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Vaccine strategies

Selection of new COVID-19 genotypes following mass vaccination: The Rotavirus model☆

Selección de nuevos genotipos de COVID-19 tras la vacunación en masa: el modelo Rotavirus

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RNA-based vaccines have been shown to be safe and effective in protecting humans from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Other vaccines have already been shown to be effective in preventing infection.[1] Concerns arose over four variants and other nine are currently being studied. The Delta variant, characterized by peculiar mutations of the Spike protein, was found in nearly 95% of sequenced cases and in 92% of genotyped cases analyzed between 7 and June 21, 2021.[2] However, the two Covid-19 vaccines which are the BNT162b2 and ChAdOx1 nCoV-19, resulted in being highly effective against the Delta variant after the double shot vaccine injection,[3] therefore, the current mass vaccination campaign aims at immunizing the population with a two doses vaccine injection. Regarding the viral mutation and replication principles, even if the mutation frequency is independent of the population (intrinsic property), the probability to find an individual mutation or indel is directly proportional to the spread of the circulating virus (extrinsic property).[4] In case of generation of a new resistant variant, large-scale vaccination would then exert a selective action which would favor its prevalence over the dominant strains in a short time. If a vaccine-resistant variant develops at the time between vaccination and exposure, the vaccinated individual could be left unprotected. In the case of widespread of a resistant viral variant, the vaccination campaign might be retroactively ineffective. Moreover, since most of COVID-19 vaccine target either the viral Spike protein or the Spike protein receptor binding domain, the development of a resistance could destabilize at the same time the effectiveness of other vaccines. This phenomenon in the case of antimicrobial drugs is referred to as “cross” or “collateral” resistance.[5] Large-scale vaccination can unbalance the relationships between the host and the virus by selecting different genotypes, drastically reducing the spread of dominant strains.[6] Rotavirus vaccination campaigns can be considered as an important epidemiological model for evaluating how genotype fluctuations of SARS-CoV-2 can occur in the post-vaccine era. In the vaccination campaigns against Rotaviruses carried out in Finland, a strong impact was observed on the reduction of the disease burden measured as hospitalization and outpatient episodes among the very young. However, this led to the selection of non-dominant genotypes with a shift in the incidence in the age groups.[7] New genotypes seem to have appeared to replace the dominant genotypes in the pre-vaccination era. It is interesting to evaluate the prevalence of the G1 and non-G1 genotypes in consecutive rotavirus seasons, as RotarixTM mainly has been used in Belgium. A significant increase in the prevalence of the G2 genotype has been observed (above 30%) since the introduction of the rotavirus vaccines. This remained the case for the 2007/2008 and 2008/2009 seasons. Very low numbers of G2 strains were found in seasons before vaccine introduction (1999/2006) and the prevalence of G2 genotypes never surpassed 20% in contrast to other circulating

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genotypes.[8] Similar observations have been reported in the USA[9] and in China where a continuous evolution of rotavirus has been highlighted.[10] Regarding the hepatitis A immunization, vaccination programs have been run among preadolescents in the Catalonia Autonomous Community of Spain. Four variants were isolated which were localized very close to the immune-dominant site and to residues substituted in two MAR mutants (C6 and P29 monoclonal antibody-resistant). This shows a viral phenotype resistant to commercial vaccines protection.[11] It is interesting to note that several studies have been looking at important animal pathogens, such as bovine respiratory Syncytial virus (BRSV), bovine herpesvirus-1 (BoHV-1), foot and mouth disease virus (FMDV), and Marek's disease virus (MDV). These studies reported evidence regarding the development of viral pathogens within vaccinated population, and found evidence that the evolution of a pathogen widespread in a population is not only an important implication for vaccine resistance but also it might contribute to the generation of new variants with different pathogenicity or altered host tropism.[12] A clear example of viral mutation is represented by the case of BRSV. This virus combines a high rate of sequence evolution that provides local genetic differentiation and justifies the related geographic groupings seen in phylogenetic trees, with an elevated high rate of amino acid changes in some other regions of the G protein. Considering that G protein are antigenic, these modifications allow the virus to possibly escape previously established immunity, controlled in vitro with HRSV, and isolates from countries where vaccination campaign is extensively applied demonstrate large changes in the amino acid sequences found in these specific regions.[13] A further study supports evolutionary evidence in favor of the Classical swine fever virus (CSFV) vaccination strategies based on genotype 1 strains which results in advantageous immune environments for the survival of genotype 2 CSFV strain, constantly evolving in order to escape the immune system. Nevertheless, other experimental challenge studies revealed that current vaccine strains which are based on genotype 1 isolates, could result in protecting against the current CSFV strains. Therefore, in this example, effective and efficient vaccination strategies are necessary to diminish and control the development of CSFV in swine herds and to prevent the generation of vaccine-escaping variants.[14] Another example of the molecular variation related to vaccination is represented by the vaccines against porcine circovirus 2 (PCV2) where the PCV2 populations variability showed to be different in samples obtained from vaccinating and non-vaccinating farms.[15] The high mortality rate due to the infection and socio-economic impact related to the SARS-CoV-2 pandemic leads to massive vaccination campaigns that will eventually affect the dominant viral cluster. This process can facilitate the selection of non-dominant genotypes resistant to immunization. The spread of non-dominant viral genotypes may change the clinical and epidemiological aspects of the infection.[18] Currently, there is no evidence supporting that the vaccination of the entire population can be effective. More generally, a universal vaccine has never been obtained for influenza infection.[16] Mainly all vaccination campaigns were carried out on risk groups; the SARS-CoV-2 vaccination campaign is the first one extended to the entire population. The aim of the vaccination campaign should not be only to prevent the infection of one of the COVID-19 genotypes but to prevent deaths related to it.[17] The results of Rotavirus vaccination campaigns can be used to predict the effects of SARS-CoV-2 vaccination campaigns. The reported immunization campaigns, that may be used as models for the SARS-CoV-2 vaccination programmes, have showed that immunization can have a selective action on resistant viral genotypes, promoting their prevalence compared to dominant genotypes. Therefore, continuous surveillance is necessary to identify the prevalence of new genotypes resistant to the immunization process.[19]

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