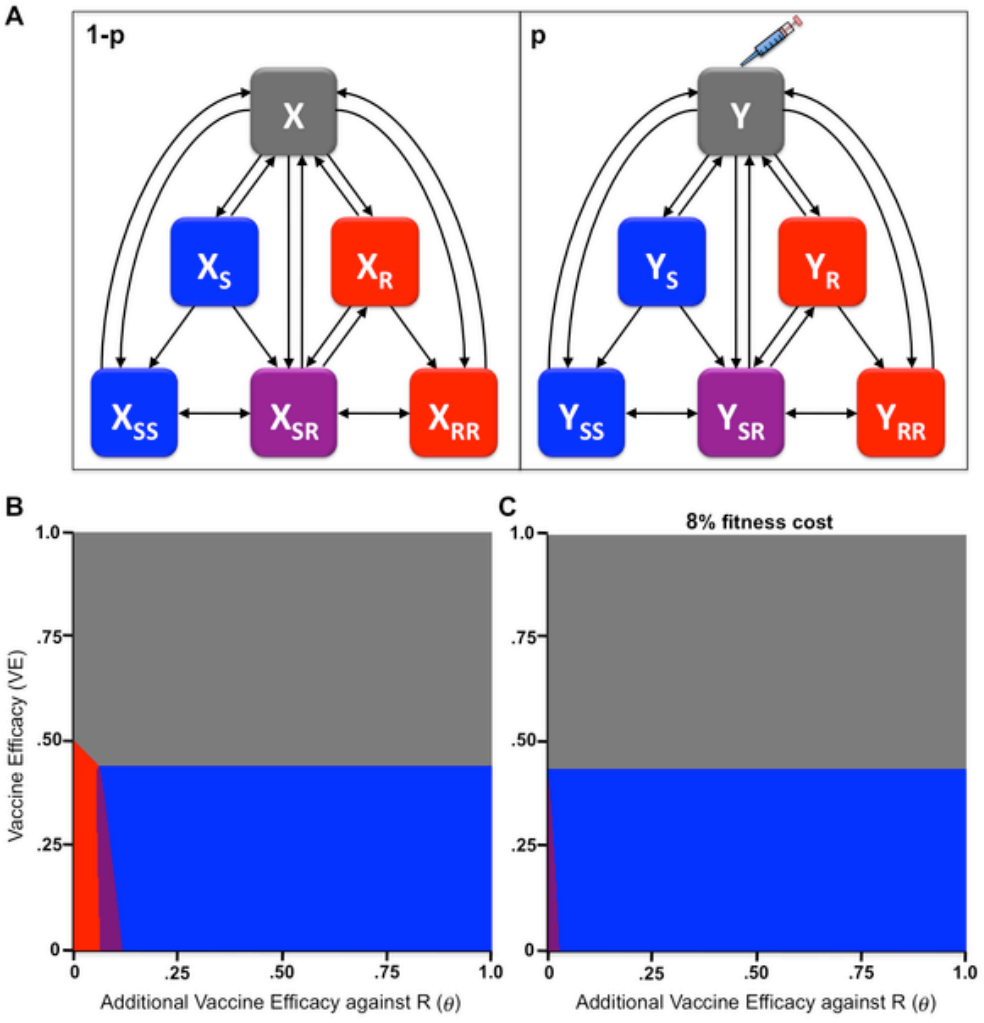
……A high incidence of pneumococcal infections is combined with a constantly growing antibiotic resistance of this pathogen. The growing resistance is thought to be associated with misuse of antibiotics and emerging of resistant clones that may spread throughout the entire population. Pneumococcal polysaccharide 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

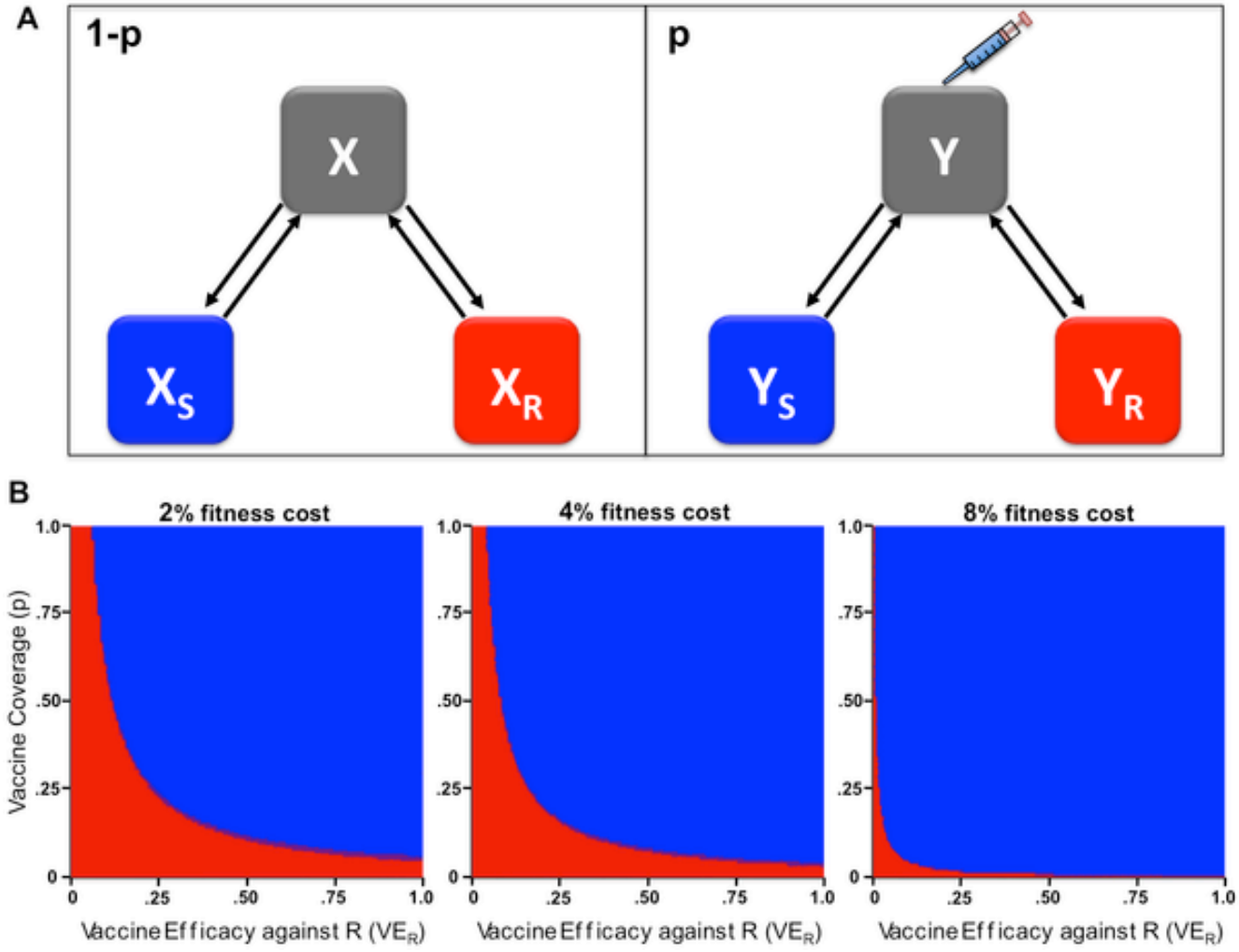
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0068940

Figure 1. Modeling a vaccine with increased efficacy against drug-resistance determinants for an endemic colonizing pathogen (*S. pneumoniae*).



Joice R, Lipsitch M (2013) Targeting Imperfect Vaccines against Drug-Resistance Determinants: A Strategy for Countering the Rise of Drug Resistance. PLoS ONE 8(7): e68940. doi:10.1371/journal.pone.0068940
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*).



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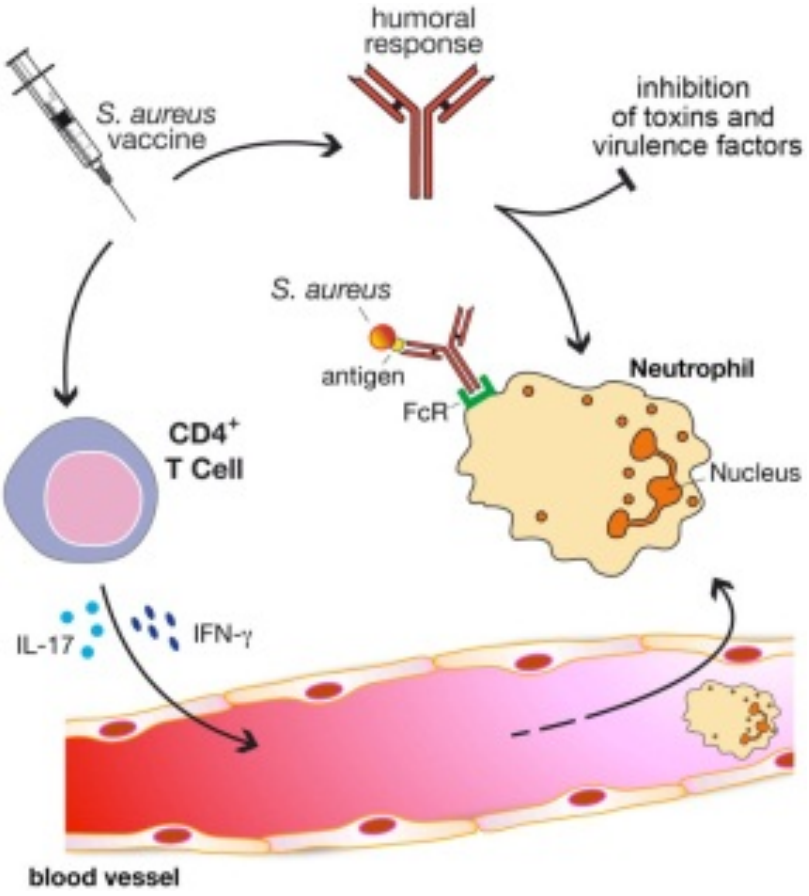
Bagnoli *et al*. Inferring reasons for the failure of *S. aureus* vaccines in clinical trials. Cell Infect Microbiol 2012

- 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