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Revising ecological assumptions about Human papillomavirus interactions and type replacement

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HIGHLIGHTS

- With a model we evaluated competing hypotheses of HPV type interactions.
- Independence and facilitation are not necessary for coexistence of types inside hosts.
- Spatial heterogeneity can lead to underappreciated complex type interactions.
- Conditions for type replacement are possible at the within-host level.

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ABSTRACT

The controversy over whether vaccine-targeted HPV types will be replaced by other oncogenic, non-vaccine-targeted types remains unresolved. This is in part because little is known about the ecology of HPV types. Patient data has been interpreted to suggest independence or facilitative interactions between types and therefore replacement is believed to be unlikely. With a novel mathematical model, we investigated which HPV type interactions and their immune responses gave qualitatively similar patterns frequently observed in patients. To assess the possibility of type replacement, vaccination was added to see if non-vaccine-targeted types increased their 'niche'. Our model predicts that independence and facilitation are not necessary for the coexistence of types inside hosts, especially given the patchy nature of HPV infection. In fact, independence and facilitation inadequately represented co-infected patients. We found that some form of competition is likely in natural co-infections. Hence, non-vaccine-targeted types that are not cross-reactive with the vaccine could spread to more patches and can increase their viral load in vaccinated hosts. The degree to which this happens will depend on replication and patch colonization rates. Our results suggest that independence between types could be a fallacy, and so without conclusively untangling HPV within-host ecology, type replacement remains theoretically viable. More ecological thinking is needed in future studies.

1. Introduction

Infection by Human Papillomavirus (HPV) is responsible for approximately 270,000 cervical cancer deaths and roughly 97,000 cases of other cancers (e.g. anal, oropharyngeal) globally every year (Tota et al., 2011b). The significance of finding a virus as a causal agent to cancer cannot be understated since it permits us to prevent cancers with vaccines. Two vaccines, Cervarix® and Gardasil®, are used to prevent cancer by the two most common oncogenic high-risk (HR) HPV types, namely, HPV-16 and -18. Controversy has surfaced around the strain specificity of the HPV vaccines, since other strain-specific vaccines have led to strain replacement (reviews in Gandon and Day, 2008; Martcheva et al., 2008), such that strains not targeted by the vaccine increase in prevalence over time. Thus, the removal of these vaccine-targeted types ('vaccine types') could lead to an increase of other HR types not targeted by the vaccine ('non-vaccine types'). Alarmingly, a recent increase in prevalence of non-vaccine types was measured in vaccinated young women and in the study population (Kahn et al., 2012) – a potential first warning that type replacement in HPV is occurring.

Whether a population will expand its niche once another population is removed from a shared environment is fundamentally an ecological question. Indeed, predicting the outcome of removing the vaccine types, HPV-16 and -18, first requires understanding how HPV types interact ecologically during co-infections.

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In fact, untangling HPV type interactions could also help us understand disease progression (Spinillo et al., 2009). Yet, despite these important reasons, little is known about HPV type interactions and ecology. Here, we analyze this problem using an ecological framework and we consider the impact the vaccine has on the within-host ecology of HPV.

The only interaction between HPV types that has been clearly demonstrated is that some types interact via the immune response. Types phylogenetically related to HPV-16 (i.e. types in the species α-9) have a negative effect on its viral load (Williams et al., 2002; Xi et al., 2009). Likewise, types with similar epitopes on the vaccine-targeted capsid protein, L1, to those of the vaccine-types HPV-16 and -18 (Christensen and Bounds, 2010) experience some cross-protection by the vaccine (HPV-31, -33, -45, -51 (Wheeler et al., 2012)). Together these studies demonstrate 'immune-mediated apparent competition' (Mideo, 2009) between some related types.

Of all HPV infections 30–50% are multiple infections and, concurrent acquisition (presumably due to co-transmission) of various types is common (Plummer et al., 2011; Thomas et al., 2001). How such a large diversity of HPV types can regularly coexist inside hosts is not understood and has led to speculations of facilitative or 'synergistic' interactions between types (Elbasha and Galvani, 2005; Woodman et al., 2007) or that types are independent (Plummer et al., 2007; Stanley et al., 2006). In contrast, there is some evidence that HPV types may compete for resources (McLaughlin-Drubin and Meyers, 2004), either by co-infecting the same cells and competing for intra-cellular resources or by competing for cells via blocking cell entry. Overall, then, the picture as to how HPV types interact inside hosts is not clear.

Clarifying how types interact should have predictive power. Two prior mathematical transmission models (Elbasha and Galvani, 2005; Poolman et al., 2008) found that the occurrence of type replacement will depend on whether types compete or facilitate, and so, their results hinge on the assumptions about within-host interactions. However, the within-host interactions were a black-box in these models, and they continue to be so today.

Based on common interpretations of epidemiological data, there are two main hypotheses of how HPV types interact: facilitation or independence. Support for the former comes from studies that have found that seropositive patients are more likely to become seropositive with another type (Dillner et al., 2010). The latter is supported by several studies that have not found patterns of clustering at the epidemiological level (reviews Dillner et al., 2010; Tota et al., 2013). It is reasoned that the random distribution of types at the population level implies that within hosts there is 'no competition' or 'no interactions' (Garnett and Waddell, 2000; Tota et al., 2013) and that competition between types should be detectable epidemiologically because types that compete would not be found together in co-infections (Kaasila et al., 2009; Palmroth et al., 2012). Underlying this is the concept of 'superinfection' (Levin and Pimentel, 1981; Nowak and May, 1994), where a host already infected by one strain can become infected by another but due to strong within-host competition the new strain quickly excludes the other, thus implying that strains cannot coexist inside hosts, i.e. co-infections are not possible. Given that independence is the most accepted hypothesis, it is believed that the vaccines will not affect non-vaccine types (Schiller and Lowy, 2012).

Here we test these hypothesized interactions by investigating which interaction scenario behaves most like HPV co-infections. Using a within-host model we investigated independence, facilitation, resource competition (a form of competition that has been largely ignored) and their combinations. This within-host approach allows us to look inside the black-box by explicitly considering the behaviour of different possible interactions inside unvaccinated and vaccinated hosts.

We found that within-host ecological interactions that are not solely independent or facilitative can readily give rise to observed co-infection dynamics. Hence, we caution that the current interpretations of epidemiological data require more support.

2. Methods

2.1. Model

HPV is a small double stranded DNA virus that infects epithelial cells. As a non-lytic virus, HPV's replication cycle is linked to the life cycle of the host cell, meaning that HPV must infect basal epithelial cells (Kines et al., 2009; Schiller et al., 2010) and follow them up through the epithelial column until they die naturally at the surface of the skin (Doorbar et al., 2012). Therefore, new virions are not released until the cells die at the surface (Fig. 1(a)i.) and HPV needs abrasions in the skin to reach and infect new basal epithelial cells (Fig. 1(a)ii.) (Doorbar, 2005; Doorbar et al., 2012). This spatial restriction implies that HPV infections are localized, which leads to characteristic lesions or warts (Doorbar, 2005). HPV infection should thus be conceptualized as occurring in various "patches" distributed across space (Fig. 1(a)).

We developed a novel patch model that represents HPV co-infections that is based on the Levins metapopulation models from ecology (Levins, 1969), which is a useful framework for understanding

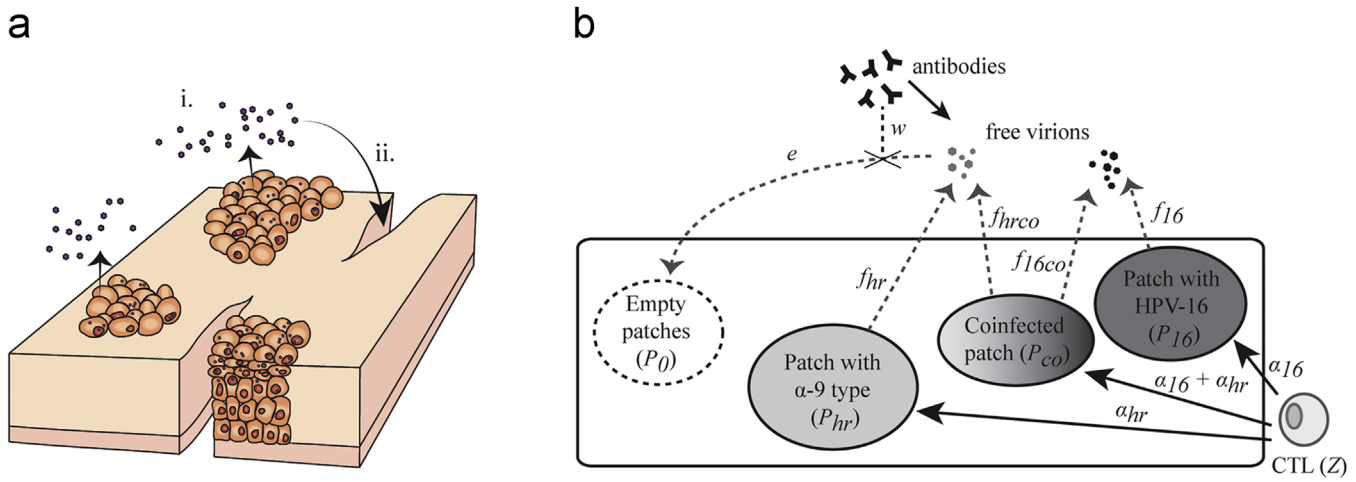

Fig. 1. (a) An illustration of layered squamous cell infections; a top-down and cross-section view of the epidermis. Free virus particles are released at the surface (i) and need an abrasion in the epidermis to reach basal cells to start a new patch (ii). (b) A schematic of the model. See methods for description of symbols.