

Human Papillomavirus

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States. The relationship of cervical cancer and sexual behavior was suspected for more than 100 years and was established by epidemiologic studies in the 1960s. In the early 1980s, cervical cancer cells were demonstrated to contain HPV DNA. Epidemiologic studies showing a consistent association between HPV and cervical cancer were published in the 1990s. The first vaccine to prevent infection with four types of HPV was licensed in 2006.

Human Papillomavirus

Human papillomaviruses are small, double-stranded DNA viruses that infect the epithelium. More than 100 HPV types have been identified; they are differentiated by the genetic sequence of the outer capsid protein L1. Most HPV types infect the cutaneous epithelium and cause common skin warts. About 40 types infect the mucosal epithelium; these are categorized according to their epidemiologic association with cervical cancer. Infection with low-risk, or nononcogenic types, such as types 6 and 11, can cause benign or low-grade cervical cell abnormalities, genital warts and laryngeal papillomas. High-risk, or oncogenic, HPV types act as carcinogens in the development of cervical cancer and other anogenital cancers. High-risk types (currently including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 73, 82) can cause low-grade cervical cell abnormalities, high-grade cervical cell abnormalities that are precursors to cancer, and anogenital cancers. High-risk HPV types are detected in 99% of cervical cancers. Type 16 is the cause of approximately 50% of cervical cancers worldwide, and types 16 and 18 together account for about 70% of cervical cancers. Infection with a high-risk HPV type is considered necessary for the development of cervical cancer, but by itself it is not sufficient to cause cancer because the vast majority of women with HPV infection do not develop cancer.

In addition to cervical cancer, HPV infection is also associated with anogenital cancers less common than cervical cancer, such as cancer of the vulva, vagina, penis and anus. The association of genital types of HPV with non-genital cancers is less well established, but studies support a role for these HPV types in a subset of oral cavity and pharyngeal cancers.

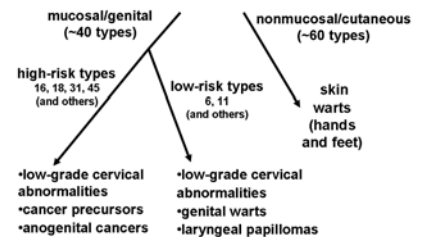
Pathogenesis

HPV infection occurs at the basal epithelium. Although the incidence of infection is high, most infections resolve spontaneously. A small proportion of infected persons become persistently infected; persistent infection is the most

Human Papillomavirus (HPV)

- Small DNA virus
- More than 100 types identified based on the genetic sequence of the outer capsid protein L1
- 40 types infect the mucosal epithelium

Human Papillomavirus Types and Disease Association



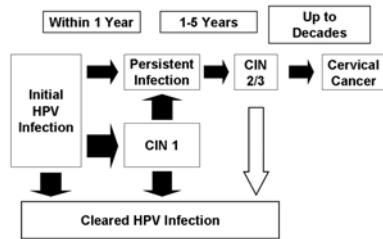
HPV-Associated Disease

Type	Women	Men
16/18	70% of cervical cancers 70% of anal/genital cancers	70% of anal cancers Transmission to women
6/11	90% of genital warts 90% of RRP lesions	90% of genital warts 90% of RRP lesions Transmission to women

* RRP = recurrent respiratory papillomatosis

Human Papillomavirus

Natural History of HPV Infection



HPV Clinical Features

- Most HPV infections are asymptomatic and result in no clinical disease
- Clinical manifestations of HPV infection include:
 - anogenital warts
 - recurrent respiratory papillomatosis
 - cervical cancer precursors (cervical intraepithelial neoplasia)
 - cancer (cervical, anal, vaginal, vulvar, penile, and some head and neck cancer)

important risk factor for the development of cervical cancer precursor lesions. The most common clinically significant manifestation of persistent genital HPV infection is cervical intraepithelial neoplasia, or CIN. Within a few years of infection, low-grade CIN—called CIN 1—may develop, which may spontaneously resolve and the infection clear.

Persistent HPV infection, however, may progress directly to high-grade CIN, called CIN2 or CIN3. High-grade abnormalities are at risk of progression to cancer and so are considered cancer precursors. A small proportion of high-grade abnormalities spontaneously regress. If left undetected and untreated, years or decades later CIN2 or 3 can progress to cervical cancer.

Infection with one type of HPV does not prevent infection with another type. Of persons infected with mucosal HPV, 5% to 30% are infected with multiple types of the virus.

Clinical Features

Most HPV infections are asymptomatic and result in no clinical disease. Clinical manifestations of HPV infection include anogenital warts, recurrent respiratory papillomatosis, cervical cancer precursors (cervical intraepithelial neoplasia), and cancers, including cervical, anal, vaginal, vulvar, penile, and some head and neck cancer.

Laboratory Diagnosis

HPV has not been isolated in culture. Infection is identified by detection of HPV DNA from clinical samples. Assays for HPV detection differ considerably in their sensitivity and type specificity, and detection is also affected by the anatomic region sampled as well as the method of specimen collection.

Currently, only the Digene Hybrid Capture 2[®] (hc2) High-Risk HPV DNA Test is approved by the Food and Drug Administration for clinical use. The hc2 uses liquid nucleic acid hybridization and detects 13 high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). Results are reported as positive or negative and are not type-specific. The hc2 test is approved for triage of women with equivocal Papanicolaou (Pap) test results (ASC-US, atypical cells of undetermined significance) and in combination with the Pap test for cervical cancer screening in women 30 years of age and older. The test is not clinically indicated nor approved for use in men.

Epidemiologic and basic research studies of HPV generally use nucleic acid amplification methods that generate type-specific results. The PCR assays used most commonly in epidemiologic studies target genetically conserved regions in the L1 gene.

The most frequently used HPV serologic assays are VLP-based enzyme immunoassays. However, laboratory reagents used for these assays are not standardized and there are no standards for setting a threshold for a positive result.

Medical Management

There is no specific treatment for HPV infection. Medical management depends on treatment of the specific clinical manifestation of the infection (such as genital warts or abnormal cervical cell cytology).

Epidemiology

Occurrence

HPV infection occurs throughout the world.

Reservoir

Viruses in the papillomavirus family affect other species (notably rabbits and cows). However, humans are the only natural reservoir of HPV.

Transmission

HPV is transmitted by direct contact, usually sexual, with an infected person. Transmission occurs most frequently with sexual intercourse but can occur following nonpenetrative sexual activity.

Studies of newly acquired HPV infection demonstrate that infection occurs soon after onset of sexual activity. In a prospective study of college women, the cumulative incidence of infection was 40% by 24 months after first sexual intercourse. HPV 16 accounted for 10.4% of infections.

Genital HPV infection also may be transmitted by nonsexual routes, but this appears to be uncommon. Nonsexual routes of genital HPV transmission include transmission from a woman to a newborn infant at the time of birth.

Temporal Pattern

There is no known seasonal variation in HPV infection.

Communicability

HPV is presumably communicable during the acute infection and during persistent infection. This issue is difficult to study because of the inability to culture the virus. Communicability can be presumed to be high because of the large number of new infections estimated to occur each year.

HPV Epidemiology

• Reservoir	Human
• Transmission	Direct contact, usually sexual
• Temporal pattern	None
• Communicability	Presumed to be high

HPV Disease Burden in the United States

- Anogenital HPV is the most common sexually transmitted infection in the US
 - estimated 20 million currently infected
 - 6.2 million new infections/year
- Common among adolescents and young adults
- More than 80% of sexually active women will have been infected by age 50
- Infection also common in men

Cervical Cancer Disease Burden in the United States

- The American Cancer Society estimates that in 2008
 - 11,070 new cervical cancer cases
 - 3,870 cervical cancer deaths
- Almost 100% of these cervical cancer cases will be caused by one of the 40 HPV types that infect the mucosa

Risk Factors

Risk factors for HPV infection are related to sexual behavior, including the number of sex partners, lifetime history of sex partners, and the partners' sexual history. Most studies suggest that young age (less than 25 years) is a risk factor for infection. Results of epidemiologic studies are less consistent for other risk factors, including young age at sexual initiation, inconsistent condom use, number of pregnancies, genetic factors, smoking, lack of circumcision of male partner, and oral contraceptive use.

Disease Burden in the United States

Anogenital HPV infection is believed to be the most common sexually transmitted infection in the United States. An estimated 20 million persons are currently infected, and an estimated 6.2 million new HPV infections occur annually. HPV infection is common among adolescents and young adults. Prevalence among adolescent girls is as high as 64%. Up to 75% of new infections occur among persons 15–24 years of age. Modeling estimates suggest that more than 80% of sexually active women will have been infected by age 50.

HPV infection is also common in men. Among heterosexual men in clinic-based studies, prevalence of genital HPV infection is often greater than 20%. Prevalence is highly dependent on the anatomic sites sampled and method of specimen collection.

The two most common types of cervical cancer worldwide, squamous cell carcinoma followed by adenocarcinoma, are both caused by HPV. The American Cancer Society estimates that in 2008 about 11,070 new cases of cervical cancer will be diagnosed in the United States. Approximately 3,870 women will die as a result of cervical cancer. HPV is believed to be responsible for nearly all of these cases of cervical cancer. HPV types 16 and 18 are associated with 70% of these cancers.

In addition to cervical cancer, HPV is believed to be responsible for 90% of anal cancers, 40% of vulvar, vaginal, or penile cancers, and 12% of oral and pharyngeal cancers.

Population-based estimates, primarily from clinics treating persons with sexually transmitted infections, indicate that about 1% of the sexually active adolescent and adult population in the United States have clinically apparent genital warts. More than 90% of cases of anogenital warts are associated with the low-risk HPV types 6 and 11.

About 4 billion dollars are spent annually on management of sequelae of HPV infections, primarily for the management of abnormal cervical cytology and treatment of cervical neoplasia. This exceeds the economic burden of any

other sexually transmitted infection except human immunodeficiency virus.

Prevention

HPV Infection

HPV transmission can be reduced but not eliminated with the use of physical barriers such as condoms. Recent studies demonstrated a significant reduction in HPV infection among young women after initiation of sexual activity when their partners used condoms consistently and correctly. Abstaining from sexual activity (i.e., refraining from any genital contact with another individual) is the surest way to prevent genital HPV infection. For those who choose to be sexually active, a monogamous relationship with an uninfected partner is the strategy most likely to prevent future genital HPV infections.

Cervical Cancer Screening

Most cases and deaths from cervical cancer can be prevented through detection of precancerous changes within the cervix by cervical cytology using the Pap test. Currently available Pap test screening can be done by a conventional Pap or a liquid-based cytology. CDC does not issue recommendations for cervical cancer screening, but various professional groups have published recommendations. The American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS), and the U.S. Preventive Services Task Force (USPSTF) guidelines recommend that all women should have a Pap test for cervical cancer screening within 3 years of beginning sexual activity or by age 21, whichever occurs first. While the USPSTF recommends a conventional Pap test at least every 3 years regardless of age, ACS and ACOG recommend annual or biennial screening of women younger than age 30, depending on use of conventional or liquid-based cytology. According to these national organizations, women over age 30 with three normal consecutive Pap tests should be screened every 2 to 3 years.

The use of HPV vaccine does not eliminate the need for continued Pap test screening, since 30% of cervical cancers are caused by HPV types not included in the vaccine.

Human Papillomavirus Vaccine

Characteristics

Two HPV vaccines are currently licensed in the United States. Both vaccines are inactivated subunit vaccines. The antigen for both vaccines is the L1 major capsid protein of HPV, produced by using recombinant DNA technology. L1 proteins

Cervical Cancer Screening

- Cervical cancer screening – no change
 - 30% of cervical cancers caused by HPV types not prevented by the quadrivalent HPV vaccine
 - vaccinated females could subsequently be infected with non-vaccine HPV types
 - sexually active females could have been infected prior to vaccination
- Providers should educate women about the importance of cervical cancer screening

Human Papillomavirus Vaccine

- HPV L1 major capsid protein of the virus is antigen used for immunization
- L1 protein produced using recombinant technology
- L1 proteins self-assemble into virus-like particles (VLP)
- VLP are noninfectious and nononcogenic

HPV Vaccines

- HPV4 (Gardasil)
 - contains types 16 and 18 (high risk) and types 6 and 11 (low risk)
 - approved for females and males 9 through 26 years of age
- HPV2 (Cervarix)
 - contains types 16 and 18 (high risk)
 - approved for females 10 through 25 years of age

self-assemble into noninfectious, nononcogenic units called virus-like particles (VLP).

Quadrivalent HPV (HPV4) vaccine (Gardasil, Merck) was approved by the Food and Drug Administration in June 2006. The vaccine is approved for females and males 9 through 26 years of age. Each 0.5-mL dose of HPV4 contains 20 µg HPV 6 L1 protein, 40 µg HPV 11 L1 protein, 40 µg HPV 16 L1 protein, and 20 µg HPV 18 L1 protein. The vaccine antigen is adsorbed on alum adjuvant. The vaccine also includes sodium chloride, L-histidine, polysorbate 80, and sodium borate. HPV4 does not contain a preservative or antibiotic. The vaccine is supplied in single-dose vials and syringes.

Bivalent HPV (HPV2) vaccine (Cervarix, GlaxoSmithKline) was approved by the Food and Drug Administration in October 2009. The vaccine is approved for females 10 through 25 years of age. HPV2 is not approved for males. The L1 antigen is adsorbed onto aluminum (as hydroxide salt). The unique adjuvant system, AS04, is composed of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed on to aluminum (as hydroxide salt). Each 0.5-mL dose contains 20 mcg of HPV type 16 L1 protein, 20 mcg of HPV type 18 L1 protein, 50 mcg of the 3-O-desacyl-4'-monophosphoryl lipid A (MPL), and 0.5 mg of aluminum hydroxide. The vaccine also contains sodium chloride and sodium dihydrogen phosphate dihydrate. HPV2 does not contain a preservative or antibiotic. It is available in vials and 2 types of prefilled syringes. One type of prefilled syringe has a tip cap which may contain natural rubber latex and a plunger which does not contain latex. The other type has a tip cap and a rubber plunger which contain dry natural latex rubber. The vial stopper does not contain latex.

Immunogenicity and Vaccine Efficacy

Both HPV vaccines are highly immunogenic. For both vaccines more than 99% of recipients develop an antibody response to HPV types included in the respective vaccines 1 month after completing the three-dose series. However, there is no known serologic correlative of immunity and no known minimal titer determined to be protective. The high efficacy found in the clinical trials to date has precluded identification of a minimum protective antibody titer. Further follow-up of vaccinated cohorts may allow determination of serologic correlates of immunity in the future.

Both HPV vaccines have been found to have high efficacy for prevention of HPV vaccine type-related persistent infection and adenocarcinoma in-situ (AIS). Clinical efficacy for HPV4 against cervical disease was determined in two double-blind, placebo-controlled trials in women 16-26 years of age. Vaccine efficacy for HPV 16 or 18-related CIN 2/3 or AIS was

97%. Efficacy against any CIN due to HPV 6, 11, 16, or 18 was 95%. HPV4 efficacy against HPV 6, 11, 16 or 18-related genital warts was 99%. HPV4 efficacy against HPV 6 or 11-related genital warts was 90%.

HPV2 efficacy was evaluated in two randomized, double-blind, controlled clinical trials in females aged 15 through 25 years. Efficacy against HPV 16 or 18-related CIN grade 2 or 3 or AIS was 93%.

Although high efficacy among females without evidence of infection with vaccine HPV types was demonstrated in clinical trials of both HPV vaccines, there is no evidence of efficacy against disease caused by vaccine types with which participants were infected at the time of vaccination (i.e., the vaccines had no therapeutic effect on existing infection or disease). Participants infected with one or more vaccine HPV types prior to vaccination were protected against disease caused by the other vaccine types. Prior infection with one HPV type did not diminish efficacy of the vaccine against other vaccine HPV types.

The duration of protection following HPV vaccine is not known. For both vaccines a subset of participants have been followed for more than 60 months with no evidence of waning protection. Study populations will continue to be followed for any evidence of waning immunity.

Vaccination Schedule and Use

ACIP recommends vaccination with HPV2 or HPV4 for prevention of cervical cancers and precancers. Both vaccines might provide protection against some other HPV-related cancers in addition to cervical cancer, although there are currently only data sufficient to recommend HPV4 for protection against vulvar and vaginal cancers and precancers. HPV4 is recommended also for prevention of genital warts.

ACIP recommends routine vaccination of all females 11 or 12 years of age with 3 doses of either HPV2 or HPV4. The vaccination series can be started beginning at 9 years of age at the clinician's discretion. Vaccination is recommended for females 13 through 26 years of age who have not been vaccinated previously or who have not completed the 3-dose series. If a female reaches age 26 years before the vaccination series is complete, remaining doses can be administered after age 26 years.

The 3-dose series of HPV4 may be given to males 9 through 26 years of age to reduce their likelihood of genital warts. HPV2 is not approved for use in males.

Ideally, vaccine should be administered before potential

HPV Vaccine Efficacy

- High efficacy among females without evidence of infection with vaccine HPV types
- No evidence of efficacy against disease caused by vaccine types with which participants were infected at the time of vaccination
- Prior infection with one HPV type did not diminish efficacy of the vaccine against other vaccine HPV types

Routine HPV Vaccination Recommendations

- ACIP recommends routine vaccination of females 11 or 12 years of age
- The vaccination series can be started as young as 9 years of age at the clinician's discretion
- Catch-up vaccination recommended for females 13 through 26 years of age

HPV Vaccination Schedule

- Routine schedule is 0, 2, 6 months
- Third dose should follow the first dose by at least 24 weeks
- An accelerated schedule using minimum intervals is not recommended
- Series does not need to be restarted if the schedule is interrupted

exposure to HPV through sexual contact; however, females who may have already been exposed to HPV should be vaccinated. Sexually active females who have not been infected with any of the HPV vaccine types will receive full benefit from vaccination. Vaccination will provide less benefit to females if they have already been infected with one or more of the HPV vaccine types. However, it is not possible for a clinician to assess the extent to which sexually active females would benefit from vaccination, and the risk of HPV infection may continue as long as persons are sexually active. Pap testing or screening for HPV DNA or HPV antibody is not recommended prior to vaccination at any age.

Both HPV vaccines are administered in a three-dose series of intramuscular injections. The second and third doses should be administered 2 and 6 months after the first dose. The third dose should follow the first dose by at least 24 weeks. An accelerated schedule for HPV vaccine is not recommended.

There is no maximum interval between doses. If the HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be given as soon as possible, and the second and third doses should be separated by an interval of at least 12 weeks. If only the third dose is delayed, it should be administered as soon as possible.

Whenever feasible, the same HPV vaccine should be used for the entire vaccination series. No studies address interchangeability of HPV vaccines. However, if the vaccine provider does not know or have available the HPV vaccine product previously administered, either HPV vaccine can be used to complete the series to provide protection against HPV 16 and 18. For protection against HPV 6 or 11-related genital warts, a vaccination series with less than 3 doses of HPV4 might provide less protection against genital warts than a complete 3-dose HPV4 series.

HPV vaccine should be administered at the same visit as other age-appropriate vaccines, such as Tdap and quadrivalent meningococcal conjugate (MCV4) vaccines. Administering all indicated vaccines at a single visit increases the likelihood that adolescents and young adults will receive each of the vaccines on schedule. Each vaccine should be administered using a separate syringe at a different anatomic site.

Females who have an equivocal or abnormal Pap test could be infected with any of more than 40 high-risk or low-risk genital HPV types. It is unlikely that such females would be infected with all HPV vaccine types, and they

may not be infected with any HPV vaccine type. Women younger than 27 years with a previously abnormal Pap test may be vaccinated. Women should be advised that data do not indicate the vaccine will have any therapeutic effect on existing HPV infection or cervical lesions.

Females who have a positive HPV DNA test (Hybrid Capture 2[®]) done in conjunction with a Pap test could be infected with any of 13 high-risk types. This assay does not identify specific HPV types, and testing for specific HPV types is not done routinely in clinical practice. Women younger than 27 years with a positive HPV DNA test may be vaccinated. HPV DNA testing is not a prerequisite for vaccination. Women should be advised that the vaccine will not have a therapeutic effect on existing HPV infection or cervical lesions.

A history of genital warts or clinically evident genital warts indicate infection with HPV, most often type 6 or 11. However, these females may be infected with HPV types other than the HPV4 vaccine types, and therefore they may receive HPV4 vaccine if they are in the recommended age group. Women with a history of genital warts should be advised that data do not indicate HPV4 vaccine will have any therapeutic effect on existing HPV infection or genital warts.

Because HPV vaccines are subunit vaccines, they can be administered to females who are immunosuppressed because of disease or medications. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent. Women who are breastfeeding may receive HPV vaccine.

Contraindications and Precautions to Vaccination

A severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of HPV vaccine is a contraindication to receipt of HPV vaccine. A moderate or severe acute illness is a precaution to vaccination, and vaccination should be deferred until symptoms of the acute illness improve. A minor acute illness (e.g., diarrhea or mild upper respiratory tract infection, with or without fever) is not a reason to defer vaccination.

HPV vaccine is not recommended for use during pregnancy. The vaccine has not been associated with adverse pregnancy outcomes or with adverse effects on the developing fetus. However, data on vaccination during pregnancy are limited. Initiation of the vaccine series should be delayed until after completion of the pregnancy. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the three-dose

HPV Vaccine Special Situations

- Vaccine can be administered
 - equivocal or abnormal Pap Test
 - positive HPV DNA test
 - genital warts
 - immunosuppression
 - breastfeeding

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HPV Vaccine Contraindications and Precautions

- Contraindication
 - severe allergic reaction to a vaccine component or following a prior dose
- Precaution
 - moderate or severe acute illnesses (defer until symptoms improve)

HPV Vaccination During Pregnancy

- Initiation of the vaccine series should be delayed until after completion of pregnancy
- If a woman is found to be pregnant after initiating the vaccination series, remaining doses should be delayed until after the pregnancy
- If a vaccine dose has been administered during pregnancy, there is no indication for intervention
- Women vaccinated during pregnancy should be reported to the respective manufacturer

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HPV Vaccine Adverse Reactions

- Local reactions (pain, swelling) 20%-90%
- Fever 10%-13%*
- No serious adverse reactions associated

*similar to reports in placebo recipients

HPV Vaccine Storage and Handling

- Store at 35°–46°F (2°–8°C)
- Protect from light
- Administer immediately after removing from refrigeration
- Do not expose to freezing temperature

regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is indicated. A vaccine in pregnancy registry has been established; patients and healthcare providers are urged to report any exposure to HPV vaccine during pregnancy by contacting the respective manufacturer.

Adverse Reactions Following Vaccination

The most common adverse reactions reported during clinical trials of HPV vaccines were local reactions at the site of injection. In prelicensure clinical trials, local reactions, such as pain, redness or swelling were reported by 20% to 90% of recipients. A temperature of 100° F during the 15 days after vaccination was reported in 10% to 13% of recipients of either vaccine. A similar proportion of placebo recipients reported an elevated temperature. Local reactions generally increased in frequency with increasing doses. However, reports of fever did not increase significantly with increasing doses. No serious adverse events have been associated with either HPV vaccine based on monitoring by CDC and the Food and Drug Administration.

A variety of systemic adverse reactions were reported by vaccine recipients, including nausea, dizziness, myalgia and malaise. However, these symptoms occurred with equal frequency among both vaccine and placebo recipients.

Syncope has been reported among adolescents who received HPV and other vaccines recommended for this age group (Tdap, MCV). Recipients should always be seated during vaccine administration. Clinicians should consider observing persons for 15–20 minutes after vaccination.

Vaccine Storage and Handling

HPV vaccines should be stored continuously at 35°–46°F (2°–8°C) and should be protected from light. The vaccine should be removed from refrigeration immediately before administration. The vaccines must not be exposed to freezing temperature. Vaccine exposed to freezing temperature should never be administered.

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