JMCP

JOURNAL OF MANAGED CARE PHARMACY®

The Value of Preventive Medicine: A Look at Vaccine Management

Edward P. Armstrong, PharmD, FASHP

H. Eric Cannon, PharmD

Jonathan A. McCullers, MD

Neil B. Minkoff, MD

Supplement

September 2007

Vol. 13, No. 7, S-b

Continuing Education Activity

JMCP

Editor-in-Chief

Frederic R. Curtiss, PhD, RPh, CEBS
(830) 935-4319, fcurtiss@amcp.org

Managing Editor

Tamara C. Faggen
Jamie Kunkle, (703) 671-1358
jkunkle@amcp.org

Assistant Editor

Diane P. Britton
drbritton@verizon.net

Peer Review Administrator

Jennifer A. Booker, (703) 317-0725
jmcpreview@amcp.org

Graphic Designer

Kathleen Furey, Furey Design

Account Manager

Peter Palmer, (856) 795-5777, ext. 13
peter@promedgroup.net

Publisher

Judith A. Cahill, CEBS
Executive Director
Academy of Managed Care Pharmacy

This supplement to the Journal of Managed Care Pharmacy. (ISSN 1083-4087) is a publication of the Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314; (703) 683-8416; (703) 683-8417 (fax).

Copyright© 2007, Academy of Managed Care Pharmacy.
All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, without written permission from the Academy of Managed Care Pharmacy.

POSTMASTER: Send address changes to JMCP,
100 North Pitt St., Suite 400, Alexandria, VA 22314.

Supplement Policy Statement

Standards for Supplements to the Journal of Managed Care Pharmacy

Supplements to the *Journal of Managed Care Pharmacy* are intended to support medical education and research in areas of clinical practice, health care quality improvement, or efficient administration and delivery of health benefits. The following standards are applied to all JMCP supplements to assure quality and assist readers in evaluating potential bias and determining alternate explanations for findings and results.

1. Disclose the principal sources of funding in a manner that permits easy recognition by the reader.
2. Disclose the existence of all potential conflicts of interest among supplement contributors, including financial or personal bias.
3. Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.
4. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.
5. Seek and publish content that does not duplicate content in the *Journal of Managed Care Pharmacy*.
6. Subject all supplements to expert peer review.

FACULTY

Edward P. Armstrong, PharmD, FASHP, is a professor, Department of Pharmacy Practice and Science, and an investigator, Center for Health Outcomes and Pharmacoeconomic Research, University of Arizona College of Pharmacy, Tucson. He served as a visiting professor for Kobe-Gakuin University in Japan and has consulted with health systems in Eastern Europe and Southeast Asia. Armstrong has written numerous articles and delivered many presentations on pharmacoeconomic applications, ambulatory medication use evaluations, and disease management. His specific research interests focus upon managed care database evaluations and disease state modeling that involve asthma, depression, heart failure, dyslipidemias, prostate disease, hepatitis C, infectious diseases, diabetes mellitus, epilepsy, community acquired pneumonia, and hypertension. Armstrong earned his bachelor of science in pharmacy from the University of Arizona and his doctorate in pharmacy from the University of Missouri-Kansas City. He completed a pharmacy residency at Truman Medical Center in Kansas City and is a fellow of the American Society of Health Systems Pharmacists.

H. Eric Cannon, PharmD, is the director of pharmacy, SelectHealth, an Intermountain Healthcare company in Salt Lake City, Utah. At SelectHealth, he has responsibility for the management and administration of all pharmaceuticals. He is actively involved in the development and implementation of programs to control cost and utilization of pharmaceuticals as well as in Intermountain's efforts on clinical integration, disease management, and research. Cannon serves as cochair of the SelectHealth Pharmacy and Therapeutics Committee, which helps promote physician/pharmacy education programs, formulary development and maintenance, and the inclusion of outcomes-based pharmacoeconomic research in the formulary processes.

In addition to his responsibilities for pharmacy, Cannon oversees all health and wellness programs for SelectHealth. In this role, he is working with employers to implement health management strategies to improve employee productivity and decrease absenteeism. As a member of the Academy of Managed Care Pharmacy, he recently served as chair of the legislative committee. Cannon received his doctor of pharmacy degree from Idaho State University. He has experience in hospital, retail, long-term care, and home health settings. He has authored multiple publications and made numerous presentations. Cannon recently served on the Institute of Medicine committee reviewing medication errors.

Jonathan A. McCullers, MD, is an associate member, Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee, where he oversees a basic science laboratory that focuses on secondary bacterial infections following influenza as a means to provide targets for prevention and treatment using drugs and vaccines. He is a member of the American Society of Virology, the Pediatric Infectious Diseases Society, the American Society of Microbiology, and the Infectious Diseases Society of America. He has published more than 40 research articles in journals such as *Infection and Immunity*, *Pediatrics*, *The Journal of Infectious Diseases*, *Virology* and the *Journal of Virology*. McCullers is a graduate of the University of Virginia and received his medical degree from the University of Alabama at Birmingham. He joined the St. Jude staff in 1996.

Neil B. Minkoff, MD, serves as the medical director for network services and pharmacy for Harvard Pilgrim Health Care, Wellesley, Massachusetts, rated the number 1 health plan in America by the National Committee for Quality Assurance in both 2005 and 2006. He has previously served as the associate medical director of Partners Community Healthcare, Inc., an integrated provider network of 8 hospitals and more than 4,000 physicians. He has been cochair of medical management and cochair of pharmacy & therapeutics for the CareGroup Provider Service Network and medical director for Deaconess-Waltham Hospital.

Minkoff attended Bowdoin College, where he graduated *summa cum laude* in history, and received his medical degree from Dartmouth Medical School. He received an executive education certificate from the Wharton School at the University of Pennsylvania. He trained in internal medicine at the Lahey Clinic and practiced as an internist. He is the author and editor of multiple publications and has served on numerous advisory panels and boards. Minkoff was awarded a bronze United States Congressional Medal in 1986. He is also an instructor at Harvard Medical School. In 2005, Minkoff was recognized by the Boston Business Journal as one of their "40 Under 40" business leaders. He is one of the Boston Chamber of Commerce's Future Leaders of 2007.

Table of Contents

The Value of Preventive Medicine: A Look at Vaccine Management

S2 Evolution, Benefits, and Shortcomings of Vaccine Management

Jonathan A. McCullers, MD

S7 Pharmacy Management of Vaccines

H. Eric Cannon, PharmD

S12 Economic Benefits and Costs Associated with Target Vaccinations

Edward P. Armstrong, PharmD, FASHP

S16 Multiple Vaccines: How Do We Choose?

Neil B. Minkoff, MD

S21 Continuing Education*: CE Submission Instructions and Posttest Worksheet

Target Audience

Physicians and pharmacists practicing in a managed care environment

Learning Objectives

After completing this activity, the participant should be better able to

1. describe current vaccine management practices;
2. identify vaccine management best practices and shortcomings within the health care system;
3. outline steps toward plan attainment of vaccination goals based on HEDIS measures, surrogate markers, and desired outcomes;
4. describe how to apply new management principles to improve clinical, human, and economic results of vaccination; and
5. describe how to evaluate current plan practices in order to design and launch new quality improvement initiatives that will enhance vaccination standards.

This supplement was funded by an educational grant from GlaxoSmithKline. Articles in this supplement are based on the proceedings of a symposium held April 11, 2007 at the Academy of Managed Care Pharmacy's 19th Annual Meeting and Showcase in San Diego, California. The symposium was supported by an educational grant from GlaxoSmithKline.

*A total of 0.15 CEU (1.5 contact hours) for pharmacists (ACPE Program No. 809-999-07-076-H01) and a maximum of 1.5 AMA PRA Category 1 Credit(s)[™] will be awarded for successful completion of this continuing education activity. For faculty disclosures, please see pages S6, S11, S15, and S20. For accreditation information, please see page S21.

The articles published in this supplement represent the opinions of the authors and do not reflect the official policy or views of the Academy of Managed Care Pharmacy, the authors' institutions, or GlaxoSmithKline unless so specified. The authors have disclosed if any unlabeled use of products is mentioned in their articles. Before prescribing any medicine, clinicians should consult primary references and full prescribing information.

Evolution, Benefits, and Shortcomings of Vaccine Management

Jonathan A. McCullers, MD

ABSTRACT

BACKGROUND: The reduction of childhood mortality by vaccines has been one of the greatest public health successes of the past century. However, many targets for immunization remain uncontrolled, and new or improved vaccines are emerging to meet these challenges.

OBJECTIVE: To review the evolution of vaccination and take an objective look at current vaccine development technologies, thereby framing the discussion of vaccine management.

SUMMARY: The genesis of vaccinology is generally considered to have been a direct result of the observation that persons who had contracted smallpox rarely developed a second case. From this observation, the concept of variolation was born, which involved the inoculation of uninfected individuals using material collected from smallpox lesions with the goal of inducing immunity to future infection. The use of attenuated, live virus to induce immunity was the next step in the evolution of vaccinology, followed by inactivation of the virus when diseases caused by organisms not amenable to attenuation were targeted. More recently, a variety of adjuvant strategies have been developed to improve the immunogenicity of inactivated vaccines, and genetic engineering has been employed to increase the safety, reduce the reactogenicity, and improve the immunogenicity of different vaccines.

CONCLUSION: Clinical (efficacy and safety) and economic (cost and profit) considerations are competing priorities that need to be reconciled within a discussion encompassing the government, the public, the pharmaceutical industry, third-party payers, and private individuals or companies who administer these vaccines.

KEYWORDS: Vaccine, History, Management, Adjuvant, Safety

J Manag Care Pharm. 2007;13(7)(suppl S-b):S2-S6

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

Author

JONATHAN A. MCCULLERS, MD, is an associate member, Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee.

AUTHOR CORRESPONDENCE: Jonathan A. McCullers, MD, Associate Member, Department of Infectious Diseases, St. Jude Children's Research Hospital, 332 N. Lauderdale St., Memphis, TN 38105-2794. Tel: (901) 495-5164; Fax: (901) 495-3099; E-mail: jon.mccullers@stjude.org

The use of vaccination to prevent disease is the greatest public health success of the last century. For many diseases previously considered to be scourges of mankind, including smallpox, polio, diphtheria, and measles, annual mortality has been reduced by more than 99.9% in the United States¹ and in many other countries. However, no vaccines are currently licensed for 2 of the 3 most prolific infectious killers, human immunodeficiency virus (HIV) and malaria, and the only vaccine licensed for the third agent, tuberculosis, offers limited effectiveness. In addition, morbidity and mortality remain high for many diseases for which vaccines are used, including influenza, which accounts for 36,000 deaths annually in the United States² and an estimated 500,000 annually worldwide.³ Although childhood mortality has been virtually eliminated by the widespread use of pertussis vaccines, morbidity continues to be a problem, accounting for more than 25,000 cases per year in the United States, mostly in adults for whom immunity has waned.⁴ For some newer vaccines, the impact is not yet apparent. An example is a new human papillomavirus (HPV) vaccine (Gardasil), which was licensed in 2006 in the hope of preventing some of the 3,900 annual deaths from cervical cancer related to HPV infection.⁵

The Birth of Vaccinology

The genesis of vaccinology came through the evolution of attempts to control smallpox. The observation that persons who had contracted smallpox rarely developed a second case suggested the concept of immunity to disease. The Chinese are generally credited with the development of variolation more than a thousand years ago on the basis of this idea, whereby a small amount of dried secretions from a smallpox scab was insufflated into the nose, with the hope of conferring immunity to subsequent exposures.⁶ Modification of this measure in India led to the practice, termed scarification, of scratching the agent into the skin. This method of prevention spread westward into Europe in the 17th century, although results were mixed and significant complications often ensued.

In 1796, Edward Jenner combined the practice of variolation with the observation that milkmaids who had previously contracted cowpox rarely contracted smallpox, and he performed the first immunization by inoculating an 8-year-old boy with cowpox. The boy failed to develop a typical variolation scar upon challenge with smallpox 6 weeks later.⁷ Development of a vaccine based on this principle led to eradication of smallpox in the 20th century.

Attenuation as a Strategy for Vaccine Development

The discovery of attenuation came serendipitously in the fall of 1881, when Louis Pasteur returned from summer vacation and attempted to inoculate chickens with a culture of *Pasteurella*

multocida that he had left out on the laboratory bench. After the chickens failed to show disease, he challenged them with a fresh batch of bacteria and realized that they were protected from the virulent strain because of prior exposure to the attenuated strain.⁶ He coined the term “vaccinate” to describe the use of attenuated organisms to protect against their virulent forms.⁸ After developing chemical methods of attenuation, he went on to develop vaccines against rabies and anthrax.^{6,9} The anthrax vaccine was developed for use in animals and thus served as a forerunner of human anthrax vaccines developed in the 20th century.

Following this lead, French scientists Albert Calmette and Camille Guérin developed the Bacille Calmette-Guérin (BCG) vaccine against tuberculosis by serial passage of *Mycobacterium bovis* 230 times through artificial media between 1908 and 1921.⁹ BCG was adopted by the League of Nations in 1928, but controversy during a clinical trial in Lubeck in 1929-30 caused Germany to reject the vaccine. A contaminated batch of vaccine caused the deaths during that study of at least 72 infants, leading to a sensationalistic trial of the physicians involved that presaged some of the public-private-governmental tensions that surround vaccine management today. The United States also declined to adopt the vaccine, taking the alternative approach of continuing successful screening programs put into place by the U.S. Public Health Service.⁹

Although the growth of serial cultures in media served to attenuate some bacteria, viruses could not be attenuated by passage in this manner. Some viruses, such as influenza virus or yellow fever virus, could be attenuated by passage in susceptible animals (which led to the development in the 1930s of an attenuated yellow fever vaccine that was used until 1982),¹⁰ but most viruses did not have an acceptable animal host. The breakthrough came in the 1940s when the team of John Enders, Thomas Weller, and Frederick Robbins developed tissue culture cultivation of viruses and demonstrated that viruses could be attenuated through passage in these cultures.¹¹ Their work on the attenuation of poliomyelitis virus won the Nobel Prize in Medicine in 1954.

Numerous viral vaccines have been developed by this method, many of which are still in use today (see Table). One problem that has not been solved by attenuation is the changing antigenicity of influenza viruses that necessitate update of the strains included in the vaccine each year. However, since the genes of influenza are carried on 8 RNA gene segments, a process called reassortment can be used to mix the prevailing strain with a strain attenuated by passage in animals (for the inactivated influenza vaccine) or cell culture (for the live attenuated influenza vaccine) so both antigenicity and attenuation can be achieved. A similar process has been used to develop a rotavirus vaccine that is a reassortant taking antigens from the human virus but attenuating features from a bovine strain.¹²

TABLE Vaccine Development Strategies and Targets

Inactivated Vaccines		Live Vaccines	
Strategy	Target	Strategy	Target
Whole organisms		Chemical attenuation	
	Typhoid		Rabies
	Cholera		Anthrax
	Plague		Typhoid
	Pertussis	Passage in media	
	Influenza		BCG
	Poliovirus		Yellow fever
	Hepatitis A	Passage in animals	
Extracts and subunits			Yellow fever
	Japanese encephalitis		Influenza
	Anthrax	Passage in cell culture	
	Influenza		Poliovirus
	Rabies		Measles
Toxoids			Mumps
	Diphtheria		Adenoviruses
	Tetanus		Varicella
Polysaccharides			Rotavirus
	Pneumococcus	Cold adaptation	
	Meningococcus		Rubella
	<i>H. influenzae</i> type B		Influenza
	Typhoid		
Conjugation			
	<i>H. influenzae</i> type B		
	Pneumococcal		
	Meningococcal		
Recombinant proteins			
	Hepatitis B		
	Pertussis		
	Lyme		
	Human papillomavirus		

Note: Vaccines for targets in bold type are currently available in the United States. BCG=Bacille Calmette-Guérin.

■ Inactivation: A Safer Alternative?

Although many organisms are amenable to attenuation, not all are, and safety concerns about side effects and the potential for reversion from an attenuated to a virulent form exist. An alternative in many cases has been the use of inactivated organisms. In 1886, Daniel Salmon and Theobald Smith demonstrated the utility of injections of heat-killed organisms to induce immunity in pigeons.⁸ However, whole-cell preparations were quite often toxic, which led to purification of protein components, polysaccharide capsules, or inactivated toxins as preferred immunogens (Table).

A good example is the acellular pertussis vaccine. Using centrifugation techniques, lab technicians separate portions of culture supernatant containing the antigenic proteins from the rest of the material, which contains the inflammatory product lipopolysaccharide (LPS) that is responsible for most of the reactions to whole-cell pertussis vaccines.⁴ However, the reduction in reactogenicity typically comes at a price: reduced immunogenicity. In many cases, high doses of antigen, multiple exposures, or both are needed to induce an effective immune response to inactivated vaccines. In the case of purified polysaccharide vaccines, the polysaccharide itself elicits only B-cell-mediated humoral immunity, without the stimulation of T-cells required for immunologic memory and a secondary immune response.¹³ Protection from disease is often short-lived, and some target groups such as infants respond very poorly to the antigens.

■ Are Adjuvants the Answer?

The need to improve the immunogenicity of inactivated vaccines has spurred the development of a variety of adjuvant strategies. Adjuvants act by 1 of 2 basic mechanisms: either by improving presentation of the antigens to the immune system or by stimulating the immune system so a more robust or broader response is achieved. This may improve immunogenicity, allow for dose reduction without compromising immunogenicity, or both. Conjugation of inactivated toxoids to purified polysaccharides is one extremely successful form of adjuvantation. This process is responsible for conjugate vaccines directed against *Haemophilus influenzae* type B, *Neisseria meningitidis*, and *Streptococcus pneumoniae*. It is thought to work by improving helper T-lymphocyte responses to the antigen and generating an anamnestic response, particularly in infants who do not respond well to purified polysaccharides without the presence of the toxoid.¹⁴

The only compounds approved in the United States for concomitant use with vaccines as adjuvants are mineral salts such as calcium phosphate and alum. Since the 1920s, alum as aluminum hydroxide or aluminum phosphate has been the most widely used adjuvant in humans. Its mechanism of action is thought to be creation of a depot site so that slow, sustained release of the antigen improves presentation to the immune

system.¹⁵ Immunostimulatory compounds derived from plants, animals, or bacteria are common components of many adjuvants and act by stimulation of the immune system, usually through activation of Toll-like receptors or other components of innate immunity.

Combination adjuvants are also being tested. An example is the proprietary adjuvant AS04, a mixture of alum with monophosphoryl lipid A (a detoxified form of LPS), used by GlaxoSmithKline as a component of its investigational cervical cancer vaccine (Cervarix), which is awaiting U.S. Food and Drug Administration (FDA) approval.⁵ The primary antigen is delivered in replication-defective virus-like particles mixed with the adjuvant AS04. In the molecular biology age, direct expression of cytokines or agonists of the innate immune systems may be used in adjuvantation strategies.

■ The Era of Genetic Engineering

Molecular biology and genetic engineering have had a dramatic effect on the field of vaccinology, although many of the important advances have not yet made it into the market. The first success story in this area was the development of the hepatitis B vaccine, which was licensed in 1986.¹⁶ The surface protein of hepatitis B virus is expressed from a DNA plasmid in yeast cells, purified and adsorbed on alum for injection.

It is likely that all future vaccines will be genetically engineered to increase safety, reduce reactogenicity, and improve immunogenicity. Toward this end, a variety of new technologies have been developed to create, deliver, or enhance vaccines. Important antigens are cloned into DNA plasmids, which can be used directly as vaccines themselves (naked DNA) or used to produce proteins for vaccination as with the hepatitis B vaccine. With some viruses, several proteins can be expressed together and will assemble into pseudo-virions termed virus-like particles (VLPs) that can act as a vaccine or can be used as a delivery vehicle for another antigen.⁵ The powerful technique of creating cloned DNA copies of RNA viruses allows manipulation of the genomes, expression of the involved proteins, or re-creation of entire viruses with custom-made changes.¹⁷ Manipulation of viral genomes to remove proteins associated with virulence and to allow insertion of foreign genes has resulted in the creation of numerous viral vectors that may be used as vaccine carriers.¹⁸ In addition to expression of the antigen, these techniques allow for the incorporation of sequences coding other genes of interest, such as cytokines or Toll-like receptor agonists that may act as adjuvants.

These new techniques also offer the promise of preventing or controlling numerous disease states for which effective vaccines have not yet been developed using standard methods. At the top of the priority list are HIV, malaria, and tuberculosis as well as potential agents of bioterrorism. Novel vaccines are in development for a number of common infectious agents for which we have had no success, including respiratory syncytial

virus (RSV), herpes simplex virus (HSV), and *Candida albicans*. Amelioration of the symptoms of chronic infections, including HIV and hepatitis B, are being considered, and 1 product directed against the prevention of recurrent, painful outbreaks of varicella zoster is already in the market (the live varicella zoster vaccine, Zostavax).

The strategy of vaccinating pregnant women to protect their newborn babies via transplacental antibody is being explored, as is prevention of a number of noninfectious conditions. For example, treatment of addiction may be possible by vaccinating against nicotine so that it no longer crosses the blood-brain barrier to engage the corresponding receptors. Prevention of pregnancy may be possible by vaccination against chorionic gonadotrophin and luteinizing hormone, key players in preparing the uterus for conception.⁶ Other innovative targets are being considered as these technologies mature.

■ Challenges in the Management of Vaccines

Many challenges exist in the management of vaccines currently on the market as well as the many potential vaccines that may enter the market. The most visible issue in the last decade has been high-profile shortages of influenza vaccine and some of the childhood vaccines, particularly new entries into the market. The reasons for this are mainly basic economics. Pharmaceutical companies typically have a low profit margin on vaccines and therefore produce limited supplies. When demand increases, they are often unable to distribute more vaccine to the end user in a timely fashion, and any manufacturing-related delays exacerbate the shortage. This is particularly problematic for vaccines with a defined shelf life, such as influenza, because companies do not want to discard unused vaccine at the end of the season. The result of high development costs, low profit margins, and increasing regulatory hurdles is that few companies are in the marketplace.

The other group that suffers from poor profit margins with vaccines is the front-line caretakers who administer the vaccine. High upfront expenditures are necessary, and profits are low or even negative in some cases. One recent report estimated that the cost to the physician of administering all the currently recommended vaccines to a child from birth to 18 years is \$1,662.¹⁹ In addition, vaccine administration takes significant time and effort that could be spent on activities with higher profit margins, such as seeing acutely ill patients.²⁰

Although vaccines in general often have limited financial benefit for industry and physicians, they have obvious cost-benefit advantages for society. Many childhood vaccines save costs to society as a whole, and others provide benefits at a cost considered reasonable for society.^{21,22} As more vaccines come into the marketplace, this dichotomy between cost savings and cost benefit has become more obvious. The shift from targets that cause a great deal of mortality to those that cause significant morbidity and economic loss has led to a careful appraisal of

cost-effectiveness compared with the cost of alternate treatments. A comprehensive vaccination policy must take into account the cost of development and production of vaccines, the cost of distribution and administration, the benefits to both individuals and society as a whole, profit for companies and those who administer the vaccines, and the government's role in balancing these various needs.

One noticeable trend in the development and approval of new vaccines has been an emphasis on safety. There is a growing public demand for the safety of vaccines, engendered by a lack of overt disease that creates the perception that vaccines are no longer necessary. This perception is fueled by antivaccination activist groups. As individuals opt out of vaccination programs, herd immunity decreases, reducing the effectiveness of these programs. Herd or community immunity is generally defined as having a large percentage of the population vaccinated in order to prevent the spread of certain infectious diseases. When herd immunity exists, even individuals not vaccinated (such as newborns and those with chronic illnesses) are offered some protection because the disease has little opportunity to spread within the community.

Failure to participate in the "social contract" results in outbreaks of disease and morbidity in unvaccinated populations.²³ The social contract in this context is the concept that an implicit agreement exists between a people and their government to accept vaccination and its attendant risks for the benefit of not only the individual but also of society as a whole, in return for services and protection of rights provided by the government. The impact on vaccine development of individuals failing to participate for reasons that have no scientific merit is that both real and imagined safety concerns have to be thoroughly addressed in the current climate in order to bring a vaccine to market. New vaccines have to demonstrate a better safety profile than established vaccines, which can create problems balancing immunogenicity and reactogenicity, particularly when adjuvants are considered.

■ Decision Making in the Era of Multiple Vaccines

As more vaccines enter the market, decisions on management of those vaccines will become increasingly complex. Two examples serve to illustrate this point.

A new live, attenuated influenza vaccine (LAIV) (FluMist) was licensed for use in 2003 and entered the market at a noncompetitive price level compared with the existing inactivated vaccine. Issues over pricing, reimbursement, and a limited indication have resulted in poor uptake and use of LAIV. However, recent published data indicate that LAIV has superior efficacy in children,²⁴ and pricing differences between LAIV and the inactivated vaccine are now minimal. In addition, it is widely anticipated that LAIV will receive an expanded indication from the FDA this year. Physicians, pharmacies, and managed care organizations will now have to make decisions on which vaccine to use or whether

to offer both, weighing the efficacy data against factors such as cost, availability, and patient choice.

Another example is the projected entry into the market of a second HPV vaccine in the coming year. The FDA-approved HPV vaccine manufactured by Merck (Gardasil) targets HPV serotypes 16 and 18, which cause around 70% of cervical cancers, as well as 6 and 11, which are the most common causes of noncancerous genital warts, and includes alum as an adjuvant.⁵ A new HPV vaccine produced by GlaxoSmithKline (Cervarix) is expected to enter the market in the upcoming year, targeting only HPV 16 and 18. However, this vaccine makes use of the novel adjuvant AS04, which may extend the breadth of protection of the vaccine to cover additional cancer-causing serotypes. If this is substantiated, individuals and organizations may have to weigh the benefit of reducing genital warts against the possibility of preventing additional cases of cervical cancer by choosing between 2 vaccines with similar safety profiles and similar efficacy against their primary targets, HPV 16 and 18.⁵

Conclusions

New and existing vaccines need to be safe, effective, and cost-effective for both society and for those who manage health care programs. In addition, they must be profitable for those who develop, manufacture, and administer the vaccines. It is increasingly obvious that proper stewardship of vaccines requires a partnership between government, industry, health care organizations, and individuals in both academic and private practice. However, the different interests of these parties and competing priorities can create tensions that must be acknowledged and resolved. Navigating the many issues that surround the management of vaccines in today's society is a complex matter, and it is easy to lose sight of the ultimate goal of benefit to public health.

DISCLOSURES

This article is based on a presentation given by the author at a symposium, "The Value of Preventive Medicine: A Look at Vaccine Management," held April 11, 2007, at the Academy of Managed Care Pharmacy's 19th Annual Meeting and Showcase in San Diego, California. The symposium was supported by an educational grant from GlaxoSmithKline. The author discloses that he has received an honorarium for participation in the presentation and in this supplement. He also discloses that he has been a consultant to and has received honoraria for speaking at seminars for GlaxoSmithKline and MedImmune.

REFERENCES

- Centers for Disease Control and Prevention. Achievements in public health, 1900-1999: impact of vaccines universally recommended for children—United States, 1990-1998. *MMWR Morb Mortal Wkly Rep.* 1999;48:243-48.
- Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA.* 2003;289:179-86.
- Stohr K. Preventing and treating influenza. *BMJ.* 2003;326:1223-24.
- Cherry JD. Historical perspective on pertussis and use of vaccines to prevent it. *Microbe.* 2007;2:139-44.
- Lowy DR, Schiller JT. Prophylactic human papillomavirus vaccines. *J Clin Invest.* 2006;116:1167-73.
- Plotkin SA. Vaccines: past, present and future. *Nat Med.* 2005;(suppl);11:S5-S11.
- Baxby D. Edward Jenner's Inquiry; a bicentenary analysis. *Vaccine.* 1999;17:301-07.
- Plotkin SA. Six revolutions in vaccinology. *Pediatr Infect Dis J.* 2005;24:1-9.
- Baker JP, Katz SL. Childhood vaccine development: an overview. *Pediatr Res.* 2004;55:347-56.
- Barnett ED. Yellow fever: epidemiology and prevention. *Clin Infect Dis.* 2007;44:850-56.
- Enders JF, Robbins FC, Weller TH. Classics in infectious diseases. The cultivation of the poliomyelitis viruses in tissue culture by John F. Enders, Frederick C. Robbins, and Thomas H. Weller. *Rev Infect Dis.* 1980;2:493-504.
- Dennehy PH. Rotavirus vaccines—an update. *Vaccine.* 2007;25:3137-41.
- Stein KE. Thymus-independent and thymus-dependent responses to polysaccharide antigens. *J Infect Dis.* 1992;165(suppl 1):S49-S52.
- Bilukha O, Messonnier N, Fischer M. Use of meningococcal vaccines in the United States. *Pediatr Infect Dis J.* 2007;26:371-76.
- Aguilar JC, Rodriguez EG. Vaccine adjuvants revisited. *Vaccine.* 2007;25:3752-62.
- Stevens CE, Taylor PE, Tong MJ, et al. Yeast-recombinant hepatitis B vaccine. Efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission. *JAMA.* 1987;257:2612-16.
- Hoffmann E, Krauss S, Perez D, Webby R, Webster RG. Eight-plasmid system for rapid generation of influenza virus vaccines. *Vaccine.* 2002;20:3165-70.
- Liniger M, Zuniga A, Naim HY. Use of viral vectors for the development of vaccines. *Expert Rev Vaccines.* 2007;6:255-66.
- Nelson JD, McCracken GHJ. The high cost of vaccines. *Pediatr Infect Dis J.* 2007;26: yellow pages.
- Szilagyi PG, Iwane MK, Schaffer S, et al. Potential burden of universal influenza vaccination of young children on visits to primary care practices. *Pediatr.* 2003;112:821-28.
- Strutton DR, Stang PE. Prophylaxis against respiratory syncytial virus (RSV), varicella, and pneumococcal infections: economic-based decision-making. *J Pediatr.* 2003;143(suppl):S157-S162.
- Newall AT, Beutels P, Wood JG, Edmunds WJ, MacIntyre CR. Cost-effectiveness analyses of human papillomavirus vaccination. *Lancet Infect Dis.* 2007;7:289-96.
- Centers for Disease Control and Prevention. Measles—United States, 2005. *MMWR Morb Mortal Wkly Rep.* 2006;55:1348-51.
- Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med.* 2007;356:685-96.

Pharmacy Management of Vaccines

H. Eric Cannon, PharmD

ABSTRACT

BACKGROUND: Although standard vaccines have traditionally been granted full coverage in managed care, the recent introduction of several novel vaccine products has necessitated the revision of pharmacy management strategies throughout the nation.

OBJECTIVE: To review pharmacy management strategies for a number of emerging vaccines, with unique plan perspectives from SelectHealth, an Intermountain Healthcare company serving approximately 500,000 members in Utah.

SUMMARY: Because several recently introduced vaccines target previously unaddressed diseases and carry higher costs than traditional vaccines, several plans have adapted a novel approach to manage vaccine coverage on an individual product basis. At SelectHealth, recently introduced vaccines for rotavirus, respiratory syncytial virus (RSV), herpes zoster, and human papillomavirus (HPV) have required special attention in terms of pharmacy management. After carefully weighing acquisition and administration costs, anticipated uptake and use, direct and indirect health care costs averted, and quality of life issues, plan leadership decided to cover many of the new vaccines (i.e., rotavirus, RSV, and herpes zoster) under a nonstandard vaccination benefit. However, because substantial cost savings and high use of the quadrivalent HPV vaccine was anticipated within SelectHealth, the plan decided to fully cover the product.

CONCLUSION: Although they complicate traditional pharmacy management, novel vaccines provide clinical benefit that managed care organizations cannot ignore. One universal strategy will not suffice in managing all the different vaccines entering the market, and a tailored approach should be employed based on the individual characteristics and use of each product.

KEYWORDS: Vaccine, Pharmacy & therapeutics; Herpes zoster, Rotavirus, RSV, HPV

J Manag Care Pharm. 2007;13(7)(suppl S-b):S7-S11

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

Author

H. ERIC CANNON, PharmD, is director of pharmacy and director of Health and Wellness, SelectHealth, Intermountain Healthcare, Salt Lake City, Utah.

AUTHOR CORRESPONDENCE: H. ERIC CANNON, PharmD, Director of Pharmacy and Director of Health and Wellness, SelectHealth/Intermountain Healthcare, 4646 W. Lake Park Blvd., Salt Lake City, UT 84130. Tel: (801) 442-5352; Fax: (801) 442-3006; E-mail: Eric.Cannon@selecthealth.org

Overall, the U.S. Food and Drug Administration (FDA)-approved vaccines in use today are known to be safe and effective agents, and immunizations play a key role in the management of diseases with previously significant morbidity and mortality in the United States and worldwide. Still, more than 100,000 people (primarily adults) are affected by a vaccine-preventable disease per year in the United States alone.¹ This apparent inconsistency indicates a need for improved vaccine management in the United States, and this need has only become more pressing in the advent of emerging vaccines for previously untargeted diseases and of combination products or vaccines employing novel delivery technologies. These factors have created an environment in which new vaccine management strategies are necessary to combat preventable disease.

As a framework for vaccine management in managed care organizations (MCOs), the National Committee for Quality Assurance's Health Plan Employer Data and Information Set (HEDIS) immunization measures provide an ideal starting point. Currently, 2 different measures exist: 1 for children and 1 for adolescents.² For children, the measure accounts for the percentage of individuals who turned age 2 during the measurement year and who received the following vaccinations by their second birthday: 4 doses DTP (diphtheria-tetanus-pertussis), 3 doses OPV or IPV (polio), 1 dose MMR (measles-mumps-rubella), 3 doses HIB (*Haemophilus influenzae* type B), 3 doses hepatitis B, 1 dose VZV (varicella, or chicken pox), and 4 doses pneumococcal conjugate (meningitis and blood infections). For adolescents, the measure accounts for enrolled patients who received the following vaccinations by their 13th birthday: 2 doses MMR, 3 doses hepatitis B, and 1 dose VZV.²

Although improvement in immunization rates has been observed since the institution of the HEDIS measures in 1999, a quality gap still remains in the United States, with more than 20% of children and approximately 50% of adolescents missing 1 or more recommended immunizations.² This lag in recommended immunization performance demonstrates a significant area for improvement in managed care. The emergence of new vaccines indicated for use in childhood or adolescence, such as those for rotavirus or human papillomavirus (HPV), only serves to complicate the issue further and necessitate additional vaccine management interventions by MCOs.

New Vaccine Issues

One MCO, SelectHealth, an Intermountain Healthcare company, has experienced changes in vaccine use and spending in the wake of a number of new vaccines being introduced to the market. At this commercial plan serving approximately 500,000 members in Utah, total vaccine spending averages \$2.0 to \$2.4 million per quarter, with an approximate 25% increase during

TABLE 1 Estimates Related to Epidemiology of Rotavirus Gastroenteritis for the Economic Analysis (CDC)⁴⁻⁶

Input	Low	High
Deaths	20	70
Hospitalizations	55,000	70,000
ED visits	205,000	272,000
Office visits	410,000	410,000
Hospitalization Length of stay	2.4 days $\leq$ 1 year 2.0 days $>$ 1 year	3 days
Work days missed	5 days for hospitalization/death 2 for others	5 days for hospitalization/death 3 ED; 2 for others

CDC=Centers for Disease Control and Prevention; ED=emergency department.

flu season. In terms of vaccination trends within the plan, use of Tdap (tetanus, diphtheria, acellular pertussis) has increased significantly, essentially replacing Td (tetanus, diphtheria) in light of the reemergence of pertussis (whooping cough) in the general population. In addition, anticipated adult vaccination recommendations for health care workers and those with young children are likely to further increase use of Tdap.

Another vaccine experiencing increased use at SelectHealth, despite issues surrounding limited supply, is ProQuad, the combination vaccine for MMR and varicella. Although the increased cost of this combination product would be expected to increase plan spending, the injection-reducing regimen of the product makes increased use of the MMR/varicella vaccine an essentially cost-neutral trend. Other recently introduced vaccines, such as those for HPV (Gardasil), rotavirus (RotaTeq), and herpes zoster (Zostavax), have experienced slower uptake than expected at SelectHealth. A discussion of the impact and management of emerging vaccines for these and other diseases in managed care follows, with direct experience from SelectHealth's plan perspective.

Rotavirus. Rotavirus-related gastroenteritis is associated with approximately \$250 million to \$300 million in direct costs and \$700 million to \$900 million in indirect costs in the United States.³ Estimates place the number of nationwide deaths associated with rotavirus-related gastroenteritis at approximately 20 and 70 on the low and high ends, respectively. In addition to causing an estimated maximum of 70,000 hospitalizations, 272,000 emergency department (ED) visits, and 410,000 office visits, the disease is associated with up to 5 missed work days per year per infected patient (Table 1).^{4,5}

In the Rotavirus Efficacy & Safety Trial (REST), the rotavirus vaccine demonstrated efficacy in reducing health care use and work loss, compared with placebo.⁶ Most prominently, the vaccine offered a 95.8% rate reduction in the number of

hospitalizations due to rotavirus-related gastroenteritis. ED visits, office visits, and work loss days also experienced rate reductions with the vaccine, compared with placebo (93.7%, 86.0%, and 86.6%, respectively).⁶

With an eligible population of 12,300 at SelectHealth and a relatively high uptake (80%) of the orally administered rotavirus vaccine, the plan would expect to spend approximately \$2.6 million per year on vaccination. Direct annual medical cost savings attributed to the vaccination of SelectHealth members against rotavirus are estimated to be about \$90,000 to \$135,000.⁷ Although minimal savings from vaccine administration would be realized, based on modeling, vaccine administration costs would mitigate societal costs by approximately \$265 per patient per year in terms of missed work days, inconvenience, and use of health care services.

As savings to the plan are projected to be minimal and the vaccine's benefit is likely to be largely societal, SelectHealth established a new benefit line termed a "nonstandard vaccination" to cover the rotavirus vaccine. With the application of regular medical coinsurance, the plan member is responsible for 20% of the cost of the vaccine; the rest is covered by SelectHealth. Rotavirus vaccine coverage policies are explained to patients during dialogue with their providers, at which time the providers can offer a recommendation on whether the patient should receive the vaccine. Weighing their portion of the cost of the vaccine against providers' recommendations allows the patients to make an educated decision on immunization against rotavirus. Also playing a part in SelectHealth's decision to cover the rotavirus vaccine was the fact that plan decision makers anticipated a recommendation from the Advisory Committee on Immunization Practices (ACIP) that all pediatric patients be immunized, although no such recommendation existed at the time coverage was instituted.

Respiratory syncytial virus (RSV). In healthy adolescents and adults, RSV usually causes severe colds with limited complications; however, in infants, infection with the virus can lead to serious respiratory complications. As the RSV vaccine, palivizumab (Synagis), has been on the market for several years, use within SelectHealth has been established as a seasonal phenomenon. Approximately \$1 million is spent per quarter during the season in which use of the vaccine is highest. The RSV season typically runs from November through April.

To effectively manage use of palivizumab within the plan, the pharmacy department at SelectHealth collaborated with plan neonatologists and pediatricians to establish a measure indicating the beginning of the RSV season. A decision was made to open the RSV season when there were 5 positive tests for the virus within the system during any given week (typically, sometime in November). Testing data are collected and maintained by Intermountain Laboratory Services at Primary Children's Hospital in Salt Lake. Infectious disease specialists at Primary Children's Hospital monitor collected data.

Once the RSV season starts, SelectHealth notifies pediatricians that the RSV season has begun and that their authorizations for palivizumab are approved. Pediatricians can then begin vaccinating their patients. The RSV season is closed when there are fewer than 5 positive tests for the virus within the system during any given week. The goal of this protocol is to maintain use of the palivizumab as close to the 5 recommended doses as possible.

As with SelectHealth's policy with the rotavirus vaccine, the plan covers palivizumab under the nonstandard vaccination benefit, and patients are responsible for 20% of the cost of the **vaccination**. This policy was enacted because it was discovered that parents could take several steps to significantly reduce their children's exposure to RSV, and the burden of 20% of the vaccination cost encouraged them to take a more active role in preventing the disease.

HPV. HPV types 16 and 18 are implicated in 70% of cervical cancer, of which more than 12,000 cases are diagnosed in the United States every year. The quadrivalent HPV vaccine was approved in June 2006 and targets these HPV types as well as types 6 and 11, which are implicated in 90% of genital wart cases. The vaccine was evaluated in 4 randomized, placebo-controlled, double-blind clinical trials (N=15,719), with a median follow-up of 2 to 4 years, in concurrent administration with hepatitis B vaccine (n=1,871) and in combination with hormonal contraceptives (n=13,293).

The quadrivalent HPV vaccine is indicated for immunization in females aged 9 to 26 years and is administered as a 3-dose injection series. ACIP recommends routine vaccination of patients aged 11 to 12 years (starting as early as 9 years, based on provider discretion), in sync with their current pre-middle school vaccination schedule, and "catch-up" injections are recommended for patients aged 13 to 26 years. Vaccination of male patients has not been studied and is not recommended by ACIP.

The cost of the quadrivalent HPV vaccine (average wholesale price [AWP] minus 10%) is \$140 per dose, comprising \$134 in vaccine cost plus a \$6 administration fee. At SelectHealth, approximately 72,000 plan members are eligible for the vaccine, including 9,000 in the 11- to 12-year-old group and 63,000 in the 13- to 26-year-old "catch-up" group. The estimated uptake in vaccination in the group of 11- to 12-year-old plan members is initially slow, at 6% in the fall of 2006, rising a steady state of 40% to 60% by 2009. Breaking this down in terms of cost, SelectHealth projected a cost of \$228,000 for the vaccine in the fall of 2006, building to steady state at approximately \$1.52 to \$2.27 million in 2009. In consideration of the initially larger "catch-up" population at SelectHealth, cost estimates for the plan were approximately \$800,000 in 2006, with 2007 and 2008 estimates being just more than \$3 million. Assuming that nearly all of the "catch-up" within the plan will take place within 2007 and 2008, the cost estimates within this

TABLE 2 Estimated Annual Savings Associated With the Quadrivalent HPV Vaccine*

Disease State	Estimated No. of Cases	Estimated Total Avoidance (\$)
Cervical cancer	15	478,548
CIN 2/3	447	1.10 million
CIN 1	325	356,815
Abnormal Pap test/ no CIN	2,973	711,175
Genital warts	297	135,918
Total	4,057	2.78 million

* Possible annual vaccine cost savings: fewer treated for CIN 1/2/3, AIS, cancer (assume FULL vaccination)

CIN=cervical intraepithelial neoplasia.

population will likely drop to zero by 2009.

For the bottom-line cost of the quadrivalent HPV vaccine for SelectHealth, the estimates remain at approximately \$1 million for 2006, more than \$4 million for 2007 and 2008, and between \$1.52 and \$2.27 million once use hits steady state in 2009. In terms of total costs surrounding cervical cancer, it remains uncertain whether screening (i.e., pap tests) will continue in the long run at SelectHealth in light of the new vaccine. However, the continuation of screening is very likely, considering that the vaccine will not prevent all cases of cervical cancer. Still, the vaccine is estimated to save the plan approximately \$2.7 million per year at steady state, assuming full vaccination (Table 2).

When plan decision makers considered these substantial cost savings at steady state and the anticipated high use of the quadrivalent HPV vaccine in light of the demographics of SelectHealth's population, they decided to fully cover the vaccine for the remainder of 2006 and provide budgeting to allow for full coverage in the future. In other words, as opposed to the nonstandard vaccination benefit decision made with the rotavirus vaccine and palivizumab, SelectHealth plan leaders opted to make the quadrivalent HPV vaccine available to appropriate members at standard immunization status.

Although this decision was fairly straightforward at SelectHealth, considerations in the coverage of HPV immunizations in the future will likely be clouded by the emergence of new vaccines, the most prominent being the anticipated release of a bivalent HPV vaccine (Cervarix) within the next year. As new HPV vaccines become available, a new set of criteria will need to be evaluated to manage the products and provide the most clinically sound and cost-effective options to plan members. Among these criteria will be clinical considerations, such as the activity of new vaccines against different HPV types, the indications of the new vaccines, and any trial data available, with head-to-head data being the most preferable.

TABLE 3 Efficacy of the Herpes Zoster Vaccine in the Shingles Prevention Study⁹

Age (Years)	No. of Zostavax Subjects	No. of HZ Cases	Incidence per 1,000 Persons/Year	No. of Placebo Subjects	No. of HZ Cases	Incidence per 1,000 Persons/Year	Efficacy (%) (95% CI)
Overall	19,254	315	5.4	19,247	642	11.1	51 (44-58)
60-69	10,370	122	3.9	10,356	334	10.8	64 (56-71)
70-79	7,621	156	6.7	7,559	261	11.4	41 (28-52)
>80	1,263	37	9.9	1,332	47	12.1	18 (29-48)

Notes: Mean duration of follow-up: 3.1 years.

Primary efficacy analysis: 30 days postvaccination HZ development.

Highest efficacy in 60-to-69-year olds, lesser efficacy in older patients.

CI=confidence interval; HZ=herpes zoster.

Other plan-specific considerations at SelectHealth in light of new HPV vaccines becoming available will include the current use of the quadrivalent HPV vaccine, the plan's ability to contract for the different products, and the difficulty surrounding integration of new products. These factors become increasingly important because SelectHealth/Intermountain Healthcare is an integrated system.

Herpes zoster. The single-dose herpes zoster vaccine (Zostavax) was approved in May 2006 for the prevention of postherpetic neuralgia (PHN, i.e., shingles) in patients aged 60 years or older. One unique issue in the recent consideration of the herpes zoster vaccine in Intermountain's hospital pharmacy and therapeutics committees is that the product is a live-virus vaccine. Hospitalists raised concerns about using a potentially infectious agent around immunocompromised patients. This issue may hold specific implications for integrated systems. Still, PHN was one area in which plan leaders felt there was a significant opportunity for cost savings and overall benefit to the plan population.

In the Shingles Prevention Study, the herpes zoster vaccine demonstrated the greatest clinical benefit in patients aged 60 to 69 years, with 64% efficacy (Table 3).⁸ In patients developing PHN, the mean duration of clinically significant pain (greater than 3 on a 10-point scale) was 20 days in the vaccine group versus 22 days in the placebo group. Overall, the vaccine was 39% efficacious against PHN in patients who developed herpes zoster after vaccination. In addition, zoster-related complications were similar in the vaccinated and placebo groups.⁸

The cost of the herpes zoster vaccine (AWP minus 10%) is approximately \$178, including the administration fee. At SelectHealth, which has a generally younger population, approximately 21,000 patients are eligible for the vaccine, but the overall uptake is expected to be low, with higher uptake

during flu vaccination season. Total costs to the plan are expected to be \$112,000 initially with low uptake (3%), ramping up to \$299,000 at steady state uptake (8%) in 2009.

For the financial implications of the vaccine, there was \$388,000 in herpes zoster-related costs at SelectHealth in 2005. With an assumption of 50% immunization with the herpes zoster vaccine and 64% efficacy, the potential savings are as much as \$124,000. The bottom-line cost of the herpes zoster vaccine to SelectHealth is estimated to be \$240,000 to \$300,000 annually, but this cost could be reduced if the coverage required member coinsurance and/or a deductible. For example, 20% coinsurance would reduce plan costs by \$60,000 annually. Taking this into consideration, along with a relatively low expected uptake of the vaccine, decision makers at SelectHealth opted to make the herpes zoster vaccine available to plan members under a nonstandard immunization benefit, applying a 20% coinsurance requirement.

Conclusion

Although they complicate traditional pharmacy management, novel vaccines provide clinical benefit that MCOs cannot ignore. Furthermore, with several new vaccines on the market and even more on the horizon, the management of vaccines within managed care is of increasing importance. Although vaccine coverage was relatively unmanaged in the past, tremendous opportunities exist now in the immunization arena for MCOs to provide cost-effective, clinical benefits to their plan members.

Clearly, in the case of SelectHealth, benefit design has been critical to the management of vaccines within the plan population. Plan decision makers have taken many components into consideration, including clinical, economic, and governmental factors, and changes have been made accordingly to Select Health's existing benefit design.

Obviously, a single strategy will not suffice in managing all the different vaccines entering the market, and a tailored approach should be employed based on the individual characteristics and use of each product. Each vaccine management strategy available to managed care stakeholders has inherent strengths and weaknesses. The nonstandard vaccination strategy employed at SelectHealth, in particular, relies heavily on plan physicians to discuss with their patients the benefits and disadvantages of a specific vaccine. Decision makers at SelectHealth acknowledge that, ultimately, other vaccination strategies will need to be employed. Emerging vaccines will require plan leaders to continually revisit SelectHealth's benefit design to provide clinically and economically sound immunization options to its members.

DISCLOSURES

This article is based on a presentation given by the author at a symposium, "The Value of Preventive Medicine: A Look at Vaccine Management," held April 11, 2007, at the Academy of Managed Care Pharmacy's 19th Annual Meeting and Showcase in San Diego, California. The symposium was supported by an educational grant from GlaxoSmithKline. The author discloses that he has received an honorarium for participation in the presentation and in this supplement. He discloses no potential bias or conflict of interest relating to this article.

REFERENCES

1. Poland GA. Standards for adult immunization practices. *Am J Prev Med.* 2003;25(2):144-50.
2. National Committee on Quality Assurance. State of health care quality. 2006. Available at: http://www.ncqa.org/Communications/SOHC2006/SOHC_2006.pdf. Accessed March 20, 2007.
3. Centers for Disease Control and Prevention. CDC's advisory committee recommends new vaccine to prevent rotavirus. Press release. February 21, 2006. Available at: <http://www.cdc.gov/od/oc/media/pressrel/r060221.htm>. Accessed July 2, 2007.
4. Velazquez FR, Matson DO, Calva JJ. Rotavirus infection in infants as protection against subsequent infections. *N Engl J Med.* 1996;335:1022-28.
5. Parashar U, Bresee JS, Gentsch JR, Glass RI. Rotavirus. *Emerg Infect Dis.* 1998;4(4). Available at: <http://www.cdc.gov/ncidod/EID/vol4no4/parashar.htm>. Accessed July 2, 2007.
6. Lee BP, Staat M, Louie L. Nonmedical costs associated with rotavirus disease. *Pediatr Infect Dis J.* 2005;24:984-88.
7. Vesikari T, Matson DO, Dennehy P. Safety and efficacy of a pentavalent human bovine (WC3) reassortment rotavirus vaccine. *N Engl J Med.* 2006;354(1):23-33.
8. Oxman MN, Levin MJ, Johnson GR. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med.* 2005;352:2271-84.

Economic Benefits and Costs Associated With Target Vaccinations

Edward P. Armstrong, PharmD, FASHP

ABSTRACT

BACKGROUND: As a therapeutic class, vaccines are generally considered to be the health care intervention that provides the best value. In the pharmacoeconomic study of vaccines, it is common for researchers to conduct their analyses from a societal perspective, including direct medical costs as well as indirect costs.

OBJECTIVE: To discuss the data elements of pharmacoeconomic analyses of vaccines and review recently published analyses of emerging vaccines.

SUMMARY: Myriad pharmacoeconomic analyses of vaccines currently in use have been conducted with varying results. A number of products, such as the diphtheria-tetanus-acellular pertussis, hepatitis B, and varicella vaccines, have been shown to be cost-effective from a societal perspective. Yet, other products, such as the pneumococcal conjugate vaccine, have demonstrated less benefit than the cost of their respective vaccination programs. In general, these analyses can be used as a starting point to frame the benefits of specific vaccines in managed care with a balanced view of the necessary societal perspectives. To date, 6 pharmacoeconomic models have evaluated vaccination against human papillomavirus, with all demonstrating some cost benefit when the vaccine was used in female patients who fell within the indicated age range.

CONCLUSIONS: In general, as a therapeutic class, vaccines are extremely cost-effective agents. In addition, they are one of the few public health interventions that may directly lower medical costs. In conducting pharmacoeconomic analyses for agents in this class, researchers must consider costs incurred at both the health system and societal levels, as well as cost savings realized through the prevention of disease.

KEYWORDS: Pharmacoeconomic, Cost, Cost-effective, Vaccine, HPV, Hepatitis
J Manag Care Pharm. 2007;13(7)(suppl S-b):S12-S15

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

As a therapeutic class, vaccines are generally considered to be the health care intervention that provides the best value.¹ Vaccine products are known to have provided more benefit to society than expense, and they have been estimated to save society more than \$5 for each dollar spent on most routine pediatric vaccinations.² Two vaccines that have had a remarkable impact on eliminating diseases are the polio and smallpox vaccines.³ Other serious diseases that have been prevented include diphtheria, tetanus, whooping cough, invasive *Haemophilus influenzae* type b disease, rubella, mumps, and measles. In light of the success of vaccines to date, high immunization rates remain the key for society to continue to benefit from these preventive treatments.

Vaccines have had an impressive impact on decreasing disease morbidity within the United States, as evidenced by the Centers for Disease Control and Prevention's annual morbidity estimates for a range of diseases both before the introduction of vaccines and their current estimates (Table 1).^{4,5} It is noted that the annual burden for these 9 diseases has either approached or exceeded a 90% reduction through the use of vaccines.^{4,5}

In addition to the impact of vaccines within the United States, vaccination programs have also had a worldwide effect in reducing the number of deaths from specific diseases.¹ Table 2 highlights that nearly 3 million lives have been saved globally from vaccine-preventable diseases because of increased vaccine coverage.¹ Ehreth¹ has compiled data demonstrating the following:

- Savings in direct medical costs due to the eradication of smallpox in 1977 exceed \$300 million dollars per year.
- One case of measles is estimated to cost 23 times the amount spent to vaccinate 1 child against measles.
- For every dollar spent on measles-mumps-rubella vaccine, more than \$21 is saved in direct medical costs.
- For every dollar spent on diphtheria-tetanus-acellular pertussis vaccine, more than \$24 is saved.
- For every dollar spent on *H. influenzae* type b vaccine, more than \$2 is saved.

Data Elements of Pharmacoeconomic Analyses of Vaccines

For many pharmacoeconomic analyses, the study perspective has often been that of a health system, and the primary cost data collected are direct medical costs (e.g., medication costs, cost of hospitalizations for severe illness, costs associated with the management of adverse events). However, in pharmacoeconomic studies of vaccines, it is common for researchers to conduct their analyses from a societal perspective, including direct medical costs as well as indirect costs. Indirect costs include considerations for cost savings resulting from the preventive elements of vaccines, such as fewer missed work days.⁶ For

Author

EDWARD P. ARMSTRONG, PharmD, is a professor, pharmacy practice and science and pharmaceutical services, College of Pharmacy-Drachman Hall, University of Arizona, Tucson.

AUTHOR CORRESPONDENCE: Edward P. Armstrong, PharmD, Professor, College of Pharmacy-Drachman Hall, University of Arizona, Tucson, AZ 85721. Tel: (520) 626-5764; Fax: (520) 626-7355; E-mail: armstrong@pharmacy.arizona.edu

TABLE 1 Comparison of Morbidity Before and After Introduction of Vaccines^{4,5}

Disease	Annual Morbidity Before Introduction ¹	Current Annual Morbidity ²	% Decrease
Diphtheria	175,885	0	99.9
Measles	503,282	37	99.9
Mumps	152,209	236	99.8
Pertussis	147,271	18,957	87.1
Polio (paralytic)	16,316	0	100
Rubella	47,745	12	99.9
Congenital rubella syndrome	823	0	100
Tetanus	1,314	26	98.0
<i>H. influenza</i>	20,000	172	99.1

TABLE 2 Estimated Impact of Increased Vaccine Coverage on Vaccine-Preventable Diseases¹

Disease	Annual Deaths Prevented
Hepatitis B	900,000
Measles	888,000
<i>Hemophilus influenza b</i>	400,000
Pertussis	346,000
Neonatal tetanus	215,000
Tetanus	195,000
Yellow fever	30,000
Diphtheria	5,000
Poliomyelitis	720
Total	2,979,720

example, the calculated vaccine benefit when considering indirect costs may include the savings realized when parents do not need to take time off from work because the administered vaccine prevented pediatric infections from occurring. Similarly, because vaccines may prevent death, another benefit considered in pharmacoeconomic analyses of vaccines is that they allow children to mature into productive members of society. In these analyses, vaccine intervention costs may be compared against reduced disease treatment costs, work loss costs, and patient mortality costs. Including indirect costs in pharmacoeconomic analyses provides the broadest assessment of vaccines and improves their cost-effectiveness because they include financial benefits that occur outside of health systems.

Review of Pharmacoeconomic Analyses of Vaccines

Using the aforementioned direct and indirect cost considerations, myriad pharmacoeconomic analyses of vaccines currently in use have been conducted with varying results. In general, these analyses can be used as a starting point to frame the benefits of specific vaccines in managed care with a balanced view of necessary societal perspectives. The following review of select published pharmacoeconomic analyses of vaccines demonstrates the value of conducting these analyses in managed care when all relevant criteria are considered.

The diphtheria-tetanus-acellular pertussis vaccine has been shown to be cost-effective from both the societal and health system perspectives.⁷ The hepatitis B vaccine has been shown to be cost-effective from a societal perspective, costing \$1,522 per year of life gained when administered to infants from a health system perspective.⁸ The varicella vaccine has been shown to be cost-effective from a societal perspective and to cost \$2,500 per year of life gained from a health system perspective.⁹ However, the pneumococcal conjugate vaccine has been shown to cost \$80,000 per year of life gained from a societal perspective (i.e., the benefit was less than the cost of the vaccination program).¹⁰ The authors noted that although the pneumococcal conjugate vaccine can be a useful and important vaccine, it provides less value economically at the manufacturer's list price.

One analysis compared the cost-benefit and cost-effectiveness of varicella, hepatitis A, and pneumococcal conjugate vaccines.¹¹ The authors reviewed U.S. cost-effectiveness studies and assessed each vaccine from both a health system and societal perspective. From a societal perspective, the varicella vaccine had a cost-benefit ratio between \$4.76 and \$5.61 for each dollar spent. From a societal perspective, the hepatitis A vaccine had a cost-benefit ratio of \$1.96 for each dollar spent. However, from a societal perspective, the pneumococcal conjugate vaccine had a benefit of \$0.68 for each dollar spent (i.e., the financial benefit was less than the cost of the vaccination program). The authors noted that the pneumococcal conjugate vaccine would cost twice the amount of the varicella and hepatitis A vaccines combined and would be less cost-effective than the other vaccines.

Pharmacoeconomic analyses can also be applied to evaluate the use of different forms of the same vaccine (e.g., inactivated vs. live attenuated) compared with simply evaluating use versus nonuse. One study created cost-benefit and cost-effectiveness models to compare the introduction of inactivated poliovirus vaccine to reduce vaccine-associated paralytic poliomyelitis, an uncommon complication that is associated with the live-attenuated oral poliovirus vaccine.¹² Use of the inactivated poliovirus vaccine was estimated to cost at least \$3 million for each case of vaccine-associated paralytic poliomyelitis that was avoided.

In addition to assessing the value of specific vaccines in managed care, pharmacoeconomic analyses can also be used to evaluate different strategies for vaccination. One study created a decision-analytic model using direct medical costs to

TABLE 3 Projected Clinical Outcomes of Human Papillomavirus Vaccination¹⁶

Outcome*	HPV Vaccination	No HPV Vaccination	Lifetime Cases Averted	No. Needed to Vaccinate to Prevent 1 Case
HPV	1,460,699	1,684,954	224,255	9
SIL	417,549	530,259	112,710	18
Cervical cancer	13,374	16,690	3,316	600
Cervical cancer deaths	5,121	6,461	1,340	1,484

* Assumes program that successfully administers a vaccine against high-risk HPV to the current U.S. cohort of 12-year-old girls.

HPV=human papillomavirus; SIL=squamous intraepithelial lesions.

TABLE 4 Projected Cost-Effectiveness of Human Papillomavirus Vaccination¹⁶

Outcome*	No HPV Vaccination	HPV Vaccination
Cost, \$	39,682	39,928
Incremental cost, \$		246
Life expectancy, years	28.785	28.793
Incremental life expectancy, days		2.8
Quality-adjusted life expectancy, years	27.72	27.731
Incremental quality-adjusted life expectancy, days		4
Incremental cost-effectiveness \$/life-year		
\$/life-year gained		32,066
\$/quality-adjusted life-year gained		22,755

* Assumes program that successfully administers a vaccine against high-risk HPV to the current U.S. cohort of 12-year-old girls.

HPV=human papillomavirus.

routinely vaccinate incoming first-year college students living in dormitories.¹⁴ The authors determined that the cost of the needed vaccination program would far exceed the benefits of preventing meningococcal disease. It was estimated that the net cost per meningococcal case averted ranged from \$0.6 million to \$1.9 million and from \$7 million to \$20 million per death averted. The authors did not recommend routine vaccination of first-year U.S. college students living in dormitories because of the low incidence of disease and the high cost of the vaccination program.

One vaccine under particular scrutiny in managed care is the recently introduced human papillomavirus (HPV) vaccine. To date, 6 pharmacoeconomic models have evaluated vaccination against HPV.¹⁵ One model estimated the impact of vaccinating all 12-year-old girls in the United States with a vaccine active against HPV-16 and HPV-18.¹⁶ The authors estimated the number of lifetime cases of cervical squamous intraepithelial lesions and cases of cervical cancer that could be prevented with such an immunization program. Table 3 summarizes the estimated clinical benefits of HPV vaccination. The authors estimated that 18 girls would need to be vaccinated to prevent 1 case of cervical squamous intraepithelial lesion and 600 girls would need to be vaccinated to prevent 1 case of cervical cancer.¹⁶ Table 4 summarizes the cost and cost-effectiveness results from the analysis. The authors estimated the cost per quality-adjusted life-year gained to be \$22,755 for the cohort of 12-year-old girls.¹⁶

The authors then revised their model to include a range of vaccine efficacies as well as population penetration of HPV and compared the vaccination of only 12-year-old girls versus the vaccination of both girls and boys.¹⁷ They estimated that the number of expected lifetime cases of cervical cancer related to HPV-16 or HPV-18 would decrease by 95.4% and that vaccination would add an average of 6.1 quality-adjusted life-years per woman. The cost-effectiveness ratio of the HPV vaccine was estimated to be \$14,583 per quality-adjusted life-years gained. When the authors examined the vaccination of both girls and boys, it was estimated that cervical cancer cases would drop by 98.8% compared with no vaccination program and that an incremental 0.21 quality-adjusted life-year would be added per woman compared with only the vaccination of girls. However, the incremental cost-effectiveness ratio of \$442,039 per quality-adjusted life-years gained compared with only the vaccination of girls was substantial. Because this incremental ratio was so large, the authors did not recommend the vaccination of boys.¹⁷

Conclusions

Vaccinations are one of the most significant public health interventions to emerge in the past century. In conducting pharmacoeconomic analyses for agents in this class, researchers must consider costs incurred at both the health system and societal levels as well as cost savings realized through the prevention

compare 2 treatment strategies for patients with hepatitis C to be vaccinated against both hepatitis A and hepatitis B.¹³ The authors determined that a universal strategy of immunizing patients suffering from hepatitis C against both hepatitis A and hepatitis B was more effective, but more costly, than first testing patients for immunity and then selective immunization. However, the incremental cost-effectiveness ratio was only \$154 for the universal immunization strategy, indicating that this was a very good value and therefore recommended by the authors.

In assessing vaccination strategies, another study evaluated whether it was cost-beneficial, from a societal perspective, to

of disease. Overall, as a therapeutic class, vaccines are extremely cost-effective agents. In addition, vaccines are one of the few public health interventions that may directly lower medical costs. The cost of many vaccinations is less than the cost needed to treat preventable diseases. Emerging vaccines, including those targeting HPV, also appear to be cost-effective interventions.

Despite the clinical success and cost-effectiveness of many vaccination programs, it is very important to remain vigilant in achieving high vaccination rates, especially for children. Even though some previous theoretical concerns (e.g., possible autism caused from the measles-mumps-rubella vaccine) have been refuted, improved vaccination rates should still be sought.¹⁸ If vaccination rates drop, the United States would be susceptible to infection from countries where specific vaccines were either unavailable or underused.

DISCLOSURES

This article is based on a presentation given by the author at a symposium, "The Value of Preventive Medicine: A Look at Vaccine Management," held April 11, 2007, at the Academy of Managed Care Pharmacy's 19th Annual Meeting and Showcase in San Diego, California. The symposium was supported by an educational grant from GlaxoSmithKline. The author discloses that he has received an honorarium for participation in the presentation and in this supplement. He discloses no potential bias or conflict of interest relating to this article.

REFERENCES

1. Ehreth J. The global value of vaccination. *Vaccine*. 2003;21:596-600.
2. Gardner P, Pickering LK, Orenstein WA, Gershon AA, Nichol KL. Infectious Diseases Society of America. Guidelines for quality standards for immunization. *Clin Infect Dis*. 2002;35:503-11.
3. Abramson JS, Pickering LK. US immunization policy. *JAMA*. 2002;287:505-09.
4. Centers for Disease Control and Prevention. Ten great public health achievements—United States, 1900-1999. *MMWR Morb Mortal Wkly Rep*. 1999;48:242-64.
5. Centers for Disease Control and Prevention. Notifiable diseases/deaths in selected cities weekly information. *MMWR Morb Mortal Wkly Rep*. 2005;53:1213-21.
6. Meltzer MI. Introduction to health economics for physicians. *Lancet*. 2001;358:993-98.
7. Ekwuene DU, Strebel PM, Hadler SC, Meltzer MI, Allen JW, Livengood JR. Economic evaluation of use of diphtheria, tetanus, and acellular pertussis vaccine or diphtheria, tetanus, and whole-cell pertussis vaccine in the United States, 1997. *Arch Pediatr Adolesc Med*. 2000;154:797-803.
8. Margolis HS, Coleman PJ, Brown RE, Mast EE, Sheingold SH, Arevalo JA. Prevention of hepatitis B virus transmission by immunization. An economic analysis of current recommendations. *JAMA*. 1995;274:1201-08.
9. Lieu TA, Cochi SL, Black SB, et al. Cost-effectiveness of a routine varicella vaccination program for US children. *JAMA*. 1994;271:375-81.
10. Lieu TA, Ray GT, Black SB, et al. Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. *JAMA*. 2000;283:1460-68.
11. Jacobs RJ, Meyerhoff AS. Comparative cost effectiveness of varicella, hepatitis A, and pneumococcal conjugate vaccines. *Prev Med*. 2001;33:639-45.
12. Miller MA, Sutter RW, Strebel PM, Hadler SC. Cost-effectiveness of incorporating inactivated poliovirus vaccine into the routine childhood immunization schedule. *JAMA*. 1996;276:967-71.
13. Jakiche R, Borrego ME, Raisch DW, Gupchup GV, Pai MA, Jakiche A. The cost-effectiveness of two strategies for vaccinating US veterans with hepatitis C virus infection against hepatitis A and hepatitis B viruses. *Am J Med Sci*. 2007;333:26-34.
14. Scott II RD, Meltzer MI, Erickson LJ, De Wals P, Rosenstein NE. Vaccinating first-year college students living in dormitories for meningococcal disease. An economic analysis. *Am J Prev Med*. 2002;23:98-105.
15. Dasbach EJ, Elbasha EH, Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. *Epidemiol Rev*. 2006;28:88-100.
16. Sanders GD, Taira AV. Cost effectiveness of a potential vaccine for human papillomavirus. *Emerg Infect Dis*. 2003;9:37-48.
17. Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerg Infect Dis*. 2004;10:1915-23. Abramson JS, Pickering LK. US immunization policy. *JAMA*. 2002;287:505-09.

Multiple Vaccines: How Do We Choose?

Neil B. Minkoff, MD

ABSTRACT

BACKGROUND: As preventive medicine is a cornerstone of managed care, most health plans have traditionally featured automatic vaccine coverage routed through the medical benefit. However, with the advent of emerging vaccines, managed care stakeholders must revise decision-making processes and choose among multiple products targeting the same disease.

OBJECTIVE: To review the motivating forces behind traditional vaccine coverage in managed care and discuss the need for managed care organizations (MCOs) to subject their vaccine policies to greater examination in the changing landscape of emerging vaccines.

SUMMARY: While variable vaccine coverage or choices in vaccine coverage is a relatively novel concept in managed care, the evaluation of vaccines in this setting is usually most effectively performed via a traditional route for MCOs: the Pharmacy & Therapeutics (P&T) committee. In some cases, a technology assessment committee is a more appropriate avenue for evaluation, depending on the disease state, administration, and plan infrastructure. Through these routes of evaluation, criteria similar to those used for other pharmaceutical agents under review should be employed in the review of vaccine options. The primary criteria evaluated include safety, efficacy, cost, and value. In addition, a set of miscellaneous factors must also be considered, including both tangible and intangible components. For example, the relevance of an agent to the specific covered population, compliance costs offsets, quality-of-life considerations, and both patient and provider demand should all be taken into account. Human papillomavirus vaccination provides a pragmatic example for applying the aforementioned strategy for vaccine evaluation in managed care.

CONCLUSION: The changing landscape of vaccine coverage in managed care, particularly in the availability of novel agents, demonstrates a need for MCOs to subject their vaccine policies to much greater examination. Through traditional avenues such as P&T and technology assessment committees, stakeholders should seek to evaluate standard criteria such as safety, efficacy, and cost-effectiveness, with additional considerations made for factors unique to the preventive nature of vaccines.

KEYWORDS: Vaccine, P&T, HPV, Safety, Effectiveness, Cost

J Manag Care Pharm. 2007;13(7)(suppl S-b):S16-S20

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

In choosing between multiple vaccine options, managed care stakeholders currently have few definitive answers. This is due, in part, to the fact that variable vaccine coverage or choice in vaccine coverage is a relatively new concept in the industry. As preventive medicine is a cornerstone of managed care, most plans have traditionally featured automatic vaccine coverage routed through the medical benefit.¹ In fact, just 8 years ago, the National Vaccine Advisory Committee (NVAC) sponsored an article published in the *Journal of the American Medical Association*, pointing out the near-universal coverage of vaccines by managed care organizations (MCOs).^{1,2} Members traditionally had little or no cost share, depending on whether or not there was an office visit with the administration, and plans rarely chose preferred products or implemented any contracting or rebating. Instead, decisions were based on current Advisory Committee on Immunization Practices (ACIP) recommendations. If ACIP recommendations were in any way unclear or required augmentation, plans would seek the advice of different specialty groups such as the American Academy of Pediatrics.

These supplemental recommendations tended to be brought to MCO technology assessment committees (i.e., the medical benefit version of pharmacy and therapeutics committees) and were, for the most part, implemented as the benefits offered by the plan. This focus on promoting preventive medicine complemented the birth of managed care in general, particularly since health maintenance organization (HMO) models with fully insured membership was the norm during this formative period. This developmental period in managed care also featured the introduction of population management—looking beyond just the interaction between the physician and the member to a broader mix of patient types—and the early concepts of longitudinal care. Vaccines were a very obvious place to begin this level of preventive care, and the administration of these agents fit very well with the philosophies and the practices upon which managed care and HMOs were being built.

In addition to the preventive benefit of these agents, the historically universal coverage of vaccines in managed care can be attributed to the extra layer of complexity added when attempting to manage these agents due to state mandates. Although these mandates feature a significant amount of overlap (e.g., requirements for the coverage of pediatric vaccines), differences exist from state to state in terms of vaccine requirements and what each state provides. For example, in Massachusetts most of the vaccines administered by pediatricians are supplied to the doctor cost-free by the state and administered as part of the public health mission of the state.³ This added layer of complexity requires that Massachusetts MCOs know which vaccines are the responsibility of the MCO and which are provided thorough public funding. The gap between what the

Author

NEIL B. MINKOFF, MD, is medical director, and pharmacy, Harvard Pilgrim Health Care, Wellesley, Massachusetts.

AUTHOR CORRESPONDENCE: Neil B. Minkoff, MD, Medical Director, Network Services and Pharmacy, Harvard Pilgrim Health Care, 93 Worcester St., Wellesley, MA 02481. Tel: (617) 509-0170; Fax: (617) 509-9144; E-mail: neil_minkoff@harvardpilgrim.org

state mandates and what the state will fund has been a significant concern to MCOs. However, many MCOs have settled on the position of covering this gap and end up having variable coverage rules in each state in which they participate.

■ Shifting Paradigm

The traditional notion of universal vaccine coverage in managed care is changing. In turn, managed care stakeholders must be aware of the reasons for this trend and devise strategies to deal with the shifting paradigm.

Much of the need for vaccine decision making in managed care is the result of novel vaccines that have been recently released or vaccines currently in the pipeline. The need for vaccine management in managed care will only increase as time goes on, with advances in drug development predicting hundreds of disease states, including chronic infections such as human immunodeficiency virus and noninfectious conditions such as Alzheimers, whose illness burden could be potentially lessened by vaccination. In addition, more combination products are being developed and becoming available.

This is of particular interest from a formulary management perspective, since pharmacy and therapeutics (P&T) committee members will have to ascertain if specific combination vaccines are more efficacious than their respective individual counterparts and ultimately worth the additional cost. Furthermore, advancements in vaccine technology have provided potential benefits in terms of effectiveness, but this comes at a higher cost; P&T committee members will again need to determine if the additional clinical benefit justifies the increased cost in these cases. These cost considerations also come into play with newer, recently introduced single vaccines, which carry a generally high cost, in addition to combination products. This becomes even more significant when plans compare the cost of recently introduced vaccines with traditional ones that are generally less costly and sometimes provided by the state. At Harvard Pilgrim in Wellesley, MA, for example, coverage of the quadrivalent human papillomavirus (HPV) vaccine (Gardasil) will result in an increase in medical spending, which may in turn lead to rising premiums and future problems in terms of coverage issues and what employers choose to fund.

In addition to the clinical and financial components being evaluated in the coverage of recently introduced vaccines is the question of scope from an individual and population perspective. While coverage of traditional vaccines was often a matter of public health (e.g., influenza), many recently introduced and pipeline vaccines target conditions that are mainly relevant on an individual level (e.g., herpes zoster). While traditional vaccines have led to the virtual eradication of highly contagious communicable diseases, including those that involve mass mortality, some of the newer vaccines are much more focused on personal health. As a result, the public health component is beginning to be removed from vaccine management as managed

care increasingly moves toward the individual state.

The introduction of new vaccines has also initiated the issue of competition between agents targeting the same disease state. The live intranasal influenza vaccine (FluMist) provides an excellent example of an agent with competitors that has been given significant consideration. Initially, vaccination with the live intranasal influenza vaccine was not embraced by many organizations because of a noncompetitive price and concerns over the use of a live rather than attenuated virus. While MCOs wanted to encourage as many members as possible to get immunized against influenza for herd immunity, concerns remained regarding members who most needed to be immunized (i.e., elderly patients, pediatric patients, and immuno-suppressed patients) not receiving a live virus.

Data from a 2006 clinical study demonstrating safety and immunogenicity for the live intranasal influenza vaccine in the pediatric population of patients down to the age of 1 year provides additional support for the live intranasal vaccine, which is now being factored into coverage considerations.⁴ In addition, the cost of the live intranasal influenza vaccine has decreased, warranting further use of the agent in the organization. These recent developments have influenced MCOs to trust their clinicians to know which population should not have a live virus and to reserve the live virus for the members of the population that are needed to boost the herd immunity. In another disease state, these competitive considerations will come into play once more if GlaxoSmithKline's bivalent HPV vaccine (Cervarix) is approved as anticipated, since there is a quadrivalent HPV vaccine currently on the market.

■ Managed Care Adaptation Strategies

While variable vaccine coverage or choice in vaccine coverage is a relatively novel concept in managed care, the evaluation of vaccines in this setting is usually most effectively performed via a traditional route for MCOs: the P&T committee. In some cases a technology assessment committee is a more appropriate avenue for evaluation, depending on the disease state, administration, and plan infrastructure. A hybrid of both P&T and technology assessment committee evaluation is also an option, based on situational factors. Taking these routes of evaluation into consideration, adult vaccines should generally receive more scrutiny in terms of coverage than pediatric vaccines, mostly due to the fact that the more recently introduced adult vaccines have less of a public health orientation than pediatric vaccines. Furthermore, pediatricians have been a very vocal group in terms of quadrivalent HPV vaccine coverage since the product's approval, requiring many plans to change some of the manners in which they interact with their pediatric communities. The pediatric community is sensitive to coverage issues regarding vaccines since vaccines (a) generally do not face many of the cash flow issues that can occur with buying and billing by physicians and (b) have traditionally been available free from

the state. At Harvard Pilgrim, issues surrounding the coverage of the quadrivalent HPV vaccine have affected the organization's relationship with its members and its network in a number of different ways. Regardless, the industry appears to have reached a consensus to start evaluating novel vaccines in the same manner as other pharmaceutical products that have come to market.

In evaluating the various vaccine options available to MCOs, criteria similar to those used for other pharmaceutical agents under review should be employed. The primary criteria evaluated include safety, efficacy, cost, and value. In addition, a set of miscellaneous factors must also be considered, including both tangible and intangible components. For example, the relevance of an agent to the specific covered population, compliance costs offsets, quality of life considerations, and both patient and provider demand should all be taken into account. These factors have significant managed care implications in the evaluation of recently introduced and pipeline vaccines. For example, if an organization starts making a push towards combination vaccines, reduced adolescent drop-off rates may result due to a fewer number of injections necessary. Combination vaccines may also positively affect quality of life for the same reasons. Considering it is much easier and much less expensive to keep a customer than to make a customer, patient demand should be taken into account in vaccine coverage evaluation.

Although the traditional criteria of safety, effectiveness, and cost must be factored into the evaluation of recently introduced vaccines, the depth and breadth of data used in the review of other pharmacotherapeutic agents is typically not available. A comprehensive level of reporting, such as that found in AMCP dossiers, is usually not possible for novel vaccines. When evaluating data on the safety of new vaccines entering the market, MCOs must often rely only on data submitted for U.S. Food and drug Administration approval and experience in other countries. With limited follow-up data available, the long-term effects of a recently approved vaccine are unknown. Similarly, MCOs must often rely only on submission data and experience in other countries in terms of effectiveness. While limited follow-up data evaluating effectiveness is a concern to both the private and public sectors, it becomes more of a significant issue to MCOs considering the long-range financial implications of a vaccine whose effectiveness declines as time goes on. Demonstrating the significance of declining effectiveness in the long-term, the live varicella vaccine (Varivax) was initially administered as a 1-time injection for the prevention of chicken pox. However, after postmarket experience demonstrated that protection against varicella declined over time, it became apparent that booster injections would be necessary. This was a clinically significant development to MCOs: children who initially had immunity against varicella through vaccination rather than virus exposure now required booster injections or risk developing more severe disease at an older age.⁵

Evaluation of the economic factors associated with vaccines is a new area for managed care. Whereas at one time vaccines were covered in a generally universal manner, stakeholders are now presented with a complex array of financial considerations. With a discounted average wholesale price (AWP) paid through the medical benefit and currently no member cost share or rebating, the upfront costs of vaccines are clear. However, considering that the value of vaccines lies in the prevention of disease and reduced expenses in the long term, cost offsets are not realized initially. Other factors must be taken into account as well, including the rise of unfunded mandates by states, which will result in increased costs to MCOs, and demand for recently introduced vaccines from patients, providers, and administrative service organization employers.

■ An Example: HPV Vaccination

HPV vaccination provides a pragmatic example for applying the aforementioned strategy for vaccine evaluation in managed care. As mentioned earlier, the market currently features 1 available quadrivalent vaccine for HPV prevention, but approval of a bivalent vaccine is anticipated in the near future. Considering the clinical and economic implications of cervical cancer in managed care, as well as the relatively high cost of the vaccines, this example highlights many of the difficulties MCOs will face in evaluating and managing emerging vaccines.

HPV remains a significant concern in managed care, with >100 types in total and >30 types being transmitted through sexual contact.⁶ Six million new genital HPV infections occur annually in the United States, but more importantly, persistent HPV infection is the leading cause of cervical dysplasia and neoplasia.⁶ In fact, 70% of cervical cancer is linked to types 16 and 18, and an estimated 10,000 women are diagnosed with the cancer every year.⁶ Considering the prevalence of HPV, the disease's association with cervical cancer, and uncertainty surrounding the protection offered by condoms against HPV, vaccination for HPV presents a significant opportunity for MCOs to potentially decrease mortality and avert costs.

In evaluating the vaccines targeting HPV for administration in a managed care population, stakeholders must first compare the clinical characteristics of each agent. To start, both the quadrivalent and bivalent HPV vaccines provide immunity against HPV types 16 and 18, the types responsible for 70% of cervical cancer. While the quadrivalent HPV vaccine also offers immunity against types 6 and 11 and thereby provides more genital wart protection, the ASO4 adjuvant employed by the bivalent HPV vaccine has demonstrated improved immune response and potentially improved cancer protection.^{7,8} Both vaccines have demonstrated excellent safety profiles and effectiveness for patients aged >4 years. Although no direct comparative data exist for the 2 products, researchers are currently recruiting patients for a head-to-head trial.⁹ Also, as pricing for the bivalent HPV vaccine has not yet been

released, this component of the evaluation cannot yet be directly addressed.

Using only currently available public information, it is likely that both agents would be viewed favorably by a P&T committee in terms of their safety profiles. The effectiveness discussion would center around the potential benefit of the bivalent HPV vaccine adjuvant versus the quadrivalent HPV vaccine adjuvant for types 6 and 11. With these 2 criteria at a virtual stalemate due to a lack of definitive data, cost-effectiveness would likely become the deciding factor.

In the evaluation of HPV vaccines, managed care stakeholders have to take into consideration several confounding variables that may have an impact on product utility or overall costs (see Figure). Among these are state mandates on vaccination requirements, which may dictate certain subpopulations that must be vaccinated, as well as the controversy related to mandatory vaccination, which may put customers at odds with their MCO. Also confounding the evaluation of HPV vaccines are questions regarding the long-term efficacy of the products, since necessary booster shots will increase costs. Concerns from groups who believe that HPV vaccination promotes promiscuity are being voiced,¹⁰ and this confounding variable will likely only increase as an additional product is approved and mandatory vaccination policies are put into place. Finally, administrative service organization employers present a unique situation where the MCO and the employer may have opposing views on patient benefit needs in terms of vaccination.

Opportunities for MCOs

Although managed care stakeholders face uncharted territory considering the rapidly evolving vaccine environment, opportunities similar to those employed in the management of other pharmacotherapeutic agents exist to lessen the impending economic burden. For example, contracts and rebating can be combined with a preferred product to reduce direct costs and promote the use of a specific vaccine. In terms of benefit design, a rider for the coverage of certain vaccines may be layered onto the basic insurance platform in specific situations without totally revamping current policies. The tiering of vaccines on formulary with variable member cost share may be used to promote the use of the most cost-effective product while still retaining patient choice. Members may also bear greater cost share for vaccines with less public health focus, and/or nonpreferred products, so as to encourage herd immunity and reduce costs.

Conclusion

The changing landscape of vaccine coverage in managed care, particularly in the availability of novel agents, demonstrates a need for MCOs to subject their vaccine policies to much greater examination. Through traditional avenues such as P&T and technology assessment committees, stakeholders should seek to evaluate standard criteria such as safety, efficacy, and cost-effectiveness,

FIGURE Confounding Variables Associated With HPV Vaccination in Managed Care

ASO=administrative service organization; HPV=human papillomavirus.

with additional considerations made for factors unique to the preventive nature of vaccines. A greater deal of scrutiny should be placed on coverage for adult rather than pediatric vaccines since these agents are typically more individually centered instead of being based on the premise of herd immunity.

As a result of the high cost of the novel vaccines currently being introduced, manufacturers will need to demonstrate the improved cost offsets and cost-effectiveness of their products over traditional vaccines. Again, additional considerations such as the relevance of an agent to the specific covered population, compliance cost offsets, quality-of-life considerations, and both patient and provider demand will be reviewed by managed care stakeholders, so legitimate value must be evident. As many of the novel vaccines being introduced are focused on preventing disease at the individual level, state governments will need to engage in dialogue with MCOs and employers to carefully delineate where there are mandates related to public health and where vaccine coverage should remain at the individual level.

Considering the emergence of myriad novel vaccines for both previously targeted and untargeted disease states, a creative and careful strategy is necessary for MCOs to maintain patient health and plan profitability. Ultimately, a sound evaluation strategy for emerging vaccines will be based on the clinical, data-driven processes employed for other pharmacotherapeutic agents, with additional considerations made at the patient, provider, and government levels.

DISCLOSURES

This article is based on a presentation given by the author at a symposium, "The Value of Preventive Medicine: A Look at Vaccine Management," held April 11, 2007, at the Academy of Managed Care Pharmacy's 19th Annual Meeting and Showcase in San Diego, California. The symposium was supported by an educational grant from GlaxoSmithKline. The author discloses that he has received an honorarium for participation in the presentation and in this supplement. He discloses no potential bias or conflict of interest relating to this article.

REFERENCES

1. France E. Vaccine financing: the view of managed care. *Am J Prev Med*. 2000;19(3s):23-25.
2. National Vaccine Advisory Committee. Strategies to sustain success in childhood immunizations. *JAMA*. 1999;282:363-70.
3. Commonwealth of Massachusetts Department of Health. Immunization program. Available at: <http://www.mass.gov/dph/cdc/epii/imm/imm.htm>. Accessed April 12, 2007.
4. Anonymous. MedImmune presents new data from pediatric studies with FluMist at pediatric academic societies annual meeting. MedImmune Web site. Available at: <http://phx.corporate-ir.net/phoenix.zhtml?c=83037&p=irol-investornewsArticle&ID=849707&highlight>. Accessed July 24, 2007.
5. Centers for Disease Control and Prevention. Vaccines and immunizations. Available at: <http://www.cdc.gov/vaccines/vpd-vac/varicella/default.htm>. Accessed April 12, 2007.
6. National Cancer Institute. Human papillomavirus vaccines: questions and answers. Available at: <http://www.nci.nih.gov/cancertopics/factsheet/risk/HPV-vaccine>. Accessed July 2, 2007.
7. Gardasil [package insert] Whitehouse, NJ: Merck & Co; 2007.
8. Gianni SL, Hanson E, Moris P, et al. Enhanced humoral and memory B cellular immunity using HPV16/18 L1 VLP vaccine formulated with the MPL/aluminum salt combination (AS04) compared to aluminum salt. *Vaccine*. 2006;24:5937-49.
9. U.S. National Institutes of Health. ClinicalTrials.gov. Available at: <http://www.clinicaltrials.gov/ct/search?term=hpv&submit=Search>. Accessed July 2, 2007.
10. EDP24. Teen cancer jab hailed. Available at: <http://www.time.com/nation/article/0,8599,1206813,00.html>. Accessed August 13, 2007.

The Value of Preventive Medicine: A Look at Vaccine Management

The Postgraduate Institute for Medicine is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education. A total of 0.15 CEU (1.5 contact hours) will be awarded and a continuing education statement will be sent to pharmacists for successful completion of this continuing education activity, which is defined as receiving a minimum score of 70% on the posttest and completion of the Program Evaluation form. ACPE Universal Program No. 809-999-07-076-H01.

(Release date: September 2007; Expiration date: September 2008)

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and Impact Education, LLC. PIM is accredited by the ACCME to provide continuing medical education for physicians. PIM designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Continuing Education for this activity is processed solely through the AMCP.org Online Learning Center site at www.amcp.org (Learning Center/Online CE). No mailed forms will be accepted.

The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this activity, you must complete the following forms online:

1. Posttest form for this activity, "The Value of Preventive Medicine: A Look at Vaccine Management," on the AMCP.org Online Learning Center site—to receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form

Upon successful completion of this activity, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org Online Learning Center site. All information is kept confidential.

Posttest Worksheet: The Value of Preventive Medicine: A Look at Vaccine Management

1. How can infectious organisms be attenuated when the growth of serial cultures in media is not effective?
 - a. Using an alternative adjuvant
 - b. Variolation
 - c. Passaging in susceptible animals
 - d. Genetic engineering
2. Adjuvants increase a vaccine's benefit mainly by improving presentation of the antigens to the immune system or
 - a. reducing the potential for reversion.
 - b. addressing the changing antigenicity of certain infectious organisms.
 - c. increasing overall safety.
 - d. Simulating the immune system for a broader response.

3. The first major success of genetic engineering in immunization was in the development of a vaccine for which of the following?
 - a. Influenza
 - b. Hepatitis B
 - c. Herpes zoster
 - d. Respiratory syncytial virus
4. Approximately how many adolescents miss 1 or more recommended immunization?
 - a. 20%
 - b. 50%
 - c. 60%
 - d. 75%
5. SelectHealth is addressing the coverage of certain recently introduced vaccines through which of the following methods?
 - a. A preferred vaccine strategy
 - b. The utilization of state funding
 - c. A nonstandard vaccination benefit
 - d. Formulary tiering
6. The administration of “catch-up” injections are a consideration in vaccinating against
 - a. human papillomavirus.
 - b. herpes zoster.
 - c. Rotavirus.
 - d. respiratory syncytial virus.
7. Since the introduction of specific vaccines, the annual disease burden of conditions such as measles, mumps, and tetanus has been reduced by approximately
 - a. 60%.
 - b. 70%.
 - c. 80%.
 - d. ≥90%.
8. Which of the following is an indirect cost considered in the pharmacoeconomic evaluation of vaccines?
 - a. Drug acquisition costs
 - b. Missed work days
 - c. Administration costs
 - d. Hospitalizations
9. When conducting pharmacoeconomic analyses of vaccines, consideration should be given from both a health system perspective and
 - a. regulatory perspective.
 - b. societal perspective.
 - c. ethical perspective.
 - d. industry perspective.
10. While automatic vaccine coverage routed through the medical benefit has been the traditional approach in managed care, vaccines are now receiving more attention as a result of
 - a. recently introduced vaccines for previously untargeted conditions.
 - b. rising rates of infection.
 - c. poor vaccination rates.
 - d. the reemergence of eradicated diseases.
11. Assuming the anticipated availability of 2 separate human papillomavirus vaccines, the products will likely differ most significantly in terms of
 - a. safety.
 - b. adjuvants.
 - c. indication.
 - d. Both b and c
12. Which of the following is not a confounding variable that may have a significant impact on human papillomavirus vaccine utility or overall costs?
 - a. State mandates on vaccination requirements
 - b. Questions regarding long-term efficacy
 - c. Concerns from special-interest groups
 - d. Injection-site reactions

To complete this activity, go to www.amcp.org (Learning Center/Online CE), where you will access the posttest and evaluation form.

The Value of Preventive Medicine: A Look at Vaccine Management

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment of participation for this activity. (Project ID:4764-ES-17)

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree

2 = Disagree

3 = Neutral

4 = Agree

5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

Upon completion of this activity, participants should be better able to

• describe current vaccine management practices	1	2	3	4	5
• identify vaccine management best practices and shortcomings within the health care	1	2	3	4	5
• outline steps toward plan attainment of vaccination goals based on HEDIS measures, surrogate markers, and desired outcomes	1	2	3	4	5
• describe how to apply new management principles to improve clinical, human, and economic results of vaccination	1	2	3	4	5
• describe how to evaluate current plan practices in order to design and launch new quality improvement initiatives that will enhance vaccination standards	1	2	3	4	5

Overall Effectiveness of the Activity

The content presented:

• Was timely and will influence how I practice	1	2	3	4	5
• Enhanced my current knowledge base	1	2	3	4	5
• Addressed my most pressing questions	1	2	3	4	5
• Provided new ideas or information I expect to use	1	2	3	4	5
• Addressed competencies identified by my specialty	1	2	3	4	5
• Avoided commercial bias or influence	1	2	3	4	5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity:

Please list any topics you would like to see addressed in future educational activities:

Additional Comments About This Activity:

Follow-up:

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

- ☐ Yes, I would be interested in participating in a follow-up survey.
- ☐ No, I'm not interested in participating in a follow-up survey.

For Physicians Only:

I certify my actual time spent to complete this educational activity to be: _____

- ☐ I participated in the entire activity and claim 1.5 CME or 1.5 ACPE credits.
- ☐ I participated in only part of the activity and claim _____ credits..

[illegible]

JMCP

JOURNAL OF MANAGED CARE PHARMACY®

Supplement