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Conference report

Vaccination: An evolutionary engine for pathogens? Conference report

1. Introduction

In the past century, vaccines led to the eradication or substantial reduction of several transmissible diseases. However, many available vaccines are imperfect (leaky) vaccines i.e. vaccinated subjects remain partially susceptible. In this case, vaccination can lead to dramatic perturbations of the environment of pathogen populations. This can have both demographic and evolutionary consequences, allowing the pathogen to evolve and to adapt. Adaptation can lead to either epitope evolution, i.e. emergence of escape mutants that evade the vaccine, or to virulence evolution; the outcome being vaccination failure in all cases. When implementing a new vaccine, it is therefore important to determine the potential evolution of the pathogen under vaccine selection pressure.

The purpose of this paper is to report on the current state of knowledge on the fundamental mechanisms for evolution of pathogens as a result of vaccine pressure in a vaccinated world and to discuss methodologies and data that are needed to identify and combat pathogen adaptation to vaccines. The data were originated from the conference "Vaccination: an evolutionary engine for species?" that was held at the Fondation Mérieux Conference Center "Les Pensières" (Annecy-France) in November 25–27, 2013.

2. Evolutionary epidemiology theory of vaccination

Vaccination affects the life history parameters of the pathogen (transmission rate, recovery rate and virulence) and epidemiological characteristics of the disease. Beyond changes in the disease incidence, vaccination can leave other identifiable epidemiological footprints such as increasing inter-epidemic period and shift in age distribution of cases. These population level indicators of epidemiological evolution of the disease under vaccine pressure can be calculated using large-scale dynamic, time-series data such as those generated by national immunization program surveillance, and compared with predictions from dynamic models to make inferences regarding vaccine efficacy [Pejman ROHANI, Michigan-USA]. Applying dynamic models to data on *Bordetella pertussis* vaccination demonstrated that the global trends of infection overtime declined even if increases have been observed in some countries (Jackson and Rohani, 2014). A comparative study in countries for which pre-vaccine era analysis was feasible reported an average increase of 1.3 years in the inter-epidemic period in vaccinating countries (Broutin et al., 2010). Similarly, an increase in the extinction profile of pertussis has been reported by several studies (Blackwood et al., 2013; Choisy and Rohani, 2012; Rohani et al., 2000). This would suggest that pertussis vaccination prevents both infection and transmission. Epidemiological theory predicts that transmission-blocking vaccines decrease circulation of a pathogen in the population, leading to a shift in the age distribution of cases. The shift towards older age observed for pertussis in the past few decades is consistent with this theory.

The evolutionary response of pathogens to vaccine-driven selection has been often based on two distinct features. The first one is the emergence of so called "escape mutants" able to evade the immune response induced by the vaccine. Escape mutants might be existing strains or do-novo mutants. Type replacement by existing strains not included in the vaccine is a dynamics phenomenon that can occur only if (1) two different infections compete with each other during natural infection and (2) the vaccine does not afford cross-protection against competing strains [Joakim DILLNER, Stockholm-Sweden]. The phenomenon has been found for already available vaccines such as anti-*Streptococcus pneumonia* vaccine and has the potential to occur for HPV and dengue. Escape mutants can also be do-novo mutants that arise by alterations in the genes encoding the pathogen epitopes that are recognized by vaccine-induced immunity. Epitope variants are known for hepatitis B virus (HBV), influenza virus, and polioviruses. Virulence adaptation is the second feature of pathogen evolution as a result of vaccine pressure. Studies on escape mutants focus on short term evolutionary outcomes of the pathogen while studies of virulence mutants address the long terms consequences of vaccination on the pathogen 'life history" (Gandon and Day, 2007). These two features are however related to one another. A two-locus model taking into accounts both escape and virulence evolution can be therefore envisaged that allow evolutionary change to occur on any time-scale relative to that of the epidemiological dynamics (Gandon et al., 2013; Gandon and Day, 2007).

3. Evolution of viruses as a result of vaccine pressure

3.1. Hepatitis B

Hepatitis B virus (HBV) is a leading cause of acute and chronic liver disease for which effective vaccines have been available for more than 40 years. Strategies for vaccination were initially targeted to specific risk groups. Nevertheless, failure of such policies led the WHO to recommend the introduction of the vaccine into their national immunization programs. Universal vaccination, already implemented in 181 countries, has led to significant reduction in the overall burden of disease and development of the carrier state. However, despite the well-characterized safety and efficacy of licensed vaccines, concerns about escape mutants are emerging. Neutralizing antibodies (anti-HBs) induced by vaccination are mainly targeted towards the conformational epitope of

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the "a" determinant region of the antigen (HBsAg) and provide protection against all HBV genotypes. G145R substitution in the "a" determinant region is an important mutation that alters the recognition of the mutated epitope by neutralizing antibodies induced by vaccination. Breakthrough infections caused by these mutants are occasionally reported but at present they do not pose a serious threat to the established vaccination programs. A study conducted among subjects with acute hepatitis B ($n = 5156$) in Italy reported that about 3% ($n = 156$) of patients were vaccinated subjects but only 24% ($n = 37$) of them were properly vaccinated. Molecular characterization carried out in 21 cases showed that one third (33%) were escape mutants [Alessandro ZANETTI, Milan-Italy].

3.2. Influenza

Similarly, influenza vaccines have been available for several decades and vaccination is considered as the best strategy for controlling influenza in humans. Influenza viruses have the capacity to change through genetic changes known as antigenic drift and antigenic shifts. Each of these modes of variation are influenced by immune selection, thus the use of vaccines can contribute to selection of variants [Robert WEBSTER, Memphis-USA]. For example, influenza A H5N1 is now endemic in poultry farms in countries that adopted for control by using vaccination in birds (China, Vietnam, and Indonesia). Vaccination was also a driver for evolution of influenza A H5N2 and H7N3 in Mexico. One should bear in mind that (i) continuing circulation of a subtype does not preclude its reemergence; seasonal H1N1 was circulating; (ii) antigenic and structural similarities are not predictors of severity and finally (iii) a virus with pandemic potential can emerge anywhere in the world.

3.3. Polyomyelitis

Polyomyelitis is another example of a not yet eradicated viral infection, despite massive oral polio vaccine (OPV) immunisation programs. Low vaccination coverage, especially in the developing world, is thought to be a key factor in continuous circulation of poliovirus (PV), its genetic drift and the emergence of circulating pathogenic vaccine-derived PV (VDPV). Most VDPVs are recombinant between vaccine PV and other human enteroviruses (HEV) and have been implicated in polyomyelitis outbreaks in several countries [Francis DELPEYROUX, Paris-France]. The 2001–2002 and 2005 outbreaks in Madagascar were associated with type 2 or 3 VDPVs. Most of VDPVs were recombinants between the non-structural regions of PV vaccine strains and HEV-C, particularly coxsackie A viruses of type 13 and 17 (CVA-13 and 17) (Razafindratsimandresy et al., 2013). These observations led to the hypothesis that co-circulation and genetic exchange of PV with HEV-C CVA-13 and CVA-17 may favor the emergence of VDPVs elsewhere. This hypothesis was tested in Cameroon and neighboring countries by collection of stool samples from healthy children and patients with acute flaccid paralysis. The results showed intense circulation of non-polio HEVs characterized by type diversity (38 different types), genotype diversity and recombinant genotypes diversity in about 37% of infected children (Sadeuh-Mba et al., 2013).

3.4. Human papillomavirus

Human papillomavirus (HPV) type 16 and 18 are the most common HPV types associated with cervical cancers and HPV 16 is also a major cause of other anogenital and oropharyngeal cancers. HPV vaccines currently on the market include 2 (Cervarix®) and 4 (Gardasil®) HPV serotypes respectively. However, many other types exist, of which 14 also appears to be oncogenic. Thus, post-vaccination emergence of disease caused by serotypes not included in the vaccine is a theoretical concern. Comparison of prevalence of vaccine HPV genotypes in pre- and post-vaccine era in Australia showed significantly lower prevalence in both vaccinated and unvaccinated women following vaccination (Tabrizi et al., 2012).

Several epidemiological studies have addressed the question of possible competition between infection with different HPV types. Presence of type-specific antibodies for one HPV type is associated with increased risk for also being seropositive for other HPV types (Dillner et al., 2011). Therefore, it seems that the first prerequisite for type replacement- natural competition- does not apply and that type replacement is unlikely [Joakim DILLNER, Stockholm-Sweden]. Apart from the risk of serotype replacement, viral escape mutants forming new genotypes could also occur. However, the very slow mutation rate of HPV (1 pair base every 10,000 years) and the fact that so far all different viral strains and variants of HPV16 from all over the world have been found to constitute a single genotype, suggest that the risk is small [Joakim DILLNER, Stockholm-Sweden].

3.5. Dengue virus

Several candidate dengue vaccines are currently under development, but it is unknown whether vaccination program pressure will impact transmission, alter viral properties and result in a higher incidence of more severe, symptomatic clinical diseases. Better knowledge of spatial and temporal patterns of dengue virus spread is necessary to formulate optimal vaccination and vector control programs and to model the potential impact of large-scale vaccination [Jared ALDSTADT, New-York-USA]. Dengue illness is characterized by long-term immunity to the infecting serotype, short-term cross-immunity between strains and, typically, more severe disease following with a second infection. The four antigenically distinct serotypes co-circulate in endemic areas (hyperendemicity). To investigate the diversity of dengue viruses and its microevolution over time before the introduction of mass vaccination, prospective school-based surveillance and geographically based community cluster studies have been carried out in a rural region of Thailand over four dengue seasons (2004–2007) (Rabaa et al., 2013). Index cases were laboratory confirmed hospitalized cases detected in the school-based cohort. Cluster sampling was based on the enrollment of neighboring houses with active fever or a history of fever among households. The results showed that at least three serotypes co-circulated among the study population during each year of the study period. Proximity with the index houses was associated with increased number of infected vector i.e. female *Aedes aegypti* mosquitoes and increased likelihood of being serologically positive in clustered houses. A family-based cohort is ongoing to assess how mass vaccination and vector control will impact the disease burden. Questions to be answered are: How will mass vaccination and vector control impact (i) evolving interactions between vector, virus, and host occurring at the macro and micro spatial scales? (ii) Virus, vector, host response to the changing dengue virus circulation dynamics? (iii) Population level "herd immunity profile" and the impact on dengue virus evolution, micro-evolution, and clinical outcomes? and (iv) Existing herd immunity to related flaviviruses and the impact on dengue virus transmission and clinical outcomes?

3.6. Rota virus

Rota virus is the leading cause of severe diarrhea in children. Most human diseases are due to rotavirus A with multiple genotypes referred to by G- and P-types. The two currently available vaccines, Rotarix (GSK) and RotaTeq (Merck), differ in their