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Qdenga® - A promising dengue fever vaccine; can it be recommended to non-immune travelers?

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A B S T R A C T

Qdenga® has been approved by the European Medicines Agency (EMA) for individuals > 4 years of age and for use according to national recommendations. The vaccine shows high efficacy against virologically confirmed dengue and severe dengue in clinical studies on 4–16-year old's living in endemic areas. For individuals 16–60 years old only serological data exists and there is no data for individuals > 60 years. Its use as a travel vaccine is still unclear. We present the studies behind the approval and the recommendations for travelers as issued by the Swedish Society for Infectious Diseases Physicians.

Half of the world's population is living in areas where dengue fever is present [1]. Asian countries are most affected, reporting approximately 70% of all cases [2]. Although most infections are asymptomatic or mild, progress to severe dengue fever and death occurs. Dengue fever virus (DENV) constitutes four main distinct serotypes (DENV1-4). Infection with one serotype results in long term immunity against that specific serotype but only short-lived immunity against the other serotypes. A second dengue infection is a risk factor for severe disease, but this is not the case for subsequent infections [3]. The reason for this is unclear but it is commonly attributed to antibody dependent enhancement (ADE) [4], where cross reacting antibodies, forms immune complexes, instead of neutralizing the virus, resulting in increased viremia and a more severe disease. This phenomenon is important to consider in dengue fever vaccine development and any vaccine candidate should preferably induce long term immunity against all four serotypes.

At present there are two live attenuated tetravalent vaccines targeting DENV1-4, Dengvaxia® and Qdenga®. Dengvaxia® is based on a yellow fever backbone and was introduced in 2015. Clinical studies showed an efficacy against virologically confirmed dengue fever (VCD) of 60% [5]. However, during the third year of follow up the risk for hospitalized VCD was increased in the vaccine group for dengue naïve younger children compared to the placebo group [6]. The vaccine is now limited to individuals with previous dengue fever, and it is not available in non-endemic countries. Qdenga® is based on a DENV2 backbone with recombinant strains expressing surface proteins for DENV1, DENV3 and DENV4. By using a backbone of DENV2 instead of yellow fever virus it has the potential to stimulate a broader humoral and cell mediated immunological reaction [7].

Qdenga® is administered as a subcutaneous injection, two doses with 3 months interval. It is contraindicated in immunocompromised individuals as well as in pregnant and breastfeeding women. It seems to be well tolerated and no serious adverse events have been linked [8]. Co-administration with hepatitis A vaccine has been studied without increase in side effects or impaired antibody response [9]. When co-administered with yellow fever vaccine a lower level of neutralizing antibodies against DENV1 was seen, the clinical significance of which is unclear [10]. Efficacy of Qdenga® has mainly been studied in the TIDES study [11] following around 20 000 children and adolescents in eight countries in Latin America and Asia. Two thirds were vaccinated and one third received placebo. In the first year following vaccination a

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vaccine efficacy against VCD of 80% was seen and it was 95% in preventing VCD requiring hospitalization. The efficacy against VCD was highest against DENV2 (98%) and lowest against DENV3 (63%). No effect against DENV4 could be demonstrated at this time point due to few cases. The cumulative vaccine efficacy 4,5 years after vaccination [7] was 59% in preventing VCD (43–82% depending on serotype, 49% against DENV4) and 84% in preventing VCD requiring hospitalization. Vaccine efficacy was superior in individuals previously infected with dengue fever. The cumulative efficacy 4,5 years after vaccination against VCD was 50% in dengue naïve individuals compared to 63% in those with previous infection. Additionally, no protective effect against VCD caused by DENV3 and DENV4 was seen in dengue naïve individuals. Booster studies are ongoing, a booster dose is probably needed in dengue naïve individuals. Vaccine efficacy in the three months between dose 1 and 2 in preventing VCD was 81% [11].

In the third year after the second vaccine dose a higher proportion of vaccinees were hospitalized with VCD due to DENV3 compared to the placebo group in dengue naïve individuals. The explanation given is that there was a lower threshold for hospitalization due to VCD in Sri Lanka compared to other study countries (shown through subgroup analysis) and that Qdenga® fails to protect against DENV3 [7,12]. During the following 1,5 years this phenomenon has not been seen [7].

Qdenga® induces antibody responses against all four serotypes of varying levels, highest for DENV2. The neutralizing antibody levels are higher in individuals with previous dengue fever compared to dengue naïve. The levels remain above cut-off for seropositivity in most individuals for several years after vaccination [7]. There is unfortunately no defined serological correlate of protection yet [13] and no such level was found in studies on Qdenga® [7]. In individuals >16 years of age no efficacy studies have been carried out and vaccination in individuals >60 years has not been studied at all.

Since dengue fever is such a widespread disease many international travelers will visit an endemic country, but the risk is very variable between regions. Incidence data for the local population as well as for international travelers are important tools in decision making but reliable and updated estimates might be difficult to find. An approximation of the risk in European travelers visiting endemic areas between 2015 and 2019 put the travel related incidence at 2.8 per 100 000 travelers [14]. The travel related risk is also affected by duration of trip, as well as repeated travel, type of travel, frequency of outdoor activities, type of accommodation and seasonality of mosquito density. Dengue outbreaks at the travel destination are important to consider.

In summary Qdenga® showed a clear protective effect against dengue fever in children and adolescents 4–16 years living in endemic areas but dengue naïve individuals were not protected against DENV3 and DENV4 from vaccination. Comparable levels of neutralizing antibodies were seen in individuals 17-60-compared to those in 4–16-year-olds [15]. In EMA:s approval no upper age limit was set despite the above lack of data. No indication of disease enhancement has been seen in the TIDES study up until 4,5 years after the second vaccine dose. Qdenga® will have a significant effect in preventing dengue fever in endemic countries but how to use it as a travel vaccine in individuals living in non-endemic countries require some considerations, as antibody levels and their neutralizing capability after several years without exposure to dengue virus is not known. Is a previously vaccinated dengue naïve traveler at increased risk for a more severe disease when travelling after several years if not receiving a booster dose before the trip? With ageing the immunosenescence affects the ability to respond to vaccines in general and these elderly might therefore have a reduced seroprotection after Qdenga®-vaccination. Furthermore, are older individuals, due to a weakened antibody response, at risk for disease enhancement?

In Sweden, Qdenga is now available at private vaccination-policlinics at a cost of around 200 Euro per dose. The national regulatory and public health authorities have no intention to guide the use of this vaccine. Dengue fever is a notifiable disease according to the Swedish Act of Communicable Diseases, however this only applies to laboratory verified cases made while back home. In 2019, 235 cases of imported dengue fever were reported with an incidence of 2.28/100 000 which was a record high notification. Swedes are frequent travelers to dengue-endemic areas and there is already a demand and questions on how and when to use the vaccine. Therefore the Vaccine Expert group of the Swedish Society for Infectious Diseases Physicians have reviewed the literature to guide and formulate recommendations on the use of Qdenga® as a travel vaccine.

In these recommendations we propose an initial cautionary approach due to the lack of data in dengue-naive adults and especially elderly.

- For travelers with previous known self-reported (hospitalized or policlinic testing) dengue fever, vaccination is recommended before travel to an endemic country.
- For dengue naïve travelers vaccination may be considered in individuals aged 4–16 years old irrespective of travel duration.
- For travelers aged 17–60 years old we recommend considering vaccination only for longer trips and related to travel destination. We have suggested a trip for more than six weeks to South-East Asia, a region with among the highest global incidence of dengue fever, to be used as a reference.
- Since Qdenga® has not yet been studied in individuals >60 years old, we advise vaccination should be avoided in this group until data are available.

Travelling after only one vaccine dose should be avoided if possible, which is a challenge for most travelers coming with shorter notice for travel medicine advice. It can be considered, especially in individuals with previous dengue fever, given that they receive the second dose after return. As far as we know our recommendations are more cautious than in other non-endemic countries, especially regarding the upper age limit, and should be continuously revised when more information and experience become available.

Declaration of competing interest

No conflict of interest.

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