A Call for Greater Consideration for the Role of Vaccines in National Strategies to Combat Antibiotic-Resistant Bacteria: Recommendations from the National Vaccine Advisory Committee

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National Vaccine Advisory Committee

The emergence of a novel virus receives widespread attention in the news media and among the public. However, the greatest threat to public health in the United States is unlikely to be an exotic disease but, rather, the mounting threat of antibiotic resistance in commonly acquired bacterial infections. The human and economic costs of this growing crisis are notable.[1,2] In the 2013 report by the Centers for Disease Control and Prevention (CDC), *Antibiotic Resistance Threats in the United States*, it is estimated that more than two million people contract an antibiotic-resistant infection each year in the United States, and approximately 23,000 die as a result of their infection.[2] The escalating rate of resistance among bacterial pathogens is being facilitated by the abundant (and often inappropriate) use of antibiotics, and concern is rising that the arsenal of effective products to treat bacterial infections will soon run out.[3] For example, it is now estimated that 6,700 (13%) of the 51,000 health-care–associated *Pseudomonas aeruginosa* infections that occur in the United States each year are resistant to at least three classes of antibiotics, and some strains show resistance to nearly all classes of antibiotics.[2] The lack of effective antibiotic therapy will have a significant impact in nearly all areas of medicine, but especially in surgery, oncology, intensive care, and transplant medicine.

In September 2014, the White House released the President's National Strategy to Combat Antibiotic-Resistant Bacteria[4] concurrently with the President's Council of Advisors on Science and Technology (PCAST) report and recommendations to the president on combating antibiotic resistance.[5] Together, these reports identify priorities and guide coordination across U.S. government agencies to (*1*) better prevent and respond to the spread of antibiotic resistance through improved prevention and stewardship of antibiotic use; (*2*) increase surveillance of emerging antibiotic resistance in humans, animals, and the environment; (*3*) improve capabilities for detection and diagnostics; (*4*) accelerate development of new products, including new classes of antibiotics, therapeutics, and vaccines; and (*5*) enhance international collaboration.[4] The federal commitment to addressing this issue was further emphasized by Presidential Executive Order 13676,[6] which calls for the development of a five-year National Action Plan[7] that proposes concrete activities and milestones for achieving the goals outlined in the National Strategy and a presidential budget request to Congress for $1.2 billion.[8]

PREVENTING INFECTIONS AND THE SPREAD OF ANTIBIOTIC RESISTANCE

Highlighting the role of vaccines and prevention in antibiotic stewardship

The PCAST report, the National Strategy, and the National Action Plan strongly emphasize that practical and measurable actions can and should be accomplished toward the goals of improved antibiotic stewardship and the development of new products to treat antibiotic-resistant infections. We particularly welcome Objective 4.3 of the National Action Plan,[7] which would intensify research and development into new human vaccines to prevent infections, thereby reducing the development of bacterial resistance and the general overuse of antibiotics.

However, although vaccines are mentioned as one component of the overall cadre of new products needed to combat emerging antibiotic resistance in human medicine, their potential to significantly reduce antibiotic use and thereby contribute to the overarching goal of "increasing the longevity of current antibiotics

by improving the appropriate use of existing antibiotics, preventing the spread of antibiotic-resistant bacteria, and scaling up proven interventions to decrease the rate at which microbes develop resistance to current antibiotics"[5] is underrepresented. For example, Objective 1.1 of the National Action Plan[7] aims to "implement public health programs and reporting polices that advance antibiotic-resistance prevention and foster antibiotic stewardship in health-care settings and the community," but none of the milestones includes considerations for increasing vaccine uptake.

To address this apparent gap, the examples provided hereinafter are intended to emphasize the critical contribution vaccines can continue to play to combat antibiotic resistance through prevention of infections and reduced transmission of antibiotic-resistant strains.

Haemophilus influenzae type b (Hib) conjugate vaccines

Haemophilus influenzae serotype b disease can result in ear infections and invasive infections such as meningitis, blood stream infections, epiglottitis, pneumonia, and bone or joint infections. Prior to the introduction of Hib vaccines in the late 1980's, an estimated 20,000 cases of invasive bacterial disease occurred annually in U.S. children aged ≤5 years.[9] Most of these cases were of meningitis occurring in children younger than 18 months of age.[10] Notably, the percentage of ampicillin-resistant Hib isolates rose to 22% during the late 1970s and early 1980s in some locales, making treatment of invasive Hib infections more challenging as drug-resistant infections became more prevalent.[11] Fortunately, the widespread use of Hib vaccines among young children resulted in more than a 99% decline in the incidence of invasive Hib disease.[9] The Healthy People 2020 goals have been exceeded; only 30 cases of invasive Hib were reported in 2012 among children aged ≤5 years.[12,13] Moreover, the conjugate Hib vaccines have been demonstrated to reduce bacterial carriage in both vaccinated and unvaccinated individuals.[14] This reduction has resulted in lower levels of transmission and fewer infections, thereby decreasing the need for antibiotics and the number of opportunities for antibiotic-resistant strains to spread.

Pneumococcal conjugate vaccines

Pneumococcal disease includes pneumonia, meningitis, invasive disease, ear infections, and sinus infections. Every year, roughly 1.2 million illnesses and 7,000 deaths are due to drug-resistant *Streptococcus pneumoniae*.[2] The first conjugate pneumococcal vaccine (PCV-7) was licensed for use in 2000 and included seven prominent serotypes, five of which accounted for 78% of penicillin-nonsusceptible invasive infections in 1998.[15] Within four years of its licensure, PCV-7 contributed to an overall 57% drop in the incidence of multidrug-nonsusceptible strains, with an 84% decrease in the rate of multidrug-nonsusceptible invasive pneumococcal disease (IPD) in children younger than 2 years of age and a 49% decrease in penicillin-nonsusceptible IPD in adults aged ≥65 years attributable to reduced transmission by children.[16] Moreover, several studies indicated that use of the conjugate pneumococcal vaccines were associated with decreased use of antibiotics among young children because of a decreased incidence of IPD and ear infections.[17–19]

On the basis of findings from a 2003 study, the authors predicted that use of PCV-7 could potentially prevent 1.4 million antibiotic prescriptions annually in the United States.[20] In 2010, a 13-valent conjugate vaccine (PCV-13) was licensed for use in the United States; it comprises six additional serotypes, including penicillin-nonsusceptible serotype 19A, which had been increasing in incidence after introduction of PCV-7.[21] Within three years, the number of cases of antibiotic-resistant IPD declined significantly among children younger than five years of age (78%–96% decline) and adults (50%–62% decline).[22]

The aforementioned benefits are directly due to the success of the pneumococcal conjugate vaccines administered to children, with indirect benefits among adults due to reduced transmission by children. However, data from CDC's Active Bacterial Core Surveillance (ABCs) system and elsewhere estimated that 20% to 25% of IPD cases[23] and 10% of community-acquired pneumonia[24] that occurred in adults aged ≥65 years might have been prevented by greater use of the PCV-13 vaccine among adults ≥65 years of age.[23,24] In 2014, the Advisory Committee on Immunization Practices recommended that all adults ≥65 years of age receive a single dose of PCV-13 in addition to the previously recommended 23-valent polysaccharide pneumococcal vaccine.[23] Combined with prudent use of antibiotics, the increased uptake of the PCV-13 vaccine among adults is predicted to significantly reduce transmission of pneumococcus and thereby slow the spread of antibiotic-resistant infections.

Influenza vaccines

Broad-spectrum antibiotics are often prescribed to treat acute respiratory tract infections, although most of these infections are caused by viral infections such as influenza. For example, in one 2011 study, the authors found that inappropriate prescribing of antibiotics for influenza infection occurred in 79% of 58,477 influenza patients.[25] Secondary bacterial infections requiring antibiotic treatment can follow influenza infection because of damage to the respiratory

epithelium by influenza viruses (and other respiratory viruses) and other host and pathogen factors.[26] Some of these bacterial pathogens, such as pneumococcus and *Staphylococcus aureus* (*S. aureus*), can be antibiotic-resistant organisms. Influenza infections occur in 5% to 20% of the population, and more than 200,000 people are hospitalized because of influenza-related complications each year. Despite the widespread risk of influenza infection, coverage estimates from the 2013–2014 influenza season indicate that only 46.2% of all people aged ≥6 months in the United States received an influenza vaccine.[27] In one Canadian study, influenza-associated antibiotic prescriptions decreased 64% after implementation of a universal influenza immunization program.[28] Greater efforts to increase influenza vaccination coverage in the United States among all age groups are also likely to result in fewer influenza infections and fewer antibiotic prescriptions.

THE POTENTIAL OF NEW VACCINES TO TARGET BACTERIAL PATHOGENS

Vaccines will not be a practical or feasible solution for all antibiotic-resistant bacteria. Important scientific challenges unique to many of these organisms make alternative approaches to vaccination more desirable. Nonetheless, supporting the development of vaccines against some of these pathogens can substantially decrease the burden of resistant infections. For some infections, vaccines represent the most logical strategy for protecting high-risk patients who are repeatedly exposed to resistant bacterial pathogens because of frequent interactions with the health-care system and nonmodifiable host factors. When a high burden of disease for the general population exists, an effective vaccine will include protection against resistant strains of the bacterium. We provide two examples of relevant pathogens with vaccines in development.

Methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) causes more than 80,000 invasive infections and 11,000 deaths each year.[2] Although significant decreases in health-care–associated (HA)-MRSA have been reported in the past few years, MRSA infections, particularly community-associated MRSA (CA-MRSA), remain a concern.[29,30] Unlike HA-MRSA infections, CA-MRSA strains commonly infect young, previously healthy patients, causing skin and soft-tissue infections and invasive disease. In 2012, 20% of all reported invasive MRSA infections were attributed to CA-MRSA.[31] In addition, HA-MRSA strains are frequently isolated in community settings, and some researchers have argued that vaccination of a wider population, and not just high-risk individuals, should be considered to protect more broadly against *S. aureus* infections.[32,33] Although progress on an effective vaccine against *S. aureus* has been slow, successful development of a vaccine is an important public health objective.

Clostridium difficile

Clostridium difficile (*C. difficile*) is the leading cause of health-care–associated infectious diarrhea in the United States, resulting in approximately 500,000 infections and 29,000 deaths each year.[34] *C. difficile* infections are directly associated with prolonged antibiotic use that destroys healthy intestinal microflora, creating an ecological niche that favors *C. difficile* colonization.[35] Compounding this problem, hyper-virulent *C. difficile* strains have emerged during the past 15 years, leading to an increase in severe disease outcomes and in community-acquired infections in previously low-risk individuals, such as children, peripartum women, and health-care workers.[35–38]

Despite rigorous infection-control practices in health-care settings, these infections are often difficult to treat, and persistent or recurrent infections are common. Vaccination against *C. difficile* is favored not only because it provides a mechanism to prevent infection, but also because of its potential to strengthen the immune response without further disrupting the host's normal intestinal microflora in patients with recurrent and persistent infections.[38,39] Importantly, economic modeling suggests that *C. difficile* vaccines would be cost-effective, and in most scenarios, they would be cost saving across a wide range of variables (e.g., disease risk, vaccine efficacies, vaccine costs) because of the burden of *C. difficile* infections on the health-care system—currently estimated to be $1 billion to $3 billion per year.[40–42]

ECONOMIC INCENTIVES SUPPORTING ACCELERATED RESEARCH AND DEVELOPMENT FOR NEW VACCINES—WHAT WORKS AND WHAT DOESN'T

The challenges to antibiotic development have been studied and are well understood. PCAST's 2014 report on antibiotic resistance outlines a series of push-and-pull economic incentive mechanisms that may motivate industry to pursue research and development programs for antibiotics.[5] The Assistant Secretary for Planning and Evaluation (ASPE) published a framework in 2014 for analyzing the impact of various incentives on antibiotic development.[43] However, although some similar basic economic principles may apply to both antibiotics and vaccines, significant differences between vaccines and antibiotics warrant different examinations

of incentive approaches. One difference is that the share of the global pharmaceutical market attributable to vaccines is small (3% in 2010).[44] Also, traditionally vaccines are sold at a lower cost than are many therapeutic drugs, and pharmaceutical companies may not be able to justify the research and development costs for vaccines used to prevent diseases that are less prevalent and have a smaller market. Low-cost vaccines, such as those for pertussis and influenza, can also serve as a disincentive for developing improved vaccines that would be considerably more costly to develop than the vaccines already on the market. The analyses of PCAST and ASPE are important for developing research and policy agendas for antibiotic development. Likewise, it would be advantageous to have this kind of careful study of the challenges of developing and deploying vaccines to combat antibiotic resistance. Further, the National Action Plan indicates that the Combating Antibiotic Resistant Bacteria (CARB) Economic Incentives Working Group will release a separate analysis of potential economic incentives to ensure a "diverse and robust pipeline of antibiotics." We propose that a working group also evaluate the use of incentives to accelerate vaccine development as part of a comprehensive approach to mitigating antibiotic resistance.

The CARB Economics Incentives Working Group should evaluate vaccine development for vaccines most likely to enhance antibiotic sustainability and reduce the prevalence of antibiotic-resistant bacteria. This evaluation would include both vaccines to prevent bacterial infections, such as an *S. aureus* vaccine, and vaccines whose indirect effect would be to reduce the use of antibiotics, such as an improved influenza vaccine and a respiratory syncytial virus vaccine. The PCAST report and the National Action Plan both propose policies that would change the way antibiotics are evaluated and approved by the U.S. Food and Drug Administration (FDA). Unlike antibiotics, vaccines are administered preventatively, and the use of vaccines is usually not restricted to a limited population of high-risk individuals. Thus, there are different considerations for development and use. FDA's existing expedited regulatory pathways for clinical development and licensure should be used, taking into account the different market forces, to address challenges with vaccine innovation and to identify potential policy solutions to those challenges.

RECOMMENDATIONS

In full support of the strategies and objectives outlined in the President's National Strategy and National Action Plan to Combat Antibiotic-Resistant Bacteria, and in recognition of the further impact vaccines could make in long-term strategies to reduce overall antibiotic use and prevent the transmission and/or circulation of antibiotic-resistant infections, the National Vaccine Advisory Committee (NVAC) makes the following recommendations.

Recommendation 1
NVAC recommends that the Assistant Secretary for Health (ASH), as the Director of the National Vaccine Program, work with agencies of the U.S. Department of Health and Human Services (HHS) and other federal and nonfederal partners to develop a stakeholder engagement plan to ensure that both vaccine and immunization stakeholders, as well as antibiotic stewardship stakeholder efforts, include information on the role of existing vaccines in minimizing antibiotic use. These communication efforts should include information on vaccines against bacterial pathogens that may currently be or may potentially become antibiotic resistant, and viral vaccines that, by preventing viral illnesses, decrease the inappropriate use of antibiotics for viral infections as well as decrease bacterial superinfections leading to needs for antibiotics.

Recommendation 1.1
These efforts should include a comprehensive analysis modeling the reduction in disease burden due to antibiotic-resistant bacterial strains, the potential reduction in antibiotic prescribing and health-care encounters, and the anticipated cost savings to the health-care system expected from increased uptake of recommended vaccines in all age groups. Vaccines under development may also be included to support those vaccine development efforts.

Recommendation 1.2
These efforts should also tie into surveillance efforts to determine the effects that vaccine uptake has produced on minimizing disease burden due to antibiotic resistant strains in all age groups, and on the ecology of infections caused by both vaccine and non-vaccine strains. When possible, surveillance efforts also should inform on the effects that vaccine uptake, and the reduction in disease caused by vaccine, has had on the prevalence of antibiotic-resistant strains.

Recommendation 2
The NVAC strongly recommends that the ASH ensure NVAC remains regularly informed of efforts to address antibiotic resistance by revising the NVAC charter to include a liaison representative from the President's Advisory Council on Combating Antibiotic Resistant

Bacteria on the NVAC. The NVAC also encourages the ASH to support the future inclusion of an NVAC representative on the President's Advisory Council on Combating Antibiotic Resistant Bacteria to provide knowledge of vaccines and the immunization system to their discussions. Cross-representation on committees maximizes the use of subject matter expertise and stakeholder input to better harmonize departmental efforts.

Recommendation 3
The NVAC strongly encourages the ASH to communicate to the HHS Secretary and the CARB Economic Incentives Working Group that incentives proposed to stimulate antibiotic development must also be evaluated for their utility to accelerate the development of vaccines and other novel prevention strategies. Proposed incentives must be flexible enough to apply to a range of diverse technologies to ensure that we continue to move toward long-term solutions to antibiotic resistance. When incentives are not found to be cross-cutting, additional alternative incentives should be proposed and analyzed to promote a more robust and comprehensive pipeline that includes vaccines.

Recommendation 3.1
Once appropriate economic incentives are identified, the NVAC recommends that the ASH work with relevant federal and nonfederal stakeholders to prioritize promising vaccine candidates to ensure programmatic resources support for vaccine candidates with the greatest potential impact for combating antibiotic resistance and reducing the use of antibiotics in health-care and community settings.

Recommendation 4
The NVAC recommends that the ASH work with FDA and vaccine manufacturers (including pre-commercial-stage biotechnology companies) to encourage early discussion of appropriate regulatory pathways and clinical trial design requirements for the development of vaccines targeting antibiotic-resistant bacteria and vaccines that decrease the use of antibiotics.

Recommendation 5
The NVAC requests that the National Vaccine Program Office provide an annual update on the progress made in supporting the role of vaccines in strategies to combat antibiotic-resistant bacteria.

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REFERENCES

1. Review on Antimicrobial Resistance. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. 2014 [cited 2015 Mar 14]. Available from: http://www.jpiamr.eu/wp-content/uploads/2014/12/AMR-review-paper-tackling-a-crisis-for-the-health-and-wealth-of-nations_1-2.pdf
2. Centers for Disease Control and Prevention (US). Antibiotic resistance threats in the United States, 2013. 2014 [cited 2015 Mar 14]. Available from: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf
3. Keown OP, Warburton W, Davies SC, Darzi A. Antimicrobial resistance: addressing the global threat through greater awareness and transformative action. Health Aff 2014;33:1620-6.
4. The White House (US). National strategy for combating antibiotic-resistant bacteria. 2014 [cited 2015 Mar 16]. Available from: https://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf
5. President's Council of Advisors on Science and Technology. Report

to the president on combating antibiotic resistance. 2014 [cited 2015 Mar 16]. Available from: https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf
6. The White House (US). Executive order—combating antibiotic-resistant bacteria. 2014 [cited 2015 Mar 16]. Available from: https://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria
7. The White House (US). National action plan for combating antibiotic-resistant bacteria. 2015 [cited 2015 Mar 27]. Available from: https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf
8. The White House (US), Office of the Press Secretary. Fact sheet: president's 2016 budget proposes historic investment to combat antibiotic-resistant bacteria to protect public health. 2015 Jan 27 [cited 2015 Mar 16]. Available from: https://www.whitehouse.gov/the-press-office/2015/01/27/fact-sheet-president-s-2016-budget-proposes-historic-investment-combat-a
9. Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA 2007;298:2155-63.
10. Recommendations for use of *Haemophilus b* conjugate vaccines and a combined diphtheria, tetanus, pertussis, and *Haemophilus b* vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1993;42(RR-13):1-15.
11. Mason EO, Kaplan SL, Lamberth LB, Hinds DB, Kvernland SJ, Loiselle EM, et al. Serotype and ampicillin susceptibility of *Haemophilus influenzae* causing systemic infections in children: 3 years of experience. J Clin Microbiol 1982;15:543-6.
12. Adams DA, Jajosky RA, Ajani U, Kriseman J, Sharp P, Onwen DH, et al. Summary of notifiable diseases—United States, 2012. MMWR Morb Mortal Wkly Rep 2014;61(53):1-121.
13. Department of Health and Human Services (US). Healthy People 2020—immunization and infectious diseases. 2015 [cited 2015 Mar 23]. Available from: https://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives
14. Barbour ML. Conjugate vaccines and the carriage of *Haemophilus influenzae* type b. Emerg Infect Dis 1996;2:176-82.
15. Whitney CG, Farley MM, Hadler J, Harrison LH, Lexau C, Reingold A, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. N Engl J Med 2000;343:1917-24.
16. Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. N Engl J Med 2006;354:1455-63.
17. Wilby KJ, Werry D. A review of the effect of immunization programs on antimicrobial utilization. Vaccine 2012;30:6509-14.
18. Cohen R. The need for prudent use of antibiotics and routine use of vaccines. Clin Microbiol Infect 2009;15(Suppl 3):21-3.
19. Lee GC, Reveles KR, Attridge RT, Lawson KA, Mansi IA, Lewis JS 2nd, et al. Outpatient antibiotic prescribing in the United States: 2000 to 2010. BMC Med 2014;12:96.
20. Fireman B, Black SB, Shinefield HR, Lee J, Lewis E, Ray P. Impact of the pneumococcal conjugate vaccine on otitis media. Pediatr Infect Dis 2003;22:10-6.
21. Hicks LA, Harrison LH, Flannery B, Hadler JL, Schaffner W, Craig AS, et al. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998–2004. J Infect Dis 2007;196:1346-54.
22. Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Lexau C, Bennett NM, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis 2015;15:301-9.
23. Tomczyk S, Bennett NM, Stoecker C, Gierke R, Moore MR, Whitney CG, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2014;63(37):822-5.
24. Grijalva C, Wunderink R, Williams D, Al E. Distribution of pneumococccal serotypes detected through urine analysis among US adults hospitalized with pneumonia after introduction of PCV13. In: International Symposium on Pneumococci and Pneumococcal Diseases 2014; 2014 Mar 9–13; Hyderabad, India.
25. Misurski DA, Lipson DA, Changolkar AK. Inappropriate antibiotic prescribing in managed care subjects with influenza. Am J Manag Care 2011;17:601-8.
26. Kash JC, Taubenberger JK. Infectious disease theme issue: the role of viral, host, and secondary bacterial factors in influenza pathogenesis. Am J Pathol 2015;185:1528-36.
27. Centers for Disease Control and Prevention. Flu vaccination coverage, United States, 2013–14 influenza season. 2014 [cited 2015 Mar 27]. Available from: http://www.cdc.gov/flu/fluvaxview/coverage-1314estimates.htm
28. Kwong JC, Maaten S, Upshur REG, Patrick DM, Marra F. The effect of universal influenza immunization on antibiotic prescriptions: an ecological study. Clin Infect Dis 2009;49:750-6.
29. Kallen AJ, Mu Y, Bulens S, Reingold A, Petit S, Gershman K, et al. Health care-associated invasive MRSA infections, 2005–2008. JAMA 2010;304:641-8.
30. Dantes R, Mu Y, Belflower R, Aragon D, Dumyati G, Harrison LH, et al. National burden of invasive methicillin-resistant *Staphylococcus aureus* infections, United States, 2011. JAMA Intern Med 2013;173:1970-8.
31. Centers for Disease Control and Prevention (US). Active Bacterial Core surveillance report, Emerging Infections Program Network, methicillin-resistant *Staphylococcus aureus*, 2012. 2012 [cited 2015 Mar 29]. Available from: http://www.cdc.gov/abcs/reports-findings/survreports/mrsa12.pdf
32. Daum RS, Spellberg B. Progress toward a *Staphylococcus aureus* vaccine. Clin Infect Dis 2012;54:560-7.
33. Kaslow DC, Shiver JW. *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus*: emerging concepts in vaccine development. Annu Rev Med 2011;62:201-15.
34. Lessa FC, Gould C V, McDonald LC. Current status of *Clostridium difficile* infection epidemiology. Clin Infect Dis 2012;55(Suppl 2):S65-70.
35. Rupnik M, Wilcox MH, Gerding DN. *Clostridium difficile* infection: new developments in epidemiology and pathogenesis. Nat Rev Microbiol 2009;7:526-36.
36. Chitnis AS, Holzbauer SM, Belflower RM, Winston LG, Bamberg WM, Lyons C, et al. Epidemiology of community-associated *Clostridium difficile* infection, 2009 through 2011. JAMA Intern Med 2013;173:1359-67.
37. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med 2015;372:825-34.
38. Lo Vecchio A, Zacur GM. *Clostridium difficile* infection: an update on epidemiology, risk factors, and therapeutic options. Curr Opin Gastroenterol 2012;28:1-9.
39. Gerding DN, Johnson S. Management of *Clostridium difficile* infection: thinking inside and outside the box. Clin Infect Dis 2010;51:1306-13.
40. Lee BY, Popovich MJ, Tian Y, Bailey RR, Ufberg PJ, Wiringa AE, et al. The potential value of *Clostridium difficile* vaccine: an economic computer simulation model. Vaccine 2010;28(:5245-53.
41. McGlone SM, Bailey RR, Zimmer SM, Popovich MJ, Tian Y, Ufberg P, et al. The economic burden of *Clostridium difficile*. Clin Microbiol Infect 2012;18:282-9.
42. O'Brien JA, Lahue BJ, Caro JJ, Davidson DM. The emerging infectious challenge of *Clostridium difficile*-associated disease in Massachusetts hospitals: clinical and economic consequences. Infect Control Hosp Epidemiol 2007;28:1219-27.
43. Department of Health and Human Services (US), Office of the Assistant Secretary for Planning and Evaluation. Analytical framework for examining the value of antibacterial products. 2014 [cited 2015 May 30]. Available from: http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm
44. Sahoo A. Vaccines 2011: market analysis, key players and critical trends in a fast-changing industry. Rockville (MD): Kalorama Information; 2011.