



## POLICY RESPONSES TO THE GROWING THREAT OF ANTIBIOTIC RESISTANCE

POLICY BRIEF 7

MARCH 2009

### A Shot Against MRSA?

Every year in the United States, 2 million people become infected with *Staphylococcus aureus* bacteria—"staph"—and 100,000 of those people die. Skin infections are most common, but staph infections of the lung (pneumonia) and bloodstream (bacteremia) are the deadliest. A vaccine would save lives and money, reduce the use of antibiotics, and slow the spread of antibiotic resistance. That is, *if* a vaccine is targeted to people when their risk of becoming infected with staph is highest—when they go to the hospital for surgery or some other invasive procedure. That's because the science suggests that even the most successful vaccine is going to provide immunity for just a limited time.

But we are still far from being able to vaccinate against staph.

Scientific challenges and a lack of attention and priority have slowed the pace of staph vaccine development. If successful, a vaccine to prevent staph infection or its lethal effects would not have to be specially targeted to prevent the antibiotic-resistant forms of staph (collectively known as "MRSA") because vaccine targets could be independent of elements responsible for antibiotic resistance. But developing a vaccine that could prevent several strains is going to require biological finesse. This seemed less important when a variety of antibiotics could cure any staph infection<sup>1</sup> but the increasing prevalence and number of types of MRSA changes the equation. The scientific challenges are daunting but today's genetic and biochemical tools are up to the task. This dragon's scales will only fall faster if the development of a staph vaccine—and more generally—staph infection and MRSA— is made a higher priority by our nation's health leaders.

Staph vaccines (that also prevent MRSA) could be very cost-effective, at least for healthcare-associated infections, if not for those transmitted in the community. Savings include prolonging antibiotic effectiveness and reducing hospital infection control costs.

#### A Brief History of Staph Vaccine Development

Since the 1960s, various scientists and companies have tried to develop a staph vaccine with varying, but never complete, success.

---

<sup>1</sup> The need for new antibiotics is constantly ratcheting up and the pipeline is underpopulated and slow. See our May 2008 brief on the antibiotic pipeline for more details.

These have included:

- Live and inactivated whole bacteria
- Partial bacteria, such as pieces of the cell wall
- Chemically inactivated bacterial toxins
- Proteins from bacteria cell walls
- Various combinations of these strategies<sup>3</sup>

Many staph vaccines have been tested in animals, and a few have shown promise in early testing in human beings. None, however, has proven safe and effective for large-scale use.

### **Current Efforts: Three Approaches**

One caveat: reports on any type of enterprise that goes on in private industry—especially a highly competitive one like the pharmaceutical industry—are going to be incomplete. Staph vaccine development is one of these areas. We know there's more going on, but we don't know exactly what or how promising different approaches might be. The three efforts described here should, therefore, be taken as examples, but not the whole universe.

Intercell in conjunction with Merck and Co., Vaccine Research International (VRi), and Nabi Biopharmaceuticals, all have vaccines of very different types under development. These three vaccines have made it into clinical testing—testing in people—with different degrees of clinical and business success.

#### Intercell and Merck

Intercell, a small biotech company, based its vaccine candidate on a bacterial antigen (protein) common to almost all types of staph. If successful, a vaccine based on this antigen could prevent infection from a wide variety of staph strains. Intercell licensed the antigen to Merck in 2004 for development, testing and marketing. Merck's entry increases the resources available for the project. Since the partnership began, Merck has completed successful early clinical trials (Phases 1 and 2) in human beings. The company expects to begin Phase 3 trials in 2009 to evaluate the vaccine's safety and effectiveness in a larger population.

#### VRi

In 2006, VRi, a small British biotech company, completed the successful phase 1 testing of its staph vaccine, SA75. SA75 uses whole staph bacterial cells inactivated by treatment with chloroform. The vaccine was safe and provoked an immune response in the trial subjects, but whether that immune response protects against infection is still to be determined in later trials. Since 2006, however, the project has been stalled for lack of funding to conduct the next phase of testing. Scientists at VRi, however, have continued discussing the future of SA75. After discussion with the Medicines and Healthcare products Regulatory Agency, a regulatory agency in the UK, VRi has planned further tests of the SA75 vaccine, should funding become available

### *Nabi*

The Nabi story is one of ups and downs. The first version of Nabi's StaphVax consisted of antigens from the two most common staph capsules (types 5 and 8) and an antigen from the cell wall (type 336). As with Intercell and VRi, the first results with Nabi's staph vaccine were positive. In Phase 1 and 2 trials in humans, the vaccine was safe and effective, and Nabi invested significant money and resources to continue testing. If the vaccine tested positive in Phase 3 trials, it would be ready for submission to FDA for approval. Disappointingly, however, Nabi announced in 2005 that the vaccine failed the Phase 3 clinical trials. This setback led Nabi to temporarily halt further work on StaphVax, but the company resumed development in 2006, using lessons learned from the StaphVax failure to begin development of a new, modified vaccine called PentaStaph.

PentaStaph is a variation on the original StaphVax formula, adding two "virulence factors" associated with MRSA, Panton-Valentine Leukocidin (PVL) and alpha toxin. Nabi hopes to begin Phase 1 testing of PentaStaph in 2009,<sup>7,8</sup> in part, through a Cooperative Research and Development Agreement with the Uniformed Services University of the Health Sciences (USUHS).<sup>11</sup>

### **New Findings**

Last year for the first time, a vaccine protected mice against staph pneumonia.<sup>12</sup> What's encouraging about this result is that the trial followed findings from basic research implicating a particular toxin— $\alpha$ -hemolysin (Hla)—in virulent staph pneumonia in human beings. The vaccine induced antibody protection against Hla specifically, and it worked. The mice did not get sick even when they were given a dose of bacteria that sickened unprotected mice. And in a related experiment, antibodies to the vaccine form of Hla, made by other animals, were transfused into mice who were then given an infective dose of staph bacteria. They also were protected. Finally, these preformed antibodies protected human lung cells in culture from the destruction that staph would have caused. Maybe this is the basis of the vaccine we've been waiting for, at least for pneumonia. And it opens the door to both "active" immunization—people making antibodies in response to a vaccine—and "passive" immunization—giving people preformed antibodies to quickly fight off an infection. The work to develop these approaches is moving ahead but it may still be some years before products are ready to try in people.

### **Conclusion**

After decades lingering in a backwater of vaccine research, it is time for the MRSA/staph vaccine to receive serious consideration. Unlike HIV/ AIDS, Malaria, and Tuberculosis, there has never been an international or domestic program of any size to address staph—either for new treatments or a vaccine. The U.S. spent a total of about \$800 million last year on development of an HIV vaccine. This is equivalent to the country's spending for **all antimicrobial research** (a small fraction of which is related to vaccine development).<sup>13</sup> Keep in mind CDC estimates, which put the number of people dying with MRSA, 19,000, above the number dying of AIDS each year. Current U.S. investment is not commensurate with the potential benefits of a MRSA vaccine. That said, increased investment in a vaccine should be part of a comprehensive approach to controlling this infection. Staph vaccine development does not alleviate the immediate need for improved hospital infection control, but it does hold promise for getting to the root of the problem—potentially saving lives and significant costs down the road.

## References

1. Klein, E., D.L. Smith, and R. Laxminarayan, *Hospitalizations and deaths caused by methicillin-resistant Staphylococcus aureus, United States, 1999-2005*. Emerging Infectious Diseases, 2007. 13(12): p. 1840-6.
2. Afshan's vaccine table
3. Skinner, G.R.B. and A. Ahmad, *Staphylococcal Vaccines – Present Status and Future Prospects*. Zbl Bakt, 1994. 26: p. 537-50.
4. *S. aureus*. Available from: <http://www.intercell.com/SelectMenu.wa?seIDM=4839D319-387F-4598-A8F6-FE1A6B497973>.
5. Communication with John Shiver, Merck and Co.
6. Communication with Afshan Ahmad, Vaccine Research International
7. *Nabi Biopharmaceuticals Announces Completion of Outside Advisory Panel Assessment of Gram-Positive Program*. 2006. Available from: <http://phx.corporate-ir.net/phoenix.zhtml?c=100445&p=irol-newsArticle&ID=834257&highlight=>.
8. Communication with Greg Gries, Nabi Biopharmaceuticals
9. Lindsay, J.A. *Prospects for a MRSA vaccine*. Future Microbiology, 2007. 2: p. 1-3.
10. (2000) *Staph vaccine appears to be effective in stopping infections*. CNN.com. Available from: <http://archives.cnn.com/2000/HEALTH/09/20/staph.vaccine.ap/index.html>.
11. Globe Newswire. *Nabi Biopharmaceuticals enters clinical trial initiative with US military to advance PentaStaph (tm)*. Available from: <http://www.globenewswire.com/newsroom/news.html?d=156469>
12. Wardenberg, J.B. , and O. Schneewind. *Vaccine protection against Staphylococcus aureus pneumonia*. Journal of Experimental Medicine, 2008. 205(2): 287-294.
13. Peters, N.K., et al. *The Research Agenda of the National Institute of Allergy and Infectious Diseases for Antimicrobial Resistance*. The Journal of Infectious Diseases 2008 197:8, 1087-1093.
14. Klevins R.M., et al. *Invasive Methicillin-Resistant Staphylococcus aureus Infections in the United States*. JAMA, October 17, 2007; Vol 298, No. 15.