Some clear answers regarding transmission of genital human papillomavirus

The issue of how human papillomavirus (HPV) is transmitted is essential for even the most basic planning of preventive efforts. It is well established that there is little genital HPV infection among women before sexual debut, with HPV prevalence being highly dependent on both lifetime and recent number of sexual partners,[1–3] HPV is also frequently detected on hands and fingers.[4] Furthermore, HPV can remain viable outside the body for extended periods of time, meaning that studies of indirect modes of transmission were warranted;[5] however, more than 20 years of research on this topic has not provided clear answers.

In a study published in *The Lancet Infectious Diseases*, Talía Malagón and colleagues[6] followed up a cohort of female university students and their male partners and included comprehensive HPV genotyping of genital and hand samples. Although most previous studies found a clear correlation between HPV presence on genitals and hands, assessing whether the correlation might have been caused by deposition of HPV from genitals to hands or vice versa has been difficult, an issue that can be addressed by a longitudinal study design. There was indeed a high risk for genital HPV infection if an individual had HPV on their hands, but the risk disappeared after adjusting for the presence of genital HPV in their partner.

The results are in line with previous evidence. The low HPV DNA prevalence and seroprevalence among women with no experience of genital-to-genital contact[1–3] implies that hand-to-hand transmission does not occur to any important extent. On the question of whether genital-to-hand transmission might occur, the answer is clearly yes.[3] Whether detection of HPV DNA indicates the presence of an infection or merely a deposition is unclear.[3] Typical signs that an infection has indeed occurred, but has not been shown, include production of viral mRNA, production of viral proteins, and seroconversion. However, in the case of HPV-positive cancers of the fingers (typically nailbed cancers), a biologically relevant (carcinogenic) infection has clearly occurred. Sequencing studies have detected the same strain of HPV in cancers of the fingers as in cervical precancers occurring several decades earlier in the same patient,[7] making it likely that these infections had the same source.

As discussed by the Malagón and colleagues,[6] the fact that the presence of HPV DNA on the hands is commonly transient has been taken as evidence to suggest that this DNA is a result of deposition rather than infection. However, another possibility exists. The human skin has a very rapid turnover time, implying that infection of cells in the basal cell layer of the skin is required for long-term maintenance (persistence) of the infection. Indeed, persistent HPV infection appears to either require a trauma that exposes the basal cell layer to the infection or a trauma that is limited to the cervical transformation zone, where the basal cell layer is exposed.[8] A possible result of an infection that does not reach the basal cell layer could be a transient infection that disappears as the skin regenerates and the superficial layers of the skin are shed.

If genital-to-hand transmission can occur, why is there no measurable risk of hand-to-genital transmission? A possible answer comes from studies of immunostaining of HPV viral capsids. The virions can be abundant in an early genital infection, for example in cervical condylomata, but are more difficult to detect in later stages or in non-genital sites.[9] It is thus conceivable that the genital mucosa is more permissive for production of infectious viral particles, meaning that transmission of HPV will usually require contact with infected genital mucosa.

In conclusion, although studies of transmission have had to rely on indirect evidence, in the study by Malagón and colleagues[6] the epidemiological evidence now accords with the theory that hand-to-genital transmission of HPV is not an important mode of HPV transmission. With the increasing adoption of HPV-based cervical screening, reassuring women who are HPV positive that the primary mode of HPV transmission is genital-to-genital transmission is important.

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1 Rylander E, Ruusuvaara L, Almstromer MW, Evander M, Wadell G. The absence of vaginal human papillomavirus 16 DNA in women who have not experienced sexual intercourse. *Obstet Gynecol* 1994; **83:** 735–37.

2 Dillner J, Kallings I, Brihmer C, et al. Seropositivities to human papillomavirus types 16, 18, or 33 capsids and to Chlamydia trachomatis are markers of sexual behavior. *J Infect Dis* 1996; **173:** 1394–98.

3 Widdice L, Ma Y, Jonte J, et al. Concordance and transmission of human papillomavirus within heterosexual couples observed over short intervals. *J Infect Dis* 2013; **207:** 1286–94.

4 Winer RL, Hughes JP, Feng Q, et al. Detection of genital HPV types in fingertip samples from newly sexually active female university students. *Cancer Epidemiol Biomarkers Prev* 2010; **19:** 1682–85.

5 Roden RB, Lowy DR, Schiller JT. Papillomavirus is resistant to desiccation. *J Infect Dis* 1997; **176:** 1076–79.

6 Malagón T, Louvanto K, Wissing M, et al. Hand-to-genital and genital-to-genital transmission of human papillomaviruses between male and female sexual partners (HITCH): a prospective cohort study. *Lancet Infect Dis* 2019; published online Feb 8. http://dx.doi.org/10.1016/S1473-3099(18)30655-8.

7 Forslund O, Nordin P, Andersson K, Stenquist B, Hansson BG. DNA analysis indicates patient-specific human papillomavirus type 16 strains in Bowen's disease on fingers and in archival samples from genital dysplasia. *Br J Dermatol* 1997; **136:** 678–82.

8 Egawa N, Egawa K, Griffin H, Doorbar J. Human papillomaviruses, epithelial tropisms, and the development of neoplasia. *Viruses* 2015; **7:** 3863–90.

9 Wools K, Bryan JT, Katz BP, Rodriguez M, Davis T, Brown DR. Detection of human papillomavirus L1 protein in condylomata acuminata from various anatomical sites. *Sex Transm Dis* 1994; **21:** 103–06.

Long-term effectiveness of MenAfriVac

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A conjugate vaccine for *Neisseria meningitidis* serogroup A (MenAfriVac) was introduced through mass campaigns in people aged 1–29 years in the African meningitis belt and is now being added to national infant immunisation programmes.[1] Following the mass campaigns in 2010–17, incidence of *N meningitidis* serogroup A meningitis has declined from a hyperendemic pattern with regular epidemics to a few sporadic cases.[2] The hope is that control of the disease will be long lasting. The mechanism for such control would be the initial interruption of circulation of *N meningitidis* serogroup A in the population through the effect of the vaccine against asymptomatic nasopharyngeal infection, followed by sustained direct protection against disease, including in new birth cohorts. The duration of persistence of antibodies is a major variable in this scheme.

In *The Lancet Infectious Diseases*, Michael White and colleagues report results from a mathematical model,[3] originally developed for natural malaria infection but used here to estimate the kinetics of *N meningitidis* serogroup A-specific serum bactericidal antibodies (SBAs) in the African meningitis belt. The model uses serological data obtained in clinical trials[4,5] before and up to 2 years after vaccination with MenAfriVac. These trials tested a single dose of MenAfriVac in children and adults aged 12 months to 29 years.[4,5] The model predicts that vaccine efficacy after 20 years will be 52% (95 credible interval 29–73) among 12–23 month-old children and 70% (60–79) among older children and adults. These results suggest that no booster vaccination would be needed for people vaccinated with MenAfriVac at age 2 years or older.

This research is an important complement to two other approaches: first, the two clinical trials[4,5] followed SBA persistence up to 5 years after vaccination and found that after a substantial decline of 40–80% during the first year after vaccination, antibody titres were stable in all age groups between 1 and 29 years. One limitation of these estimates is that, unlike the current situation of quasi-elimination, *N meningitidis* serogroup A continued to circulate in trial populations and natural boosting might have maintained higher antibody levels. White and colleagues overcome this limitation in their model by simply not assuming any such boosting effect and also provide a long-term estimate up to 20 years after vaccination. Second, from a series of population-level cross-sectional studies in Burkina Faso and exponential extrapolation of the decline, we estimated that SBA antibody titres would return to pre-vaccination levels after 12 years at the earliest.[6] Although our work's strength was that it reflects the real-life situation of immigrating unvaccinated individuals, its ecological design and lack of document-based vaccination status for most participants in subsequent surveys was a limitation.

The results we obtained, however, shed light on an important limitation of all current work: there is no confirmed correlate of protection against *N meningitidis* serogroup A in the meningitis belt, neither for meningitis nor for asymptomatic infection. We have previously shown that the seroprevalence of putatively protective SBA titres against the *N meningitidis* serogroup A reference strain (≥1/8 or ≥1/128) does not correlate with meningitis incidence.[7] This finding was not surprising, given that the seroprevalence of these titres was more than 70% among children and adults already in the pre-vaccination era. As an alternative serological measure, we proposed the SBA against strain 3125, which should be specific for vaccine-induced protection.[8] Among children vaccinated before 5 years of age, the return to pre-vaccination levels