Upsala Journal of Medical Sciences

ISSN: 0300-9734 (Print) 2000-1967 (Online) Journal homepage: informahealthcare.com/journals/iups20

Bacterial vaccines and antibiotic resistance

Birgitta Henriques-Normark & Staffan Normark

To cite this article: Birgitta Henriques-Normark & Staffan Normark (2014) Bacterial vaccines and antibiotic resistance, Upsala Journal of Medical Sciences, 119:2, 205-208, DOI: 10.3109/03009734.2014.903324

To link to this article: https://doi.org/10.3109/03009734.2014.903324

Upsala Journal of Medical Sciences. 2014; 119: 205–208

informa
healthcare

REVIEW ARTICLE

Bacterial vaccines and antibiotic resistance

BIRGITTA HENRIQUES-NORMARK[1,2] & STAFFAN NORMARK[1,2]

[1]*Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, 171 77 Stockholm, Sweden, and* [2]*Karolinska University Hospital, 171 76 Stockholm, Sweden*

Abstract
Spread of antibiotic resistance is mediated by clonal lineages of bacteria that besides being resistant also possess other properties promoting their success. Some vaccines already in use, such as the pneumococcal conjugate vaccines, have had an effect on these successful clones, but at the same time have allowed for the expansion and resistance evolution of previously minor clones not covered by the vaccine. Since resistance frequently is horizontally transferred it will be difficult to generate a vaccine that covers all possible genetic lineages prone to develop resistance unless the vaccine target(s) is absolutely necessary for spread and/or disease development. Targeting the resistance mechanism itself by a vaccine is an interesting but hitherto unexplored approach.

Key words: β-*Lactamases, antibiotic resistance, bacterial vaccines, ESBL, Haemophilus influenzae, MRSA, Staphylococcus aureus, Streptococcus pneumoniae, transpeptidases*

Introduction

Vaccines and antibiotics have in the past been major contributors to preventing and treating community-acquired bacterial infections. In theory, a vaccine targeting most strains of a bacterial species is expected to eliminate also those that are resistant to antibiotics. Even though a vaccine may not cover all strains within a species, it has been thought that it can reduce the resistance burden by inducing protective immunity against the most prevailing resistant strains within the community. Antibiotic resistance is frequently spread in society by particular successful clonally related strains. Hence, it has even been proposed that a vaccine targeting a common antigen for such strains might be a valid approach to combat antibiotic resistance.

Effects of two bacterial vaccines included in the childhood vaccination program

The most globally used bacterial vaccines are those included in the national childhood vaccination programs. Currently, mainly two of the vaccines included target bacterial pathogens that also pose antibiotic resistance problems, namely *Haemophilus influenzae* and *Streptococcus pneumoniae* (pneumococci). Both these vaccines target a limited number of the different capsular structures or serotypes found on the surface of the bacteria, one of six in the case of *H. influenzae*, and 7, 10, or 13 out of the so-far described 93 capsular serotypes for pneumococci. To elicit a better immune response against the vaccines the capsules included have been coupled to proteins thereby evoking a T cell-dependent response in so-called conjugated vaccines. The *H. influenzae* type b (Hib) vaccine was introduced in the beginning of the 1990s and has been most successful in reducing severe infections such as epiglottitis and meningitis caused by this bacterium. The widespread adoption of Hib vaccines has resulted in the near complete disappearance of serious Hib infection in children, although it does not protect against *H. influenzae* isolates that possess one of the other types of capsule (a or c–f) or against non-typable

Correspondence: Birgitta Henriques-Normark, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, S-171 77 Stockholm, Sweden. E-mail: Birgitta.Henriques@ki.se

(Received 14 February 2014; accepted 6 March 2014)

ISSN 0300-9734 print/ISSN 2000-1967 online
DOI: 10.3109/03009734.2014.903324

isolates (NTHi). NTHi is a significant cause of otitis media, pneumonia, and bronchitis worldwide and has also been observed to cause invasive infections. It has been shown that an increase in invasive disease caused by Hie and Hif was caused by expansion of invasive strains belonging to single clones (1). These emerging non-vaccine clones have so far not been associated with β-lactam resistance. β-Lactam resistance in *H. influenzae* is caused by plasmid-mediated TEM-1 β-lactamase production. More recently, a large conjugative plasmid, recognized to be part of the *Haemophilus* integrating and conjugative elements (ICEs), correlated with resistance to ampicillin, chloramphenicol, and tetracycline (2).

Pneumococci are frequent causes of morbidity and mortality worldwide, causing local infections such as otitis media and sinusitis, but also severe infections such as pneumonia, sepsis, and meningitis. It is estimated that about 1 million children below the age of five die annually of pneumococcal infections. However, a large number of the elderly and those with underlying diseases also attract severe infections caused by this pathogen. The pneumococcal conjugate vaccines (PCVs) were introduced in the United States in the year 2000 and have since then been introduced in the national childhood vaccination programs in many countries worldwide. First the 7-valent (PCV-7) was used. This vaccine was exchanged to PCV-10 or PCV-13 from year 2010. Introduction of PCVs has led to a reduced incidence of severe invasive pneumococcal infections in vaccinated children and a herd immunity effect in other non-vaccinated age groups; however, an increase of non-vaccine type strains has also been noticed, affecting the success of the vaccines (3).

Both *S. pneumoniae* and *H. influenzae* are human adapted pathogens having their main habitat in the nasopharynx of preschool children. Up to 60%–70% of small children attending day care centers may be colonized with either or both bacteria without having a disease. It is among these colonized children that antibiotic-resistant strains establish themselves. The Hib vaccine has no effect on other *H. influenzae* types, leaving high carriage rates of *H. influenzae* also after Hib vaccine introduction. The effect on incidence of pneumococcal carriage of the PCVs differs between studies, but an increase of non-vaccine types in nasopharyngeal carriage has been observed (4).

Spread of successful bacterial clones carrying resistance determinants

S. pneumoniae is a genetically highly diverse species because of an efficient DNA-transformation system that promotes horizontal gene transfer. Pneumococcal strains of a given serotype may belong to a few but more often many clonal lineages. Likewise, a clonal lineage may just appear with one capsular serotype, but more often with many different serotypes. Molecular typing schemes reveal that the pneumococcal community consists of a number of clonal lineages, some of which are more prone to spread and colonize than others. Epidemiological studies have demonstrated that antibiotic resistance is spread globally by a limited number of particularly successful resistant pneumococcal clones. The best example comes from Iceland where penicillin-non-susceptible pneumococci (PNSP) were identified in 1988 followed by a rapid expansion caused by a single clone, Spain^{6B}-2, reaching its peak in 1993. This clone subsequently disappeared, but was followed by a large increase of PNSP of serotype 19F belonging to the international clone Taiwan^{19F}-14 (5).

It is not known what caused the decline of Spain^{6B}-2 and the subsequent expansion of Taiwan^{19F}-14. One possible explanation is an immune selection against the initial clone reducing its prevalence among healthy children and as a result a herd immunity effect in the population at large. Most likely, pneumococci establish a community where strains with different properties compete and collaborate to establish a given community structure. Elimination of a particularly successful clone may create ecological space for another clone, especially when facilitated by antibiotic selection.

It is not known what makes a pneumococcal clone prone to spread globally. The immune spectrum in the population is most certainly one factor, and the antibody response to one or more of the 93 different pneumococcal capsules could be one such factor. We noticed some years ago that up to 70% of PNSP strains in Sweden carried genes required to form adhesive pili (type 1 pili), a property that promotes colonization in the nasopharynx (6). Interestingly, several, but not all, of the globally spreading PNSP clones also express type 1 pili. These pili are also highly immunogenic, and they vary among different clones. It is interesting to note that the initial Spain^{6B}-2 clone on Iceland expresses type 1 pili of clade II, whereas its successor Taiwan^{19F}-14 expresses pili of clade I (7).

Of the 26 international PNSP strains deposited in the Pneumococcal Molecular Epidemiology Network collection (8), eight, eight, and three strains express serotypes not included in PCV-7, PCV-10, and PCV-13, respectively. Four of the 26 strains are of serotype 19A, only included in PCV-13. After the introduction of PCV-7 in the United States and in many other countries serotype 19A was shown to increase substantially, carrying reduced susceptibility

to penicillin (9). The recent expansion of serotype 19A in Italy, for example, was caused by a clonal lineage expressing type 1 pili, suggesting that its success was not only favored by being antibiotic-resistant, but also by other bacterial factors such as the presence of pili (10).

Since PCV-13 also provides protection against serotype 19A it has been thought that its recent introduction into the childhood vaccination program may reduce the incidence of resistance within a vaccinated community in a more significant way. However, no reports are available on whether or not this will be the outcome. Many clonal lineages of pneumococci associated with antibiotic resistance may express capsules of different serotypes, some of which are not covered by PCV-13. In Sweden, the piliated clonal lineage CC156 (with MLST) expressing serotypes 9V, 14, and 19F has been the dominating lineage among penicillin non-susceptible pneumococci (6). By the elimination of serotypes 9V, 14, and 19F in the PCV-vaccinated population, also this resistant lineage will be severely hit. However, even before vaccine introduction strains of clonal lineage 156 were found to express other serotypes not covered even by PCV-13. Already after a few years in the post-vaccination era, some of these serotypes have been found to expand in Sweden and elsewhere, which most certainly will have a negative effect on resistance development. However, these emerging pneumococcal strains with reduced susceptibility to antibiotics, expressing unusual capsular structures, might be less capable of causing invasive disease, at least among healthy children. This in turn could have a beneficial effect on the disease burden.

Bacterial virulence properties such as pili constitute potential vaccine candidates

Since PNSP clones frequently express type 1 pili, a pilus-based vaccine has been considered. Pneumococcal pili are composed of three subunit proteins, and immunization using recombinant subunits has been shown to generate protection in mouse models. In particular, a fusion protein containing the three major pili variants elicited antibodies against proteins from the three clades and protected mice challenged with piliated pneumococcal strains. The antiserum generated mediated complement-dependent opsonophagocytosis of piliated strains (11). However, as typically only 30% of pneumococcal strains are piliated, there have been no further attempts to develop this pneumococcal pilus vaccine. Also, following PCV-7 introduction in the US the prevalence of type 1 pili declined dramatically. However, more recently there has been a significant increase of type 1 piliated pneumococci, and the prevalence post-vaccination is now as high as before vaccine introduction, suggesting that type 1 piliated clones contribute to stabilize the new pneumococcal community that eventually becomes established after vaccine introduction. An interesting question is therefore if a combined type 1 pilus and PCV vaccine would hamper the re-establishment of a successful pneumococcal community in the nasopharynx of vaccinated preschool children, thereby reducing the carriage rates, for example.

Vaccine development against MRSA is a challenge

There are bacterial pathogens that are less genetically diverse as compared with pneumococci, providing more stable genetic lineages where vaccination directed towards particularly successful clones might be a valid approach. One example is methicillin-resistant clones of *Staphylococcus aureus* that cause community-acquired staphylococcal infections (CA-MRSA), such as the USA300 clone prevalent in the US. However, in Asia as well as in Europe CA-MRSA strains are more heterogeneous clonally than in the US, making a vaccine approach unlikely to succeed. MRSA strains are equipped with an arsenal of properties that contribute to their propensity to cause disease. One example is the staphylococcal α-hemolysin, which has been demonstrated to be an important disease factor. Immunization with a non-toxic version of this protein provided protection against MRSA-induced murine pneumonia (12). However, despite extensive efforts it has turned out to be extremely difficult to develop a staphylococcal vaccine.

Vaccination against β-lactamases and transpeptidases in β-lactam-resistant bacteria

Gram-negative bacteria able to hydrolyze the majority of β-lactams constitute the most important and pressing resistance problem in the world. Three major groups of these enzymes are usually distinguished: class C cephalosporinases (AmpC), extended-spectrum β-lactamases (ESBLs), and different types of β-lactamases with carbapenemase activity, of which the so-called class B metallo-β-lactamases (MBLs) are of the greatest concern. These enzymes are frequently encoded by transmissible plasmids and hence can be found in a number of different enterobacteria. Even though epidemic clones have been identified expressing these enzymes, a vaccine targeting common antigens among such strains will not be feasible. β-Lactamases are normally produced in the periplasm of Gram-negative bacteria but can be released extracellularly packed within outer membrane

vesicles to induce anti-β-lactamase IgG. It has been demonstrated that cystic fibrosis patients harboring *Pseudomonas aeruginosa* overproducing chromosomal AmpC β-lactamase elicit anti-AmpC IgG. In a rat model of chronic lung infection AmpC antibodies elicited by vaccination with purified enzyme resulted in a significantly lower bacterial load and better lung pathology compared with non-immunized rats or rats without neutralizing antibodies after ceftazidime treatment (13). However, a recent paper demonstrated that β-lactamase within *Moraxella catarrhalis* outer membrane vesicles is protected against neutralization by β-lactamase antibodies (14).

Methicillin-resistant *Staphylococcus aureus* (MRSA) are resistant to β-lactam antibiotics due to the production of an additional penicillin-binding protein encoded by the *mecA* gene. The transpeptidation domain of *mecA* was used as a DNA vaccine in a murine model and shown to elicit a specific immune response as well as a protective effect against an intraperitoneal challenge with MRSA bacteria (15).

Conclusions

Bacterial vaccines protect against susceptible and resistant strains alike. Due to the clonal spread of resistant strains a vaccine approach targeting one or more antigens expressed by such clones might be a valid approach to combat resistance, but is hampered by the genetic promiscuity of resistance genes that easily become transferred into new successful clonal lineages. Vaccination directed against the resistance mechanism itself can in a few cases be a possibility when resistance is mediated by an accessible enzyme whose activity can be inhibited by neutralizing antibodies.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Ladhani SN, Collins S, Vickers A, Litt DJ, Crawford C, Ramsay ME, et al. Invasive Haemophilus influenzae serotype e and f disease, England and Wales. Emerg Infect Dis. 2012; 18:725–32.
2. Harrison OB, Brueggemann AB, Caugant DA, van der Ende A, Frosch M, Gray S, et al. Molecular typing methods for outbreak detection and surveillance of invasive disease caused by Neisseria meningitidis, Haemophilus influenzae and Streptococcus pneumoniae, a review. Microbiology. 2011;157:2181–95.
3. Pittet LF, Posfay-Barbe KM. Pneumococcal vaccines for children: a global public health priority. Clin Microbiol Infect. 2012;18:25–36.
4. Collins DA, Hoskins A, Bowman J, Jones J, Stemberger NA, Richmond PC, et al. High nasopharyngeal carriage of non-vaccine serotypes in Western Australian aboriginal people following 10 years of pneumococcal conjugate vaccination. PLoS One. 2013;8:e82280.
5. Hjalmarsdottir MA, Kristinsson KG. Epidemiology of penicillin-non-susceptible pneumococci in Iceland, 1995-2010. J Antimicrob Chemother. 2013. [Epub ahead of print].
6. Sjostrom K, Blomberg C, Fernebro J, Dagerhamn J, Morfeldt E, Barocchi MA, et al. Clonal success of piliated penicillin nonsusceptible pneumococci. Proc Natl Acad Sci USA. 2007;104:12907–12.
7. Moschioni M, Donati C, Muzzi A, Masignani V, Censini S, Hanage WP, et al. Streptococcus pneumoniae contains 3 rlrA pilus variants that are clonally related. J Infect Dis. 2008;197:888–96.
8. McGee L, McDougal L, Zhou J, Spratt BG, Tenover FC, George R, et al. Nomenclature of major antimicrobial-resistant clones of Streptococcus pneumoniae defined by the pneumococcal molecular epidemiology network. J Clin Microbiol. 2001;39:2565–71.
9. McEllistrem MC, Adams JM, Patel K, Mendelsohn AB, Kaplan SL, Bradley JS, et al. Acute otitis media due to penicillin-nonsusceptible Streptococcus pneumoniae before and after the introduction of the pneumococcal conjugate vaccine. Clin Infect Dis. 2005;40:1738–44.
10. Del Grosso M, Camilli R, D'Ambrosio F, Petrucci G, Melchiorre S, Moschioni M, et al. Increase of pneumococcal serotype 19A in Italy is due to expansion of the piliated clone ST416/CC199. J Med Microbiol. 2013;62:1220–5.
11. Harfouche C, Filippini S, Gianfaldoni C, Ruggiero P, Moschioni M, Maccari S, et al. RrgB321, a fusion protein of the three variants of the pneumococcal pilus backbone RrgB, is protective in vivo and elicits opsonic antibodies. Infect Immun. 2012;80:451–60.
12. Bubeck Wardenburg J, Schneewind O. Vaccine protection against Staphylococcus aureus pneumonia. J Exp Med. 2008; 205:287–94.
13. Ciofu O, Bagge N, Hoiby N. Antibodies against beta-lactamase can improve ceftazidime treatment of lung infection with beta-lactam-resistant Pseudomonas aeruginosa in a rat model of chronic lung infection. APMIS. 2002;110: 881–91.
14. Schaar V, Uddback I, Nordstrom T, Riesbeck K. Group A streptococci are protected from amoxicillin-mediated killing by vesicles containing beta-lactamase derived from Haemophilus influenzae. J Antimicrob Chemother. 2014; 69:117–20.
15. Senna JP, Roth DM, Oliveira JS, Machado DC, Santos DS. Protective immune response against methicillin resistant Staphylococcus aureus in a murine model using a DNA vaccine approach. Vaccine. 2003;21:2661–6.