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Human Papilloma Virions in the Laboratory

Eileen F. Dunne, MD, MPH¹, Lauri E. Markowitz, MD¹, La'Shan D. Taylor^{1,2}, Elizabeth R. Unger, PhD, MD³, and Cosette Wheeler, PhD⁴

¹Division of STD Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

²Epidemic Intelligence Service Fellow (EIS), Centers for Disease Control and Prevention, Atlanta, Georgia

³Division of High-Consequence Pathogens and Pathology, Centers for Disease Control and Prevention, Atlanta, Georgia

⁴Departments of Pathology and Obstetrics and Gynecology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

Abstract

Carcinogenic human papillomaviruses can (HPV) cause cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers. Non-carcinogenic HPVs can cause anogenital warts and recurrent respiratory papillomatosis. Currently, few research laboratories propagate, isolate or generate papilloma virions. However, there have been questions about potential exposure and risk in this setting. In this brief note, we discuss the use of wild type and laboratory-generated virions in research laboratories, potential routes of laboratory exposure, and considerations for HPV vaccination of laboratory personnel.

Keywords

Laboratory safety; human papillomavirus; HPV; HPV vaccines

HPV in the Laboratory

Papillomaviruses (PV) infect and replicate in the epithelium. These non-enveloped, naked icosahedrons are comprised of a major (L1) and minor (L2) protein that encapsidates a double-stranded circular deoxyribonucleic acid (DNA) genome of approximately 8 kilobases (Howley 2007). Due to tissue and species tropism, and the requirement for differentiated

Corresponding Author: Cosette Wheeler, PhD, Departments of Pathology and Obstetrics and Gynecology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico 87131, cwheeler@salud.unm.edu, Phone: 505-272-5785, Fax: 505-277-0265.

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Conflict of interest

The findings and conclusions of this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the National Institutes of Health.

epithelium, laboratory production of PV has been challenging. Laboratory techniques performed to propagate and isolate wild type human papillomaviruses (HPV) including HPV 11, 16, 18, 31, 39 and 45 involve using infected xenografts grown in immunocompromised animals or infected keratinocytes grown in organotypic raft cultures (McCance et al., 1988; 1990; Meyers et al. 1997; Pyeon 2005; McLaughlin –Drubin 2003; Song 2010, Chow LT 2009; Fang L 2006; McLaughlin-Drubin 2004)). Generation of these infectious virions is time-consuming and technically challenging.

Newer laboratory techniques allow more efficient production of laboratory-generated virions. These virions, termed “quasi virions” and “pseudo virions”, have been useful for studying HPV assembly, entry, and life cycle (Pyeon et al., 2005; Culp et al., 2006; Buck et al., 2007). “Pseudo virions”, or PV-based gene transfer vectors, are produced in the 293TT cell system,. These synthetic “pseudo virions” consist of PV viral-like particles (VLP) encapsidating heterologous plasmid DNA typically including reporter genes for detection purposes (Buck et al., 2005 and 2007). “Pseudo virions” are believed to pose no infectious risk to laboratory workers since they are unable to propagate in cell lines and their encapsidated plasmids do not encode PV oncogenes, or other potentially harmful genes. In contrast, “quasi virions” are laboratory-generated virions synthesized in the 293TT cell system that consist of PV L1 and L2 encapsidating complete ~8 Kb PV genomes (Pyeon et al., 2005; Culp et al., 2006). “Quasi virions” are generally indistinguishable from tissue-derived PV (wild type) virions and may be infectious. In animal model studies using cottontail rabbit “quasi virions”, infectious papillomas were produced when injected in the skin of rabbits (Culp et al., 2006). Isolation and purification steps can produce highly purified virions with yields of up to 10^9 infectious units from a single 75-cm² flask of cells (Pyeon et al, 2005). Many HPV “quasi virion” types have been propagated in the laboratory to date.

Laboratory Exposure and Risk

Potential routes of exposure for laboratory personnel working with wild type virus or synthetic laboratory-generated “quasi-virions” are inhalation/respiratory routes, direct contact, or ingestion. Laboratory manipulations and use of centrifuges, vortexers, blenders, homogenizers and sonicators could aerosolize virion during production. Papillomaviruses are considered a stable fomite (Ferenczy et al., 1989; Roden et al., 1997). Most commonly used environmental surface disinfectants have been shown to be ineffective in reducing infectivity of HPV (Meyers 2014). While there are hypothetical risks, laboratory-acquired HPV infections might be difficult to document due to the few number of occupationally exposed workers and the difficulty of elucidating a transmission event. No studies to date have investigated laboratory exposures to wild type virus or synthetic laboratory generated “quasi-virions”, or detected infection or disease resulting from exposure in the laboratory.

As for all laboratory workers, using laboratory safety precautions is important for protection against potential HPV exposures. Currently laboratorians who work with papilloma virions employ modified laboratory safety precautions at bio-safety level 2 or 3 (BSL-2 or BSL-3); BSL-3 is above routine laboratory safety recommendations (BMBL). This safety level requires laboratory personnel to wear appropriate personal protective equipment and to

work with infectious material under biological safety cabinets, special designed hoods, or other physical containment devices located in a BSL-3 containment facility (Pyeon et al. 2005).

HPV Vaccines

Two prophylactic human papillomavirus (HPV) vaccines are licensed and recommended for use in the United States (U.S.); a bivalent HPV vaccine which prevents HPV types 16, 18 and a quadrivalent vaccine which prevents HPV types 16, 18, 6, 11 (CDC 2007, 2010 and 2011). The bivalent HPV vaccine is licensed for 9–25 year old females, and the quadrivalent HPV vaccine is licensed for 9–26 year old females and males. The Advisory Committee on Immunization Practices (ACIP) recommends either vaccine be given routinely to girls at age 11 or 12 years, and quadrivalent HPV vaccine be given routinely to boys at age 11 or 12 years. Either vaccine is recommended through age 26 years in females and quadrivalent HPV vaccine is recommended through age 21 years in males (CDC 2007, 2010, 2011). Clinical trials have found both vaccines have high efficacy in preventing infection and anogenital disease due to HPV types targeted by the vaccines. These vaccines do not prevent progression of existing HPV infection to disease or have a therapeutic impact on existing HPV associated disease (Hildesheim et al, 2007). While there are some data to suggest HPV vaccines will protect against other related HPV types not found in the vaccines (cross-protection), the extent of the cross protection is unclear. In a post-hoc evaluation of a bivalent clinical efficacy trial, women who had received HPV vaccine had a lower prevalence of oral HPV infection (Herrero et al.); however, there have been no clinical trials to date demonstrating efficacy for prevention of oropharyngeal cancers, nor prevention of recurrent respiratory papillomatosis. Vaccine has also been studied in females through age 45 years. Vaccine trials showed high immunogenicity in older woman, and in women without evidence of prior infection, high efficacy for prevention of cervical precancers (Grant, Castellsague, Munoz). Neither vaccine is FDA approved for use in persons over age 26 years and there are no ACIP recommendations for vaccinating women or men over the age of 26 years.

Summary

Some laboratories are currently generating or working with infectious and carcinogenic HPV virions. Although acquisition of HPV infection or development of HPV-associated diseases or cancers has not been demonstrated in humans from exposure in the laboratory, there is a considerable theoretical risk. Laboratory workers who produce or handle HPV virions should use appropriate laboratory safety precautions. Young adults working in these settings should be vaccinated according to existing guidance ((CDC 2007, 2010, 2011). Consideration of the risks and benefits of HPV vaccination for older adults working in research HPV laboratory settings and handling high-titer carcinogenic HPV is needed. Additional research on potential laboratory transmission/exposure of virions in this setting may be useful for vaccine considerations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- There are many questions about potential exposure and risk in research laboratories working with papilloma virions.
- We review use of human papilloma virions in laboratories and potential routes of laboratory exposure.
- We discuss considerations for HPV vaccination of laboratory personnel.