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"Your mother was right. Wash your hands often. Cover your mouth when you sneeze."

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Fighting Fear: Talking With Patients About Bird Flu

Patients naturally experience confusion and fear when they hear news reports about the looming threat of an avian flu pandemic. What should a primary care provider make of these news reports? Is there really a threat? Is there cause for panic? And how can clinicians best protect their patients?

The answers to those questions are yes, no, and by keeping their heads, respectively, according to David Henderson, MD.

Dr. Henderson has an informed perspective as Deputy Director for Clinical Care and Associate Director for Quality Assurance and Hospital Epidemiology at the National Institutes of Health Clinical Center, Bethesda, MD. Primary care providers, he says, can provide a reality-based context for their patients by:

1. Dousing the flames of hysteria.
2. Providing patients and staff with a working knowledge of how the disease spreads.
3. Spreading a message of prevention of seasonal flu that will prepare staff and patients alike for a pandemic.

Is There Really a Threat?

Yes. Birds get flu just like humans and many other animals do. Subtypes are categorized by the arrangement of hemagglutinin [H] and neuraminidase [N]

proteins on their surfaces.¹ The H5N1 virus is one of 16 known subtypes of avian influenza viruses.²

One particularly virulent H5N1 avian flu strain has moved from its wild hosts to devastate domestic poultry flocks. This poses a threat to humans because:

- The host reservoir is now huge, with isolated outbreaks in poultry in 59 countries.³ Despite aggressive control measures, the disease has likely become endemic in many parts of Asia.⁴
- Flu viruses mutate rapidly and can also jump to infect a new species, including humans.
- Human cases of bird flu have been reported in 10 countries. By August 23, 2006, 241 people had contracted the disease; 141 of them died.⁵

For an updated report on human cases, visit http://www.who.int/csr/disease/avian_influenza/country/cases_table_2006_08_23_en/index.htm/

Influenza Primer

Seasonal influenza is an important disease that infects 5 to 20 percent of Americans during each flu season, typically November to March. Although most people recover from the illness, more than 100,000 cases of flu require hospitalization and as >>



many as 36,000 people in the United States die from influenza or its complications annually.⁶

Seasonal vs. Pandemic Flu

Seasonal flu involves variants of type A and type B viruses that have infected humans for years. Many people have been exposed to these viruses and have developed immunity.

A *pandemic flu* develops when a virus that has previously infected other animals spontaneously acquires the ability to spread directly from human to human and then spreads rapidly around the world. Because the new flu has never significantly infected the human population before, almost no one has antibodies and no vaccine has yet been developed.

Pandemic influenza is rarer and much more deadly than seasonal flu. The last pandemic swept the globe in 1968 and most public health experts believe the world is overdue for another one.⁷

What Makes Influenza So Dangerous?

Influenza viruses are genetically unstable and their behavior cannot be predicted. "An influenza virus is a permissive replicator, which means it

makes lots of mistakes as it copies its own RNA," Dr. Henderson says. "This works to the organism's advantage because the virus's mistakes may yield some variants that escape the body's immune response."

Antigenic drift describes the mutations that vary the flu virus's surface antigens, enabling it to escape or bypass the body's defenses. "Drift is why we have to get a shot every year," Dr. Henderson says.

Antigenic shift is the genetic change that enables a flu strain to jump from one animal species to another, including humans.

How Could a Pandemic Develop?

The process of antigenic shift could cause a flu pandemic if an influenza virus develops the ability to:¹⁰

- Swap genes with another strain, for example if a person contracted both avian flu and seasonal flu simultaneously.
- Jump to directly infect an intermediate host animal which passes it to humans.
- Jump to directly infect humans who pass it to other humans.

Such jumps are usually "dead-end" infections that cannot easily spread further in the human population.⁹

Is There Cause for Hysteria?

No. Each successive pandemic has caused a lower death toll. One of the terrifying things about the 1918 Spanish flu pandemic was the number of young, and otherwise healthy, people who died. This possibility always exists, Dr. Henderson says, "because no one will have had the new pandemic flu and—generally speaking—your first interaction with influenza can be a challenging one."



However, "we have reasons to feel optimistic," Dr. Henderson suggests. "In 1918, we had no antimicrobial agents, no critical care units, no ventilators—in other words, no acute care measures for the severely ill," he says. "We have learned much since then."

Another reason for optimism is the speed with which information travels around the world today. "I think we will be able to make a concerted response quickly," says Dr. Henderson.

How quickly could a pandemic spread? "That depends," says Dr. Henderson. "I would bet it might arise in the Far East probably in a rural area with lots of domestic and wild fowl, and lots of nose-to-beak interactions." Such a remote origin would provide the world more time to prepare. "But if it happens in New York City, we in the United States would have less time."

It is also true that the H5N1 strain has been around since 1997. As Dr. Henderson >>

Figure 1

History of Pandemics ⁸				
Date	Common Name	Type	Death Toll ⁹	Note
1918	Spanish flu	H1N1	Up to 50 million globally 675,000 in U.S.	Virus has disappeared
1957-1958	Asian flu	H2N2	1-2 million globally 70,000 in U.S.	Virus has disappeared
1968-1969	Hong Kong flu	H3N2	700,000 globally 34,000 in U.S.	H3N2 viruses still circulate today
1970-present	Six different new forms of flu have appeared in human populations but none have caused a pandemic			



says, "There may even be something about this strain that makes the transmission from bird flu to pandemic flu difficult."

Role of the Media

Although many people rage against media sensationalism, Dr. Henderson has learned to take a balanced view. "I urge reporters to report and help educate the public. Clearly explaining the facts to readers is an invaluable service." However, it's especially important that the media not overplay long shot risks, he adds.

That said, a World Health Organization (WHO) report notes the value of the media's traditional watchdog role. "At WHO, rumors reported by the press now provide the first alert to more than 40% of the outbreaks eventually verified.... In the final analysis, truth will prevail: rumors and their investigation by the media will eventually uncover the facts even when the authorities attempt to conceal them."¹¹

Public Policy Issues

Today, international agriculture aside, avian flu primarily poses challenges for policy makers and planners. "A lot of preparation is going on to be sure we can respond to this as aggressively and safely as possible," Dr. Henderson says.

About NIH Vaccine Research

Seven current studies relate to the H5N1 avian flu strain. They are studying safety and efficacy in various age groups and seeking ways to stretch a relatively thin supply of vaccine directed against H5N1. Fewer than 10,000 doses of investigational (pre-pandemic) vaccines have been produced.¹¹ "Although the rapid mutation of the flu virus might mean the vaccines being tested today are no longer effective, the experience developing and testing them is good preparation," Dr. Henderson says.

Preliminary results suggest intradermal injections are as effective as intramuscular delivery and require smaller doses of vaccine. Other studies are examining the adjuvants aluminum hydroxide and MF59 to determine whether they will improve the immune response produced by the H5N1 vaccine.¹¹

Role of Primary Care Providers

"Primary care providers need to keep a level head," says Dr. Henderson. "When patients come in frightened about bird flu, reassure them it is currently a hypothetical discussion because bird flu is not causing an epidemic for humans anywhere in the world right now. We are pretty certain it will be a pandemic one of these days, but when that might happen is not so clear."

Educate Yourself

When Dr. Henderson makes presentations about avian flu, he fields a lot of questions. Many center on the difference between seasonal and pandemic flu, he says. Clinicians may misunderstand the difference between seasonal and pandemic flu.

Dr. Henderson advises clinicians to help their patients:

- Remember that pandemic flu is a future probability, while seasonal flu is an annual reality.
- Read or watch sensational reports skeptically.
- Recognize that avian influenza is a disease of birds, for which humans are simply incidental hosts.
- Prepare for a future pandemic by instituting excellent prevention, vaccination, and control procedures for seasonal flu.

Educate Your Patients

Patients need to understand that the major human-to-human transmission of influenza, whether seasonal or pandemic, will occur through large droplets. Primary care providers should emphasize the importance of:

- **Respiratory etiquette.** Cover your mouth when you cough or sneeze. Although some guidelines suggest that infected people wear surgical masks to avoid spreading their germs, there is little evidence that wearing a mask will prevent a person from catching flu.
- **Social distancing.** If you're sick, stay home. If you go out, avoid people who are sick. For example, avoid crowds by shopping at 3 A.M.



- **Hand hygiene.** Wash hands frequently, especially after coughing or sneezing and after touching any potentially contaminated surface. Use a non-antibacterial soap and warm water. "When you can't wash, use alcohol-based hand sanitizers, which are highly effective against viruses," Dr. Henderson says.

A variety of educational materials including downloadable waiting room posters, fliers, and brochures are available online.^{12,13,14}

Assess Needs of At-risk Patients

Various planning tools, including database search criteria,¹⁵ will help predict the number of high priority patients and staff who will need vaccination. People at elevated risk should receive an annual flu vaccination. If they are immunosuppressed or otherwise not likely to have good >>



results from vaccine, talk with them about appropriate measures during a seasonal outbreak. When used within two days of infection, the neuraminidase inhibitors oseltamivir (Tamiflu®) and zanamivir (Relenza®) work against the “N” proteins on the surface of the virus cell.¹⁶

Two older, inexpensive antiviral drugs, the adamantane derivatives rimantadine and amantadine, are thought to interfere with the virus’s ability to infect a host cell. “A few years ago, the H5N1 strains had clearly developed resistance to the adamantines,” Dr. Henderson says. “However, the most recent H5N1 strains appear to be susceptible to all four drugs.”

The most recent H5N1 strains appear to be susceptible to all four drugs.

Primary care providers should use this year’s seasonal flu outbreak as a “fire drill” for a future pandemic. According to congressional testimony by Anthony S. Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases, NIH, “Increasing the proportion of the population that is vaccinated annually with seasonal influenza vaccine will help to pave the way for the more intense vaccination effort that would accompany an influenza pandemic.”¹⁷

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Website Update Is Under Way



This fall we will be revising and upgrading **www.primarycarenet.org** in a variety of ways. We have set changes in motion that will help current users find the kinds of information they are seeking more effectively and efficiently.

The first change you can now see is our **new graphic design on our home page**. We will be applying this new look throughout the site this fall. Please bear with us as we phase out the old design!

Other changes to the site will be our **new CME Podcast section**, access to **the entire archive of back issues of this newsletter**, and soon you will have an opportunity to participate in our upcoming series of news and articles that will be featured in our **'Blog' section**.

We're excited about these new changes and we hope you will be to!

Author

Edward John Mayeaux, Jr., MD

Professor of Family Medicine, Obstetrics
& Gynecology

Louisiana State University, Health Sciences Center
Shreveport, LA

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Dr. Mayeaux is on the advisory board and is a consultant with GlaxoSmithKline and Merck.

Target Audience: This activity is targeted to all physicians and other healthcare professionals who are interested in preventing cervical cancer and other HPV-related diseases.

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Reducing the Burden of HPV-related Disease: Impact of Prophylactic HPV Vaccination



Introduction

Human papillomavirus (HPV) is a sexually-transmitted infection that is the etiologic cause of virtually all cervical cancers, and is highly prevalent in sexually active men and women. High-risk HPV types (e.g. 16 and 18) are associated with the development of cervical and other anogenital cancers, abnormal cervical cytology, and head and neck cancers. Low-risk HPV types (e.g. 6 and 11) are associated with genital warts, abnormal cervical cytology, and recurrent respiratory papillomatosis (RRP), a rare, yet potentially fatal condition. Prophylactic HPV vaccines have shown dramatic efficacy in the prevention of HPV-related disease. A quadrivalent HPV vaccine protecting against HPV types 6, 11, 16, and 18 has just been approved by the Food and Drug Administration for the prevention of cervical cancer; cervical, vaginal, and vulvar neoplasias; cervical adenocarcinoma *in situ*; and genital warts for girls and women 9 to 26 years of age. A bivalent HPV vaccine protecting against infection with HPV types 16 and 18 is in earlier stages of clinical development. Implementation of HPV vaccination programs is expected to substantially reduce the morbidity and mortality associated with HPV-related disease. Educational programs focused on the benefits of HPV vaccination have demonstrated success in improving acceptance rates and may assist in the acceptance of HPV vaccination among patients and parents.

Epidemiology of HPV Infection

HPV is the most common, newly acquired sexually-transmitted infection in the United States. Approximately 6.2 million individuals are infected by HPV each year, and more than 20 million people are currently infected.¹ HPV infection is most commonly found among young, sexually active women aged 15 to 24 years, who incur 74% of all new HPV infections.²



Overall, an estimated 75% of sexually active men and women are exposed to HPV at some point in their lives.³ There are more than 100 different types of HPV, but they can all be broadly classified into two groups: high-risk and low-risk.⁴ High-risk types of HPV can lead to cervical dysplasias and cancer, and are also implicated in many anal, penile, and head and neck cancers,^{5,6} whereas low-risk HPV infection can lead to low-grade cervical dysplasias, genital warts, and RRP (Figure 1).^{7,8} HPV infection has been identified in >99% of all cervical cancers,⁹ and among the high-risk HPV types, types 16 and 18 are responsible for nearly 70% of cervical cancers.¹⁰ Low-risk HPV types 6 and 11 are responsible for >90% of genital warts and the majority of cases of RRP.^{6,11}

Transmission and Risk Factors for HPV Infection

Sexual intercourse is not strictly required for HPV transmission; however, the number of sexual partners is still the major risk factor for HPV infection. In one study of female college students, 20% of those who had never had a male sexual partner were HPV positive. Women who had greater numbers of sexual partners were more likely to be HPV positive: 21% of women with 1 male sexual partner were HPV positive,

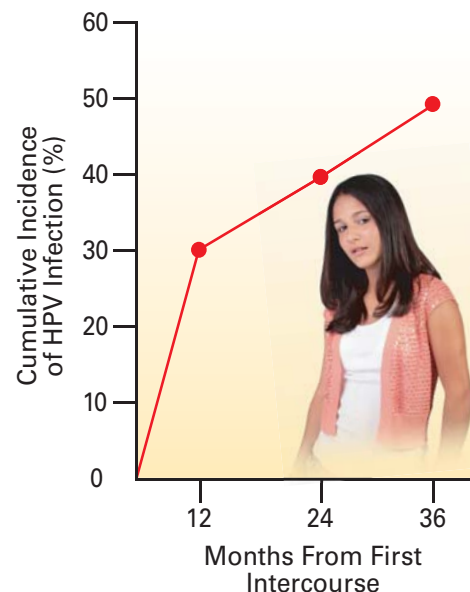
followed by 33% with 2 to 3 partners, 55% with 4 to 5, 56% with 6 to 9, and 69% with 10 or more sexual partners.¹² In addition, HPV infection is often acquired soon after onset of sexual activity. In a longitudinal study of a sample of college-age women who were virgins at baseline (n=148), the 24-month incidence of HPV infection was 38.9% for those women who became sexually active during the study (Figure 2). This incidence of HPV infection in these women was similar to women who were already sexually active when they entered the study.¹³

In addition to the number of sexual partners, additional risk factors for HPV infection in women include an earlier age of first sexual intercourse, poor immunological status, and smoking.^{14,15} Men also increase their risk of infection by having a higher lifetime number of sexual partners and a higher number of recent sexual partners. Other risk factors in men include not being circumcised and having sex with other men.^{16,17} Condoms offer partial, but not full, protection against HPV transmission.¹⁸

Natural History of HPV Infection

Most HPV infections regress following initial infection; however, persistent HPV

Figure 2
HPV Infection Among College-age Women



Cumulative incidence of human papillomavirus infection from time of first sexual intercourse (n=94) among women in Washington State, 1990-2000. Adapted from Winer RL, et al. *Am J Epidemiol.* 2003;157:218-226.

infection is a serious health concern because it is more likely to lead to cervical cancer.⁵ Persistence of HPV infection and the development of cervical cancer are especially high in infections with HPV 16.^{10,19} The median duration of all HPV infection is approximately 8 months, and among young women with an HPV infection, 60% to 75% become HPV negative after 30 months.^{20,21}

Low-grade squamous intraepithelial lesions (LSILs) of the cervix can result from infection with high- and/or low-risk HPV types. The risk of high-grade squamous intraepithelial lesion (HSIL) development is increased following infection with high-risk HPV types; women testing positive at least 3 times for high-risk HPV types have an estimated 14-fold risk of developing HSIL compared with HPV-negative women.^{20,22} Within >>

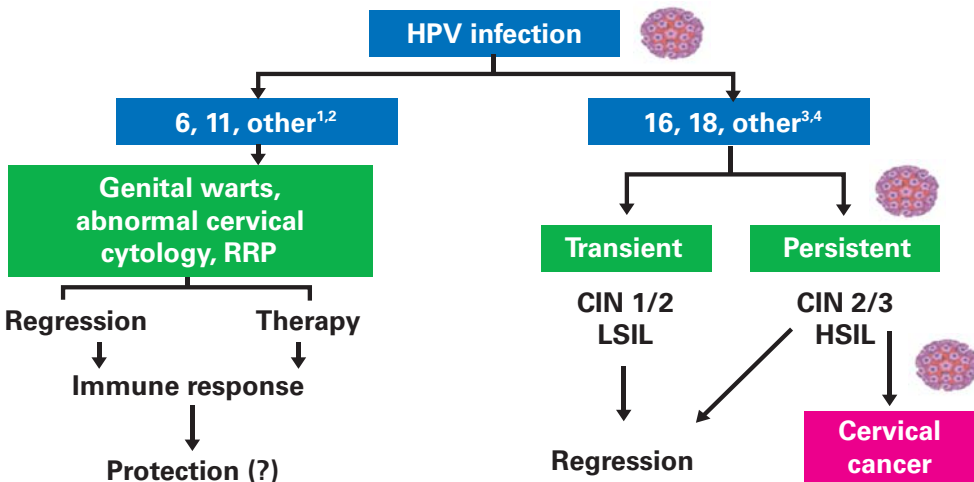
Figure 1
Common HPV Types Associated With Benign and Malignant Diseases

	HPV Types	Manifestations
High-risk	Types 16, 18, 31, 33, and 45	Low-grade cervical changes ¹ High-grade cervical changes ¹ Cervical cancer ^{1,2} Other anogenital cancers ¹ Head and neck cancer ³
Low-risk	Types 6 and 11	Benign low-grade cervical changes ¹ Condylomata acuminata (genital warts) ¹ Recurrent respiratory papillomatosis (RRP) ⁴

¹ Koutsky LA, et al. *Epidemiol Rev.* 1988; 10:122-163; ² Munoz, et al. *N Engl J Med.* 2003;348:518-527; ³ Hansson BG, et al. *Acta Otolaryngol.* 2005;125:1337-1344; ⁴ Wiatrak BJ. *Curr Opin Otolaryngol Head Neck Surg.* 2003;11:433-441.

Figure 3

The Natural History of HPV and HPV-related Diseases



CIN=cervical intraepithelial neoplasia; HSIL=high-grade squamous intraepithelial lesion; LSIL=low-grade squamous intraepithelial lesion.

¹Koutsky LA, et al. *Epidemiol Rev.* 1988;10:122-163; ²Wiatrak BJ. *Curr Opin Otolaryngol Head Neck Surg.* 2003;11:433-441; ³Munoz N, et al. *N Engl J Med.* 2003;348:518-527; ⁴Schiffman M, Kjaer SK. *J Nat Cancer Inst Monogr.* 2003;31:14-19.

a 4-year period, an estimated 15% to 30% of women testing positive for high-risk HPV types will develop HSIL.²³ HSIL test results may indicate lesions that can develop into cervical cancer over time, emphasizing the importance of routine cervical cytology screening (Figure 3).^{24,25} During a 2-year period, an estimated 1.44% of HSIL cases will develop into invasive cervical cancer.²⁶

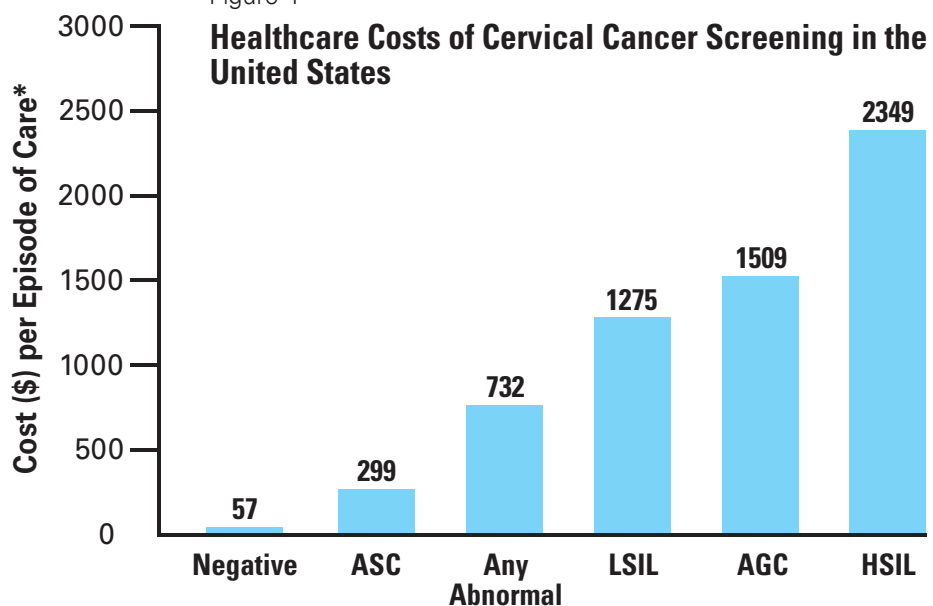
Clinical Manifestations of HPV Infection

Abnormal Cervical Cytology and Cervical Cancer

Cervical cancer is the second most common cancer in women worldwide, with an estimated 400,000 to 500,000 cases of cervical cancer diagnosed each year.²⁷ In the United States, Pap screening has reduced the incidence and morbidity associated with cervical cancer, but there are still approximately 9,710 new cases and 3,700 deaths expected to occur in 2006.²⁸ Of note, approximately 50% of cervical cancer cases will occur in women never screened and an additional 10% in women not screened within the past 5 years.²⁹ In addition to the burden of

cervical cancer, an estimated 2 million cases of abnormal cervical cytology, which includes 1.25 million and 300,000 cases of LSILs and HSILs are expected to occur each year as a result of HPV infection with both low- and high-risk types.^{7,30}

Figure 4
Healthcare Costs of Cervical Cancer Screening in the United States



Visits (n)	1	2.6	3.5	5.1	4.5	6.8
Pap tests (n)	1	2.2	2.5	3.1	2.7	3.7
Duration (months)	-	7.4	9.6	13.7	10.9	17.4

*Average age adjusted to the 1998 U.S. female population; all cost estimates were converted to 2002 dollars. AGC=atypical glandular cells; ASC=atypical squamous cells. Insinga RP, et al. *Am J Obstet Gynecol.* 2004;191:114-120.

Cervical cytological screening programs have dramatically reduced the incidence of cervical cancer; however, screening and treatment can be quite costly.^{31,32} The financial burden of treating HPV-related disease is estimated to be approximately \$5 billion annually (in 2004 U.S. dollars).³³ Treatment of any cervical cytology abnormality is associated with an average 3.5 follow-up visits and a cost of \$732 (Figure 4).³⁴ Even false-positive results incur a high cost and inconvenience, estimated at an average of \$376 and 3.3 visits.³⁴ Young women (aged 20 to 29 years) incur the highest cost among all cervical HPV-related diseases with treatment estimated at \$51,863 per 1,000 women (based on 1998 U.S. female population and in 2002 U.S. dollars); among the general population of women the cost is estimated at \$26,415 per 1,000 women.³⁴ >>

Genital Warts

Genital warts affect 1.4 million Americans a year and can be associated with emotional distress and treatment burden.^{3,35} The majority of genital warts cases are asymptomatic; however, many patients report painless bumps, pruritus, and discharge.³⁶ The presentation of genital warts is frequently associated with cauliflower lesions and single or multiple papules that can be pearly, filiform, or plaque-like in nature.³⁶



In women exposed to HPV 6 or 11, approximately two-thirds developed genital warts within 36 months (cumulative incidence 66.2% [95% CI: 52.8-79.2]).³⁷ In this same group of young women, the median time to progression from HPV 6 or 11 infection to the detection of clinical warts was 2.9 months (95% CI: 0-5.7 months).³⁷ Following the start of treatment, the median time to wart clearance was 5.9 months (95% CI: 3.9-8.0 months).³⁷ Up to 60% of patients with genital warts experience a recurrence following treatment.³⁵

The development of genital warts is associated with substantial psychological morbidity as well as costs of treatment. Patients attend approximately 300,000 initial office visits for genital warts in the United States each year,³⁸ and treatment costs per case range from \$285 to \$6,700.³⁹ An episode of genital warts is associated with an average of 3.1 physician visits for treatment.⁴⁰ In a survey of young men and women with genital warts, the diagnosis was

associated with considerable emotional distress and anxiety, pain, and concerns that genital warts could lead to cancer.³⁵

Recurrent Respiratory Papillomatosis (RRP)

RRP is characterized as recurring papillomas in the respiratory tract that can occur in children and adults, requiring multiple surgical interventions.⁸ Although RRP is rare (incidence of 3.96 per 100,000 children), it can be fatal following complications of severe airway obstruction, pulmonary failure, or malignant transformation.⁸ RRP most often occurs following vertical transmission of HPV infection from a mother to her infant, and women with vaginal condyloma are at substantially higher risk of delivering children who later develop RRP.⁸ Approximately 80% of RRP cases are associated with HPV infection, usually HPV types 6 and 11.⁶ However, the Centers for Disease Control and Prevention do not recommend cesarean sections for women with HPV infections because the procedure does not appear to be protective as the transmission of HPV appears to be low and RRP is rare.⁴¹

Screening and Diagnosis of HPV-related Diseases

Over the past 40 years, the United States has witnessed a substantial reduction in the incidence of cervical cancer due to successful prevention and early detection screening programs (i.e. Pap test).⁴² If detected early, the 5-year survival rate for invasive cervical cancer is 92%, making it one of the most successfully treated cancers. Nearly 100% survival rates have been demonstrated for women with preinvasive lesions.²⁸ The American Cancer Society (ACS) and American College of Obstetricians and Gynecologists (ACOG) guidelines recommend that cervical cytology screening should be initiated within 3 years after the initiation of sexual intercourse and no later than 21 years of

age.^{30,43} Among women up to age 30, ACS guidelines suggest annual screening with a conventional Pap test or every 2 years with a liquid-based Pap test; ACOG suggests an annual screening with either a conventional or liquid-based Pap test.^{30,43} Women older than 30 years of age are recommended to lengthen the interval of screening to every 2 to 3 years after 3 consecutive negative cytology results have been demonstrated, especially with a negative high-risk HPV DNA Hybrid Capture II test.^{30,43}

Screening may cease at age 70 in low-risk women following no positive cervical cytology within the past 10 years and 3 consecutive negative Pap tests. Women who have human immunodeficiency virus (HIV) or are immunosuppressed, have a history of cervical cancer, or have been exposed to diethylstilbestrol *in utero* should continue screening after age 70. In women who have undergone a total hysterectomy, cervical cytology screening is no longer necessary if the woman had the hysterectomy for nonmalignant reasons. Screening can be discontinued in these women following three consecutive negative cytology screening results.^{30,43}

Quadrivalent HPV Vaccine: Efficacy, Safety, and Indications

Quadrivalent HPV Vaccine: Indication
A quadrivalent HPV 6/11/16/18 vaccine has been approved by the FDA to prevent cervical cancers, CIN grades 1-3, vaginal and vulvar intraepithelial neoplasias (VaIN and VIN) grades 2 and 3, adenocarcinoma *in situ* (AIS), and genital warts associated with infection by HPV 6, 11, 16, and 18 in girls and women aged 9 to 26 years.⁴⁴ >>

Quadrivalent HPV Vaccine: Phase 3 FUTURE Studies

The quadrivalent HPV vaccine has reported phase 3 clinical findings demonstrating 100% efficacy in preventing HPV 6/11/16/18-related CIN, VaIN and VIN, cervical squamous cell carcinoma, AIS, and external genital warts. These data were generated by two large studies: Females United To Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and II.^{45,46}

In FUTURE I, women aged 16 to 23 years (N=5,455) received three doses of either vaccine or placebo, followed by periodic Pap test for approximately 2 years of follow-up. The primary end points were HPV 6/11/16/18-related CIN 1-3, cervical AIS, cervical cancer, genital warts, VaIN/VIN, and vaginal/vulvar cancer. In the per-protocol (PP) analysis, which included participants who were seronegative for HPV 6, 11, 16, and 18 at Day 1, negative for HPV 6, 11, 16, and 18 DNA between Day 1 and Month 7 (third dose), and who received all doses

of vaccine, the vaccine was 100% effective at preventing HPV 6/11/16/18-related CIN 1-3, cervical cancer, genital warts, VIN, and VaIN (Figure 5). In the modified intent-to-treat (MITT) analysis (i.e. participants who were seronegative for HPV 16 and 18 at Day 1 and received at least one dose of vaccine), the vaccine was 97% effective at preventing HPV 6/11/16/18-related CIN 1-3 and cervical cancer and 95% effective at preventing HPV 6/11/16/18-related genital warts, VIN, and VaIN.⁴⁵

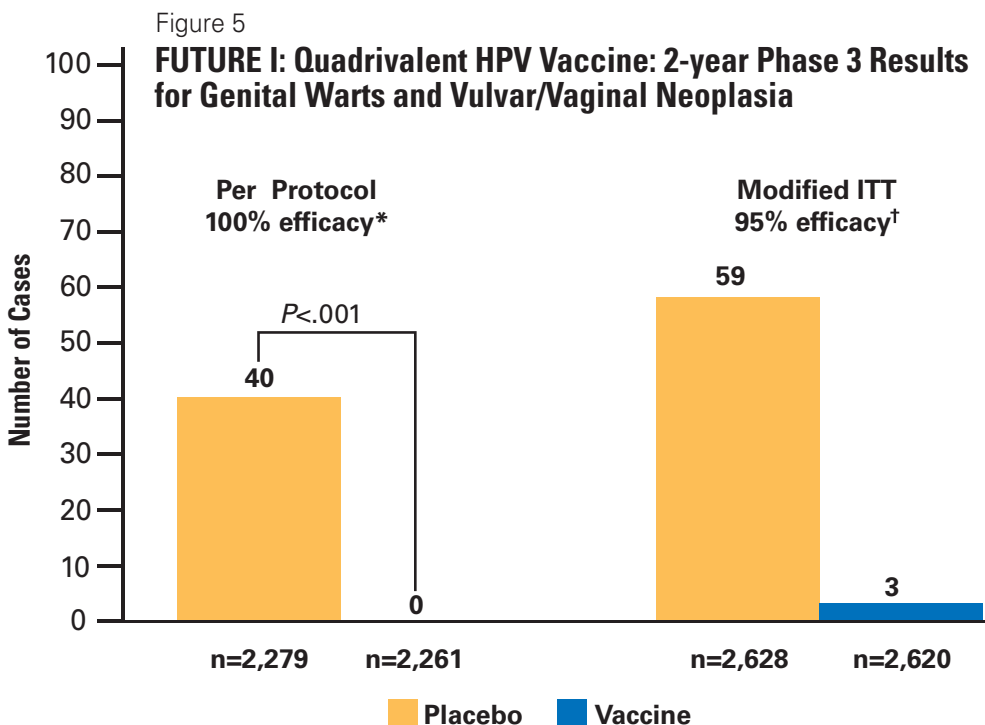
In FUTURE II, 12,167 women aged 16 to 23 years received three doses of either vaccine or placebo, followed by Pap and HPV tests at Day 1, Month 7 and then yearly from Month 12 onwards; results have been reported for the first 2 years of follow-up. The primary end point was the combined incidence of HPV 16/18-related CIN 2-3, AIS, or cervical cancer. In the PP analysis, the vaccine was 100% effective

at preventing CIN 2-3, AIS, and cervical cancer related to HPV 16 and 18 (Figure 6). In the MITT analysis, the vaccine was 97% effective.⁴⁶ MITT results are thought to be more indicative of what would be seen in real-world clinical practice, and suggest that the quadrivalent HPV vaccine is effective even when the vaccination protocol is not strictly followed. The quadrivalent HPV vaccine was well-tolerated in both FUTURE studies.^{45,46}

Quadrivalent HPV Vaccine: Pooled Analyses

The ability of the quadrivalent HPV vaccine to prevent VIN and VaIN was supported by an additional combined analysis of 3 studies in which 18,150 women aged 16 to 26 years received the quadrivalent HPV vaccine or placebo and were followed for 6- to 12-month intervals for up to 48 months. In both the PP and the MITT analyses (i.e. participants who were seronegative for HPV 16 and 18 at Day 1 and received at least one dose of vaccine), the vaccine was 100% effective in preventing HPV 16/18-related VIN 2/3 and VaIN 2/3.⁴⁷

Vaccination with the quadrivalent HPV vaccine may also offer some benefit to women who have been recently infected with HPV. In a pooled analysis of phase 2 and 3 studies with the quadrivalent HPV vaccine, women who were positive for HPV DNA but negative for antibodies to HPV received three doses of either quadrivalent HPV vaccine (n=798) or placebo (n=767). Women who received active vaccine were 27% (95% CI: 0-47) less likely to develop CIN 1-3 or AIS associated with the HPV type for which they tested positive compared with placebo.⁴⁸ It should be noted that, in addition to possible protection against the >>



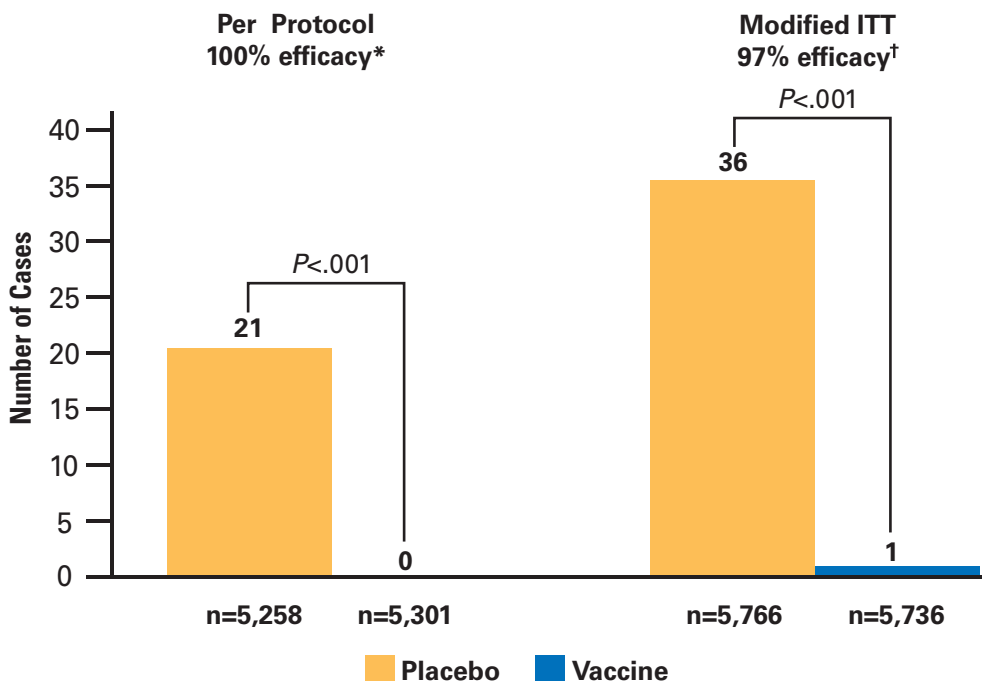
*CI: 88%-100%.

†CI: 84%-99%.

Sattler C, et al. Presented at: ICAAC; December 16-19, 2005; Washington, DC.

Figure 6

FUTURE II: Quadrivalent HPV Vaccine: 2-year Phase 3 Results for CIN 2-3, AIS, and Cervical Cancer



*CI: 76%-100%.

†CI: 83%-100%.

Skjeldestad FE, et al. Presented at: IDSA; October 7, 2005; San Francisco, CA.

sequelae of their HPV infection, these women were also protected against HPV types included in the vaccine with which they had not been infected.

Quadrivalent HPV Vaccine: Immunogenicity

Young women (N=552) aged 16 to 23 years were randomized to either the quadrivalent HPV vaccine or placebo and completed gynecological screening and Pap testing at regular intervals for up to 3 years. A subset of women (n=241) was followed for up to 5 years. Persistent disease was the primary end point and was defined by: (a) HPV DNA detected in samples collected at ≥2 consecutive visits ≥4 months apart; (b) HPV DNA detection at the last recorded visit; or (c) biopsies in which HPV DNA was detected and cervical, vulvar, vaginal dysplasia, or genital warts was diagnosed. The vaccine was associated with a 96% (95% CI: 84-100) reduction in the combined incidence of HPV 6/11/16/18-related persistent infection or

disease at up to 5 years post-enrollment. Type-specific anti-HPV geometric mean titers (GMTs) induced by the quadrivalent HPV vaccine remained at or above those following natural infection for up to 5 years.⁴⁹

The quadrivalent HPV vaccine has been shown to produce levels of HPV antibodies in children and adolescents that are equal to, if not greater than, those produced in adults. This has been established in two studies. In the first study, boys (n=510) and girls (n=506) ages 10 to 15 and women ages 16 to 23 (n=513) were given three doses of quadrivalent HPV vaccine. At Month 7, one month after the last of the three injections, 100% of the children and 96.6% of the adult women had produced antibodies to HPV 6, 11, 16, and 18. The GMTs produced in the boys' and girls' groups were not only non-inferior to those produced in adult women ($P<.001$), but actually 1.67-2.7 times higher. Males responded to vaccination as well as females, producing

GMTs comparable to those produced by females of the same age.⁵⁰

In a second study, a slightly younger group of sexually-naïve boys and girls ages 9 to 15 (N=1,781) received a course of quadrivalent HPV vaccine or placebo and were followed for one year. More than 99.5% of participants who received active vaccine developed antibodies to HPV 6, 11, 16, and 18; 92% of participants sustained these antibodies for 12 months of follow-up, and at levels higher than those seen in adults.⁵¹

ACIP Recommendations for Quadrivalent HPV Vaccine

On June 29, 2006, the Advisory Committee on Immunization Practices (ACIP) unanimously voted in favor of routine vaccination of female girls aged 11 to 12 years (see below). Per the discretion of the provider, the quadrivalent HPV vaccine can be administered as young as 9 years of age. HPV vaccines are prophylactic and should ideally be >>

ACIP Recommendations for the Quadrivalent HPV Vaccine

- Routine vaccination of girls 11-12 years of age with 3 doses of quadrivalent HPV vaccine
- Vaccination series can be started in girls as young as 9 years of age at discretion of provider
- Catch-up vaccination for adolescent and young women 13-26 years of age who have not been previously vaccinated

Available at: www.cdc.gov/od/oc/media/pressrel/r060629.htm. Accessed July 7, 2006.



administered prior to sexual activity. The ACIP also recommended catch-up vaccination for adolescent girls and women aged 13 to 26 years who have not been previously vaccinated.⁵²

Bivalent HPV Vaccine: Efficacy and Safety

Bivalent HPV Vaccine: Phase 2 Studies

A bivalent HPV vaccine that protects against HPV 16 and 18 is in earlier stages of clinical development. In phase 2 trials, the bivalent HPV vaccine or placebo was administered in three doses to women (N=1,113) aged 15 to 25 years who were followed for 18 months. The primary outcome was incident infection, and secondary outcomes included persistent infection, cervical dysplasia, and disease. In the according-to-protocol (ATP) population, the vaccine was 91.6% effective against incident cervical infection with HPV 16 and 18 ($P<.0001$). The bivalent HPV vaccine also prevented 100% of persistent cervical HPV 16 and 18 infections in the ATP group ($P=.007$), and 93.5% of atypical squamous cells of undetermined significance (ASCUS) or worse. In the intent-to-treat analysis, the bivalent vaccine was 95.1% effective in preventing persistent infection with HPV types 16 and 18, and 92.9% effective against cervical dysplasia of ASCUS or worse. The bivalent HPV vaccine is generally safe and well-tolerated.⁵³

Bivalent HPV Vaccine: Immunogenicity

Women who received all three doses of the bivalent HPV vaccine (n=393) or placebo (n=383) were included in a long-term extension phase of the original phase 2 study for up to 4.5 years. The primary objective was to assess long-term efficacy of the bivalent HPV vaccine in preventing incident HPV 16/18 infection; secondary end points included prevention of HPV 16/18-related infections. The bivalent HPV vaccine was 95% and 100% effective at preventing HPV 16/18-related incident and persistent infection, respectively, during the combined initial and follow-up phases (ATP analyses). More than 98% of vaccine recipients remained seropositive for HPV 16 and 18 at all time points with GMTs that were significantly higher than natural infection.⁵⁴

Implementation and Acceptability of Vaccines

The inclusion of males in an HPV vaccination program in terms of overall disease burden and cost reduction requires additional examination. The concept of herd immunity includes extending the benefit of the protective effect from the individual vaccinated to a larger group.⁵⁵ The benefits of herd immunity had not been seen in the United Kingdom following rubella vaccination programs that only included women. However, following the inclusion of males in rubella vaccination programs, rates of rubella

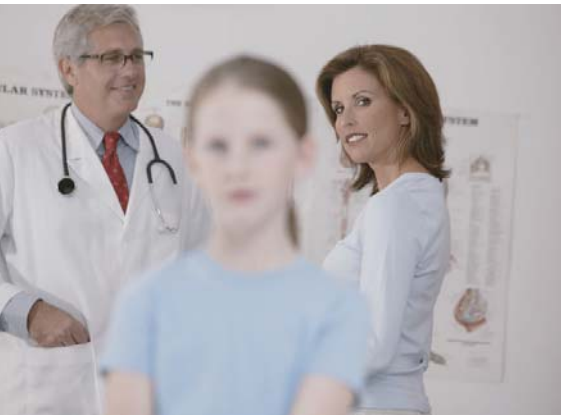
dropped substantially.⁵⁶ The impact of HPV vaccination in both men and women has not been fully examined; however, protection against genital warts and anogenital cancers that affect both genders would be expected to reduce disease burden associated with HPV infection.

Acceptability of HPV vaccines may occasionally be met with some resistance from parents, patients, and society/religious groups due to the sexually-transmitted nature of HPV. However, young women report overall positive attitudes toward HPV vaccination for themselves and their children.⁵⁷ More than 80% of surveyed young women reported that they would receive an HPV vaccine to prevent cervical cancer or make sure their daughters were immunized when the vaccine becomes available.⁵⁷ Most well-known conservative Christian groups have come out in favor of the vaccines stating that prevention of cancer in women is a major family value issue.⁵⁸ Professional society endorsement of the HPV vaccine will also likely increase its acceptability among clinicians. Surveyed fellows of ACOG reported high acceptability of an HPV vaccine and that endorsement by ACOG would be the greatest predictor of HPV vaccination utilization among gynecologists.⁵⁹

Parental perceptions that their children are at low risk for HPV infection or do not need vaccination until after sexual onset are major barriers to acceptance of HPV vaccination in children.⁶⁰ In addition, some parents express concern that vaccination against HPV infection would promote earlier sexual onset in their children.⁶¹ A brief educational intervention about HPV and HPV vaccines demonstrated increases in parental acceptability of HPV vaccination.⁶¹ Parents' belief that the HPV vaccine would be beneficial to improving their children's health is a strong predictor of vaccine acceptability.⁶² Clearly, parent attitudes and beliefs will predict HPV vaccine >>



acceptability, stressing the importance of parent-patient-clinician discussions regarding the disease risk reduction and safety of HPV vaccines.



Conclusions

HPV is a highly prevalent sexually-transmitted infection with more than three-fourths of all sexually active adults exposed at some point in their lifetime. Young women are at highest risk for HPV infection following the onset of sexual activity, and infection with high-risk HPV types (16 and 18) is associated with the majority of cases of cervical neoplasia and cancer. Genital warts, abnormal cervical cytology, and RRP are associated with infection with low-risk HPV types (6 and 11). Cervical cytology screening programs have contributed to large reductions in cervical cancer mortality rates; however, the burden and cost of HPV-related infection remains a public health concern. Prophylactic HPV vaccines that protect against the most common high- and low-risk HPV types, in combination with routine cervical screening, are expected to have a dramatic impact on HPV-related morbidity and mortality. The quadrivalent HPV vaccine was recently approved for the prevention of HPV 6/11/16/18-associated cervical cancer, CIN, VaIN, VIN, AIS, and genital warts in women aged 9 to 26 years. The ACIP recommended routine vaccination with the quadrivalent HPV vaccine in girls aged 11 to 12 years (with availability for girls as young as 9 years of age) and catch-up vaccination for young women aged 13 to 26 years. Prophylactic HPV

vaccines will be most effective if administered to children and adolescents prior to the onset of sexual activity. Education from healthcare professionals will be important to successful HPV vaccination programs as the communication of the health benefits of immunization has been shown to increase HPV vaccine acceptance among parents.

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Talking With Patients About HPV

CASE STUDY:

Case Study: A mother brings her healthy 11-year-old daughter to your office for a check-up before the start of the school year. This young girl's entire family, including her 10-year-old brother have been your patients for two years. The parents reported that both children had completed all required childhood vaccinations prior to coming to your practice. You do not know this family well and feel uncomfortable initiating discussions about sexuality issues. A quadrivalent vaccine that protects against cervical dysplasia, cervical cancer, genital warts, and vulvovaginal neoplasia (VIN/VaIN) 2-3 is available. How would you approach the subject of HPV vaccination with this family?

Parental attitudes and life experiences, including belief in the benefits of vaccines, have been shown to have the strongest relationship to parental acceptance of HPV vaccination.¹ The predominant influences on vaccination acceptance appear to be a doctor's recommendation, school requirements, and cultural and social factors.²

Despite the importance of physician recommendation, some clinicians are reluctant to discuss sexuality with adolescent patients and their parents.² Primary care providers may wish to develop skills for communicating the advantages of vaccination to adolescents and their parents.²

Simply distributing information sheets, such as those provided by the Centers for Disease Control and Prevention, for other childhood vaccinations may not in itself be effective.¹ A recommended approach is to establish a shared decision-making process that involves eliciting information, listening to patients and parents, and communicating a respectful response.³ The clinician should:

- Ask parents and adolescents what questions or concerns they have about vaccination.
- Respect and treat seriously even erroneous opinions based on misinformation.
- Offer accurate information based on evidence.
- Arrive at a joint decision about HPV vaccination.

It is not likely that patients and parents will be fully educated on the incidence of HPV and the related diseases that can result from HPV infection. HPV is one of the most common sexually-transmitted infections; over 75% of sexually active adults will be infected during their lifetime.⁴ It is important for clinicians to reinforce that it is almost impossible to know from whom or when one acquired HPV. Discussions with patients and parents should include the potential benefits of HPV vaccination including the long-term risk reduction of cervical cancer, abnormal cervical cytology, genital warts, and vaginal/vulvar

neoplasia. It may also eliminate the psychological burden of dealing with precancerous lesions.

Clinicians might consider HPV vaccination within a standardized well-child preadolescent or adolescent healthcare visit. At this time, parents could be offered a set of preventive measures that will help protect their children during adolescence and help ensure their children have long and healthy lives as adults.²

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Date	Location
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9/30	Newton, MA

Migraine, Genital Herpes, and COPD

Date	Location
10/07	Portland, ME

Asthma, Genital Herpes, and Osteoporosis

Date	Location
11/11	Worcester, MA

Migraine, Genital Herpes, Depression, and Osteoporosis

Date	Location
10/07	College Station, TX

Military Service Creates Ethical Dilemma for Healthcare Providers



Controversy continues to swirl around the role of a psychologist, psychiatrist, or physician in military interrogations. Is there in fact any proper role? If so, how should it be defined?

Suicides by Guantanamo Bay detainees in June reopened what has been described as a “festering question of medical ethics.”¹ Rumors suggest that some detainees have suffered punishments tailored to their individual weaknesses by interrogators with access to medical records. For example, one prisoner who reportedly has not seen daylight for years was rumored to have a phobia of the dark. The possibility that a mental health professional recommended such treatment raises troubling ethical questions.

Critics have suggested that the Guantanamo doctors have abandoned their ethical duty through creeping

complicity similar to that of German doctors who became part of Hitler’s killing machine.”¹

In the past 18 months, three professional associations have formulated position papers on the issue. The psychiatrists’ position forbids participation in any interrogation whether by their presence in the room, suggesting questions, or advising on the use of specific techniques. However, the association president was quoted immediately after the release as reassuring military psychiatrists that they would not be censured for such participation.²

This qualification suggests that the American Psychological, American Psychiatric, and American Medical associations agree on several basic issues: Military psychologists, psychiatrists, and physicians who follow orders to participate in interrogations will not be subject to discipline from

their respective professional associations as long as:²

- The interrogations are not coercive
- They act strictly as consultants, not caregivers
- They report coercive or abusive acts to the appropriate authorities

The “Do No Harm” rule that governs all three professional groups is clear: “Never engage in, facilitate, or countenance torture or other cruel, inhuman, or degrading treatment.”² Unlike the psychiatric group, the associations of psychologists and physicians also acknowledge a responsibility to society that includes protecting third parties and the public.

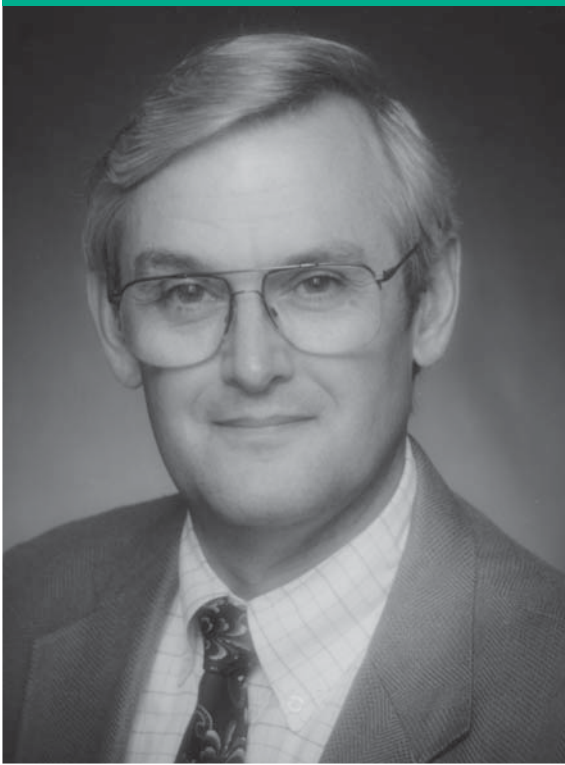
The psychologists suggest that one appropriate role they fill is to watch for and report “behavioral drift” in interrogators, and stop interrogation before it becomes abusive. Behavioral drift constitutes the deviation from professionally and ethically acceptable behavior that may arise in high stress situations where there is insufficient ethical guidance or oversight.²

The debate about these ethical questions is unlikely to be resolved any time soon. Meanwhile, the challenge for individual healthcare providers is to find and walk the fine line between avoiding harm to an individual prisoner while fulfilling a responsibility to protect the society at large.

References

- ¹ Ahuja A. The Guantanamo suicides reopen a festering question of medical ethics. <http://www.timesonline.co.uk>.
- ² Behnke S. Ethics and interrogations: Comparing and contrasting the American Psychological, American Medical and American Psychiatric Association positions. *Monitor on Psychology*. 2006;36(7):66-67.

Healthcare Profile: David K. Henderson, MD



"Your mother was right. Wash your hands often. Cover your mouth if you need to sneeze. Stay home when you're sick. Good advice when trying to avoid contracting and transmitting the flu."

"I came to the National Institutes of Health in 1979 intending to stay two to three years," says David K. Henderson, MD, Deputy Director for Clinical Care and Associate Director for Quality Assurance and Hospital Epidemiology at the National Institutes of Health (NIH)

Clinical Center, Bethesda, MD. Instead, Dr. Henderson has stayed 27 years. He found he loved being at the center of clinical research and American biomedical science, working with investigators from 20 categorical research areas. The center was designed to move basic science findings from the NIH labs into clinical care through what is called translational, or "bench-to-bedside" research.

As the first official NIH hospital epidemiologist, Dr. Henderson was charged with preventing hospital transmission of the agent responsible for AIDS, even before the agent was identified. He and other researchers devised the guidelines to reduce the risks for transmission of this blood-borne infection while preserving the confidentiality of HIV-infected patients.

Dr. Henderson recalls the early efforts to prevent the spread of AIDS, both in the community and in the healthcare setting. The lessons learned from the early management of patients with AIDS underscored the need to remain vigilant against all infectious diseases, he says.

After earning his medical degree from the University of Chicago's Pritzker School of Medicine, Dr. Henderson completed an internship and residency in internal medicine and a two-year fellowship in infectious diseases at the medical center of the University of California at Los Angeles. Subsequently, he was assistant professor of medicine at UCLA School of Medicine.

Dr. Henderson has received many awards for distinguished service from government entities and professional associations. He has been an invited speaker internationally and a frequent invited consultant to the Centers for Disease Control and Prevention. He has published more than 100 peer-reviewed journal articles as well as dozens of book chapters. His membership in medical organizations focuses particularly on those with involvement in infectious diseases, epidemiology, and AIDS. He is a member of the Bioterrorism Working Group of the Infectious Diseases Society of America.



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