Recent Updates to HPV Vaccination and Cervical Cancer Screening Guidelines

Julia Heinzerling, MPH
Rita Singhal, MD, MPH

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States. By 50 years of age, more than 80% of sexually active women are expected to be infected with HPV. Most infections are transient and asymptomatic, but persistent infection with high-risk HPV strains is the primary cause of invasive cervical cancer and genital warts. HPV infection can also lead to oropharyngeal cancer and certain genital cancers in males and females. In the U.S., cervical cancer affects approximately 12,000 women annually and HPV-associated cancers impact approximately 7,000 men.

HPV vaccination and cervical cancer screening hold the promise to reduce HPV-related morbidity and mortality. Unfortunately, vaccination and screening rates are suboptimal and inconsistent adherence to cervical cancer screening guidelines can lead to overuse and underuse of cervical cytology testing (Pap tests), increased cost, and harm. Recent changes to national guidelines, which call for routine vaccination of males and less frequent cervical cytology testing, offer the chance to increase protection against HPV and reduce potential harm from over-testing.

Revised ACIP Recommendations

Call for Vaccination of Males

In 2011, the Advisory Committee on Immunization Practices (ACIP) recommended that males, in addition to females, routinely receive three doses of HPV vaccine at 11-12 years of age. With the following two exceptions, recommendations for vaccinating males against HPV are identical to those for females:

- Males should receive quadrivalent HPV4 vaccine (Gardasil), which protects against: a) HPV 6 and 11, which cause about 90% of genital warts cases, and b) HPV 16 and 18, which cause approximately 70% of cervical cancers, 85% of anal cancers, and half of vaginal, vulvar, and penile cancers. Females may receive either HPV4 or HPV2 (Cervarix), which protects against HPV 16 and 18.

- Catch-up vaccines are routinely recommended through age 21 for males, versus age 26 for females. However, providers should vaccinate immunocompromised males, and men who have sex with men through age 26 due to their increased risk for HPV-related conditions. They may vaccinate any other males who wish to be vaccinated through 26 years of age.

Further guidance is outlined in Table 1 and detailed in the ACIP’s recommendations (www.cdc.gov/vaccines/pubs/ACIP-list.htm#hpv).

Rationale for Vaccinating Males

The recommendation to vaccinate males was based on a careful review of findings regarding vaccine efficacy, immunogenicity, safety, and cost-effectiveness for males, including the following:

- The burden of male HPV-associated infections is significant and growing. Each year, approximately 250,000 genital warts cases occur in the U.S. among sexually active males. In addition, between 1973 and 2007, the incidence of oropharyngeal and anal cancer in U.S. men increased 1% and 3% per year, respectively.

continued on page 2 >
HPV vaccine has high efficacy for the prevention of precancerous anal intraepithelial neoplasia (AIN1/2/3 and AIN2/3) and genital warts, in males.

In clinical trials, more than 99% of HPV4 vaccine recipients developed an antibody response to HPV 6, 11, 16, and 18 one month after receiving the third HPV dose.6 Six years after vaccination, there were no cases of persistent infection or disease related to any of the targeted HPV vaccine types.6

HPV4 vaccine has a strong safety profile. In pre- and post-licensure studies, the most common adverse events were pain, redness, and swelling at the injection site. Headache, fatigue, and myalgia were the most common general symptoms. A post-licensure study showed no statistically significant increased risk for Guillain-Barré syndrome, stroke, venous thromboembolism, appendicitis, seizures, allergic reactions, or anaphylaxis.9

Vaccinating males is cost-effective when vaccination rates among females are low. In 2010, only 32% of California females 13-17 years of age had received 3 HPV doses.10

**Importance of Vaccinating Males and Females On-Time**

On-time vaccination of preadolescents can protect them before the onset of sexual activity, which increases throughout adolescence. In 2006-2008, 23% of females and 21% of males had vaginal sex by age 15. By age 20, this increased to 78% of females and 84% of males.11

In addition, antibody titers are significantly higher for those vaccinated between 9 and 15 years of age, compared with those receiving the vaccine after 15 years of age.12

**Cervical Cancer Screening Guidelines: An Update**

In March 2012, the United States Preventive Services Task Force (USPSTF) issued updated cervical cancer screening guidelines.13 Concurrently, the American Cancer Society

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**Table 1. Advisory Committee on Immunization Practices HPV Vaccination Recommendations**

<table>
<thead>
<tr>
<th>Females</th>
<th>Males</th>
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<tbody>
<tr>
<td><strong>Recommended Age Ranges</strong></td>
<td><strong>Catch-up Vaccination Recommendations</strong></td>
</tr>
<tr>
<td>• Administer at 11-12 years of age, preferably at a preteen doctor visit along with other age-appropriate vaccines, such as tetanus, diphtheria, and acellular pertussis (Tdap) and meningococcal conjugate (MCV4) vaccines</td>
<td>• Routinely provide catch-up doses through age 21 to males who have not completed the 3-dose HPV vaccine series</td>
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<tr>
<td>• May be administered as early as 9 years of age</td>
<td>• Provide catch-up doses to males through age 26 who meet any of the following conditions:</td>
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<tr>
<td></td>
<td>– Immunocompromised as a result of infection (including HIV), disease, or medications</td>
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<td></td>
<td>– Has sex with other men (MSM)</td>
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<td></td>
<td>– Wants to be vaccinated and does not meet the two criteria above</td>
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<thead>
<tr>
<th>Doses</th>
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<tbody>
<tr>
<td>• 3 doses of Quadrivalent HPV4 vaccine (Gardasil) or 3 doses of Bivalent HPV2 vaccine (Cervarix)</td>
<td>• 3 doses of Quadrivalent HPV4 vaccine (Gardasil)</td>
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<thead>
<tr>
<th>Precautions and Contraindications</th>
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<tr>
<td>• Precaution: Moderate or severe acute illness</td>
<td>• Contraindication: Pregnancy</td>
</tr>
<tr>
<td>• Contraindication: Anaphylaxis to a vaccine component (i.e., yeast) or following a prior HPV vaccine dose. For a list of all vaccine ingredients, see the Cervarix and Gardasil package inserts: <a href="http://www.fda.gov/BiologicsBloodVaccines/default.htm">www.fda.gov/BiologicsBloodVaccines/default.htm</a></td>
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<tr>
<th>Administration</th>
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<tr>
<td>• 0.5 mL, administered intramuscularly, preferably in the deltoid muscle</td>
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<tr>
<td>• Seat patients during vaccination and consider observing them for 15 minutes following vaccination, since syncope has been observed in adolescents receiving immunizations</td>
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<table>
<thead>
<tr>
<th>Recommended Intervals</th>
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<tbody>
<tr>
<td>• Dose 1: Preferably at 11-12 years of age</td>
<td></td>
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<tr>
<td>• Dose 2: 2 months after the first dose, with a 4-week minimum interval</td>
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<tr>
<td>• Dose 3: 6 months after the first dose, with a 12-week minimum interval between Dose 2 and 3, and a 24-week minimum interval between Dose 1 and 3</td>
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<tr>
<td>If minimum intervals above are not met, readminister Dose 2 and/or 3. If intervals are longer than minimum intervals, follow routine dosing intervals for series catch-up. Do not restart the series.</td>
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(ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) collaboratively also released cervical cancer screening guidelines.13,14 (See Table 2)

Initiation of Screening
The USPSTF and ACS/ASCCP/ASCP recommendations agree that women younger than 21 years should not be screened regardless of risk factors, including the age of sexual initiation. Screening before age 21 can lead to over-treatment of cervical lesions that have a high probability of regressing spontaneously, and subsequent adverse effects on childbearing due to the treatment.15

Screening Intervals
Due to the slow-growing nature of cervical cancer and the potential for unnecessary procedures and treatments of lesions associated with benign, transient HPV infections, it is now recognized that women should not be screened annually at any age by any screening test, method, or modality. Screening intervals are determined based on age and modality.

Screening with cytology alone is recommended every 3 years for women 21 through 29 years. The previous screening interval of every 2 years for this age group is no longer supported because there is no significant difference in reduced lifetime cancer burden between a 2-year and 3-year interval. Cytology alone every 3 years or HPV testing combined with cytology (co-testing) every 5 years can be used to screen women 30-65 years of age. This offers a reasonable balance between benefits and harms. More frequent screening confers little added benefit, with large increases in harms.13

Under ACS/ASCCP/ASCP recommendations, co-testing is preferred to cytology alone due to an increased detection of prevalent cervical intraepithelial neoplasia grade 3 (CIN3) with a concomitant decrease in CIN3+ or cancer detected in subsequent rounds of screening.14 Alternatively, the USPSTF reports that co-testing is an option for women who want to lengthen the screening interval; however, it could result in more positive screening results, prolonged surveillance and/or more frequent testing.13 Since co-testing may not be feasible in all clinical settings, a cytology-based screening strategy of every 3 years for women 30-65 years is satisfactory and practical.

Age to Discontinue Screening
Women older than 65 years no longer require cervical cancer screening if they meet the criteria for adequate prior testing and appropriate follow-up. Adequate prior screening is defined as 3 consecutive negative cytology results or 2 consecutive negative co-tests within the 10 years before ceasing screening, with the most recent test within the past 5 years. Women with a history of CIN2+ require routine screening for 20 years, even if this extends screening past 65 years of age. A history of a new sexual partner or other risk factors is not a reason to resume screening once discontinued.

Screening Recommendations After Hysterectomy
Recommendations remain consistent that routine cytology screening after total hysterectomy for benign disease (i.e., no history of CIN2+) should be discontinued. Evidence of adequate negative prior screening is not required. Routine screening should continue for 20 years from time of diagnosis and treatment when there is a history of CIN2+.

Management of Co-Testing Screening Results
Co-testing management algorithms are presented in Table 3. If both the cytology and the HPV test are negative, rescreening is needed no sooner than 5 years. For cytology of low-grade squamous intraepithelial lesion (LSIL) or more severe, despite the HPV result, women should be referred for colposcopy and other studies per ASCCP guidelines. For cytology results of atypical squamous cells of undetermined significance (ASCUS), the HPV result defines follow-up. If HPV-negative ASCUS, no further work-up is required; rescreening should occur no sooner than 5 years. For HPV-positive ASCUS, follow-up with colposcopy and biopsy.

Perhaps most controversial is an HPV-positive and cytology negative result. No randomized control trials directly compare management strategies for these results. Given that the major-

Table 2: 2012 Cervical Cancer Screening Recommendations13,14

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Age 21 years</th>
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<tbody>
<tr>
<td><strong>Initiation of Screening</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Screening Intervals</strong></td>
<td>Age 21 through 29 years</td>
</tr>
<tr>
<td></td>
<td>Cytology alone every 3 years</td>
</tr>
<tr>
<td></td>
<td>Do not screen with HPV testing</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age 30 through 65 years</td>
</tr>
<tr>
<td></td>
<td>Cytology alone every 3 years or co-testing (cytology/HPV testing) every 5 years</td>
</tr>
<tr>
<td><strong>Cessation of Screening</strong></td>
<td>After age 65 with adequate prior testing and appropriate follow-up</td>
</tr>
<tr>
<td><strong>After Total Hysterectomy</strong> (i.e., cervix removed)</td>
<td>No screening unless history of high-grade pre-cancer or cervical cancer</td>
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ity of transient HPV infections clear by 12 months, a strategy of repeat co-testing at 12 months is currently recommended. If either test is positive on the repeat co-testing (HPV-positive or LSIL or more severe cytology), the patient should be referred to colposcopy; otherwise, she should return to routine screening.

Conclusion
Vaccinating both males and females with 3 doses of HPV vaccine, per ACIP’s newly revised HPV vaccination guidelines can significantly reduce cervical cancer, anal cancer, oropharyngeal cancer, and genital warts. Following the newly released cervical cancer screening guidelines—which call for beginning cytology testing at 21 years of age, 3-year screening intervals, evidence-based co-testing strategy, and cessation of screening for most women after 65 years of age—can increase early diagnosis and prevent possible harm. By adhering to these recommendations, providers can help to significantly reduce HPV-related morbidity and mortality for both females and males.

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REFERENCES

Table 3. Management of Co-Testing Screen Result

<table>
<thead>
<tr>
<th>Co-Testing Screen Result</th>
<th>Management of Screen Result</th>
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<tbody>
<tr>
<td>Cytology and HPV-negative</td>
<td>Rescreen with co-testing no sooner than 5 years</td>
</tr>
<tr>
<td>HPV-negative ASCUS</td>
<td>Refer for colposcopy and other studies per ASCCP guidelines</td>
</tr>
<tr>
<td>Cytology of LSIL or more severe</td>
<td>12-month follow-up co-testing. If positive on either test (HPV-positive or LSIL or more severe cytology), refer to colposcopy; otherwise, return to routine screening</td>
</tr>
<tr>
<td>HPV-positive ASCUS</td>
<td>Refer for colposcopy and other studies per ASCCP guidelines</td>
</tr>
<tr>
<td>HPV-positive, cytology negative</td>
<td>Rescreen with co-testing no sooner than 5 years</td>
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Preventing Prescription Drug Abuse and Overdoses

Heather Tindall Readhead, MD, MPH
Isabelle Sternfeld, MSPH
Jeffrey Gunzenhauser, MD, MPH

Introduction
Prescription drug abuse and overdoses have reached epidemic levels. This trend has implications for medicine, public health, social services and law enforcement. Substance abuse of any kind—alcohol, illegal drugs, or legal pharmaceutical drugs—can cause significant physical and psychosocial morbidity and increase crime. It can have far-reaching impacts on the physical, social, and economic well-being of patients, their children, and other dependents, as well as personal friends, other family members, coworkers, and strangers.

Clinicians play a key role in access to prescription drugs and, therefore, must be a part of the solution to this epidemic. Future articles in this publication will focus on factors contributing to the epidemic, including increased attention to alleviating pain, over-prescription of potent analgesics, “doctor shopping,” medical identity theft, and fraud. However, among the key actions clinicians can take now to help combat this epidemic is to educate patients about the dangers of sharing their prescription drugs with others, and procedures for the safe disposal of their unused medications.

Epidemiology
The annual rate of drug overdose deaths in the United States has more than tripled since 1990, and drug overdose deaths now exceed all other causes of injury death, including deaths from motor vehicle accidents and firearms.¹ Deaths attributed to prescription drugs now exceed deaths from illicit substances such as heroin and cocaine. Among prescription drug overdoses, opioid analgesics are responsible for the majority of these deaths.¹ In Los Angeles County, unintentional drug overdose was the sixth-leading cause of premature death (19th overall leading cause of death) in 2008, with more than 19,000 years of life lost and a death rate of 6.0 deaths per 100,000 population. The highest death rates (12 deaths per 100,000 population) were among white and black males.²

Prescription drug abuse is the fastest growing drug problem in the United States.³ Medical misuse of prescription drugs exceeds abuse of all other illicit drugs except marijuana in people over age 12.³ Opioid pain relievers are the most commonly abused prescription drugs, followed by sedatives/tranquilizers and stimulants.

Prescription Drugs Considered High Risk for Overdoses

These pharmaceutical substances, listed by their generic names and formulations, are considered high risk for overdoses:

- Codeine (tablets, oral liquid)
- Diazepam (rectal gel)
- Fentanyl (sublingual, buccal, lozenges, patch)
- Hydrocodone (tablets, oral liquid)
- Hydromorphone – immediate and extended-release (tablets, oral liquid)
- Methadone (tablets, oral solution)
- Methylphenidate (tablets, patches)
- Morphine – immediate, sustained, and extended release (tablets, capsules)
- Oxycodone – immediate and extended release (tablets, capsules, oral solution)
- Oxymorphone – immediate and extended release (tablets)
- Sodium oxybate (oral solution)
- Tapentadol – extended release (tablets)
### Fast Facts: Prescription Drug Abuse

#### In the United States

- Prescription drug abuse is the fastest-growing drug problem in the nation.
- Opioid analgesics are responsible for more deaths than heroin and cocaine combined.
- There were 14,800 deaths due to painkillers. For every death, there are an additional 10 substance abuse treatment admissions, 32 emergency room visits, 130 persons who abuse or are dependent, and 825 persons who report “nonmedical” use of opioids.

#### In Los Angeles County

- Between 2000-2009, there were more than 800 drug-related deaths per year. More than 60% involved pharmaceuticals.
- The 3 most commonly detected substances involved in drug-related deaths were types of opioid prescription pain relievers: codeine, hydrocodone, and morphine.
- More than 60% of drug-related deaths involving pharmaceuticals were among males, 61% were among whites, and 62% were among patients aged 35-54.
- Between 1997 and 2007, there was a more than 600% increase in the amount of opioids prescribed.
- More than 75% of “nonmedical users” report that they obtained drugs prescribed to someone else.

- More than 80% of all drug-related deaths were unintentional.
- 71% of drug-related deaths tested positive for legal pharmaceutical drugs.
- 40% of drug-related deaths tested positive for both legal pharmaceutical drugs and illicit drugs.
- 29% of drug-related deaths tested positive for both legal pharmaceuticals drugs and alcohol.
- 20% of drug-related deaths tested positive for 5 or more drugs.

Misuse of prescription drugs starts early in high school. In Los Angeles County, 11% of students in grade 9, 14% of students in grade 11, and 37% of students in continuation, community day, or alternative high schools reported having ever misused prescription painkillers.

Seventy-one percent of prescription drug abusers obtain the drugs from a friend or relative, usually for free, either given or taken without permission. Less than 5% obtain them from a drug dealer or stranger, and less than 1% purchase them on the Internet. In light of these statistics, clinicians should warn patients, their families, and their caretakers of the dangers of medical misuse of their prescription drugs and instruct patients to dispose of all unused prescription drugs from their homes.

The U.S. Food and Drug Administration (FDA) provides “Guidelines for Drug Disposal,” which are summarized below. Medicine take-back programs are an easy way to reduce the number of drugs available in homes and communities and, thus, reduce the risk of drug-poisoning deaths.

#### Guidelines for Drug Disposal

**Instruct patients on safe disposal of unused prescription drugs.**

- Bring unused drugs to a community drug take-back program for proper disposal. Call your city or county government’s household trash and recycling service for available take-back programs or programs for the disposal of toxic substances.

The Los Angeles County Department of Public Works sponsors a “No Drugs Down the Drain” program that offers permanent take-back locations and a schedule of collection events, all free of charge. For more information, go to its website at [http://ladpw.org/epd/hhw/nodrugs/](http://ladpw.org/epd/hhw/nodrugs/).

Follow any specific disposal instructions on the drug label or on patient information material that accompanies the medication.

Do not flush prescription drugs down the toilet unless this information specifically instructs you to do so. (This issue is addressed in further detail below.)

If there are no disposal instructions on the drug label or patient information material and there are no drug take-back programs in your area, throw out the drugs in the household trash. However, prior to disposal, be sure to do the following:

- Take the drugs out of their original containers and mix them with an undesirable substance, such as used coffee grounds or kitty litter. The medication will be less appealing to children and pets and unrecognizable to people who may intentionally go through your trash.

- Place the drugs in a sealable bag, empty can, or other container to prevent the medication from leaking or breaking out of a garbage bag.

**Some medications are so dangerous that they should be disposed of immediately by flushing down the toilet.**

The FDA provides a list of “Medicines Recommended for Disposal by Flushing” (sink or toilet) to encourage rapid disposal of potentially dangerous medications. This list includes many opioids and other controlled substances, including methylphenidate (Ritalin) and diazepam (Valium).

**Patient Education on Prescription Drug Abuse**

When prescribing medications, physicians should make patients aware of their role in helping to minimize the drug misuse epidemic. According to the National Institute on Drug Abuse, there are actions patients can take to help prevent prescription drug abuse: 1) Ask your doctor or pharmacist about your medication, especially if you are unsure about its effects. 2) Keep your doctor informed about all medications you are taking, including over-the-counter medications. 3) Read the information your pharmacist provides before starting to take medications. 4) Take your medication(s) as prescribed. 5) Keep all prescription medications secured at all times and properly dispose of any unused medications.

**Community Resource: Poison Control Centers**

Unintentional poisoning and drug overdoses are among the unintended consequences of prescription drug misuse. Poison control centers are valuable community resources that offer fast and free service to clinicians and the public by assisting in the prevention and treatment of poisonings. All patients and providers should program the California Poison Control System’s 24-Hour Helpline number (1-800-222-1222) in their cell phones. Additionally, the organization’s website (www.calpoison.org) offers free patient education materials for distribution in doctors’ offices or health care facilities, as well as detailed clinician education and reference materials, including an antidote chart, toxicology modules, and updates on current and emerging poisons in the community.

**Summary**

Prescription drug abuse and its associated deaths are largely unintentional and arguably preventable, as these substances are heavily regulated. Not only do they require a prescription by a licensed professional, they are then dispensed by another licensed professional. Further, many are paid for by insurance companies. However, even with these multiple layers in the distribution chain, the involvement of clinicians is the crucial first step in addressing this growing epidemic.

**REFERENCES**


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Of Note

New Phone Number for TB Control
To streamline its workflow, the Tuberculosis Control Program, Los Angeles County Department of Public Health, has consolidated its phone lines.

There is now one phone number for both TB Reporting and general phone calls: (213) 745-0800.

Please make a note of it.

For more information on TB Control, go to www.publichealth.lacounty.gov/tb.

Index of Disease Reporting Forms

All case reporting forms from the LA County Department of Public Health are available by telephone or Internet.

Reportable Diseases & Conditions
Confidential Morbidity Report
Morbidity Unit (888) 397-3993
Acute Communicable Disease Control (213) 240-7941

Sexually Transmitted Disease
Confidential Morbidity Report
(213) 744-3070
www.publichealth.lacounty.gov/std/providers.htm (web page)
www.publichealth.lacounty.gov/std/docs/STD_CMR.pdf (form)

Adult HIV/AIDS Case Report Form
For patients over 13 years of age at time of diagnosis
HIV Epidemiology Program (213) 351-8196
www.publichealth.lacounty.gov/HIV/hivreporting.htm

Pediatric HIV/AIDS Case Report Form
For patients less than 13 years of age at time of diagnosis
Pediatric AIDS Surveillance Program (213) 351-8153
Must first call program before reporting www.publichealth.lacounty.gov/HIV/hivreporting.htm

Tuberculosis Suspects & Cases
Confidential Morbidity Report
Tuberculosis Control (213) 745-0800
www.publichealth.lacounty.gov/tb/forms/cmr.pdf

Lead Reporting
No reporting form. Reports are taken over the phone. Lead Program (323) 869-7195

Animal Bite Report Form
Veterinary Public Health (877) 747-2243 www.publichealth.lacounty.gov/vet/biteintro.htm

Animal Diseases and Syndrome Report Form
Veterinary Public Health (877) 747-2243 www.publichealth.lacounty.gov/vet/disintro.htm

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